The development and assessment of executive functioning in preschool children with and without sickle cell anaemia

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I, Michelle Downes, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Executive functioning is the ability to execute cognitive control in high-level processes such as planning or problem solving. Executive functions are susceptible to disease. Deficits have been highlighted in many school age and adolescent patient populations, including sickle cell anaemia. However, research with preschool children largely depends on general developmental measures, non-validated behavioural measures, and parental report, making it difficult to ascertain the extent of potential executive deficits. Sickle cell anaemia, the most common hereditary disorder in the United Kingdom, is a blood disorder caused by an abnormal gene for haemoglobin. These children are at a high risk of stroke, but even without stroke, they can develop deficits in executive functioning. Although executive deficits have been identified in school-age children with sickle cell disease, there has been no research in preschool children that has attempted to delineate whether these deficits are present and/or detectable at this early stage. Early detection could lead to the development of targeted interventions and improve school readiness.

Executive tasks, including an ERP study, were developed, piloted, and validated with typically developing preschool children. One of the tasks was also normed in a larger population (N=166, 3-5 years). Tasks developed during this thesis that were considered valid were administered to children with sickle cell disease and a matched comparison group, alongside other recently developed and standardised assessments of executive functioning.

Children with sickle cell anaemia obtained poorer scores on behavioural executive tasks with differences also observed for underlying neural correlates on the ERP task. However, these differences did not translate to parental report. Specific deficits, detected by behavioural measures, may not yet have translated into everyday issues. Disease-related factors did not predict executive performance, with family functioning and sleep problems emerging as important factors for executive development. The findings from this thesis inform future research in early assessment and intervention.
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In memory of Julia Cosgrove (1926-2015)

Image by Angela Farragher
Thesis Overview

The main aim of this thesis is to develop novel ways to measure executive functioning in preschool children and to apply these means to investigate the development and predictors of executive functioning in preschool-age children with sickle cell anaemia. This section provides the reader with an overview of the contents of each chapter.

Chapter 1: General Introduction: The development and assessment of executive functioning in the preschool years with a special focus on the development of children with sickle cell anaemia

Chapter 2: General Methodology: Studying executive functioning in the preschool years using behavioural and neurophysiological methods

Chapter 3: Validation: The development and validation of measures of executive functioning for three to five year olds

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Glossary

Here I provide an alphabetised list of abbreviations used within this thesis:

**BRIEF-P**  
Behaviour Rating Inventory of Executive Function-Preschool Version

**CBFV**  
Cerebral Blood Flow Velocity

**CBQ**  
Children’s Behaviour Questionnaire

**CSHQ**  
Children’s Sleep Habit Questionnaire

**DCCS**  
Dimensional Change Card Sort

**DDTP**  
Doggie Deletion Task for Preschoolers

**EEG**  
Electroencephalography

**EF**  
Executive Functioning

**EFP**  
Early Frontal Positivity

**ERP**  
Event-related Potential

**FES**  
Family Environment Scale

**HbSC**  
Sickle cell-haemoglobin C Genotype

**HbSS**  
Sickle cell Anaemia Genotype

**IQ**  
Intellectual Quotient

**MRI**  
Magnetic Resonance Imaging

**MS**  
Milliseconds

**NHS**  
National Health Service

**NIH**  
National Institute of Health

**R&D**  
Research and Design

**SCA**  
Sickle Cell Anaemia

**SCD**  
Sickle Cell Disease

**SDB**  
Sleep Disordered Breathing

**SES**  
Socioeconomic Status
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Chapter 1: General Introduction

The development and assessment of executive functioning in the preschool years with a special focus on the development of children with sickle cell anaemia
1 General Introduction

The first aim of this introduction is to describe what is known about executive development and its neural correlates in young children with sickle cell anaemia. The second aim is to look at current means of assessment in the executive domain for children in the preschool or “in-between” years and to explore potential avenues that could bridge this research gap that seemingly exists not just in the sickle cell population but in this age range across all disorders. Research in the preschool years is required in order to better understand the development of executive skills and to implement earlier interventions. This is particularly relevant for children with sickle cell anaemia where deficits in executive function is established for school-age children but how and when they emerge is unknown due to a lack of focus on children in the preschool years. The General Introduction will close with a list of the specific aims of the thesis and how they will be investigated in the chapters to follow.

1.1 Sickle Cell Anaemia

Sickle cell anemia (SCA; HbSS), the most common and severe form of sickle cell disease (SCD), occurs when a child inherits the gene for sickle haemoglobin from both parents. It is a genetic blood disorder in which the haemoglobin in red blood cells, which transport oxygen around the body, is abnormal. Sickle cell disease refers to a group of autosomal recessive genetic disorders characterized by the Hb S variant of the beta globin gene. Other types of sickle cell disease, including complex heterozygotes with the sickle gene from one parent and a gene for another haemoglobinopathy, such as
haemoglobin C or beta-thalassaemia from the other parent, tend to have less severe symptomatology although complications are also common in children with sickle beta0-thalassaemia.

1.1.1 History and prevalence

SCD is the most common hereditary disorder in the United Kingdom, with approximately one in 2,000 infants diagnosed at birth. It is most prevalent among people with African heritage but also occurs in people of East Indian, Caribbean, Middle Eastern, South American, and Mediterranean descent. It has existed in Africa for at least 5,000 years but was first described as “sickle trait” in 1910 in the US when James Herrick and Ernest Irons first observed “sickled” cells under a microscope. In the late 1940s, James Neel’s work determined that it was a heritable condition (Horowitz & Mitchell, 1951). The prevalence of sickle cell trait in some parts of Africa, Saudi Arabia, and India is thought to be as high as 40% (Serjeant, 2013). The high rate of SCD in Africa is thought to have emerged in parallel with the high prevalence of malaria, for which sickle trait (HbAS) is protective (Ashley-Koch, Yang, & Olney, 2000).

1.1.2 Physiology

SCA is caused by a variation in the beta globin gene (HB S), which plays an integral role in the formation of haemoglobin (Ashley-Koch et al., 2000). The abnormal haemoglobin polymerises after de-oxygenation, causing the ‘sickling’ process whereby the blood cells change from their regular biconcave shape to a rigid “sickle” or crescent shape (Pauling, Itano, Singer, & Wells, 2004).
The sickled cells can cause many issues including the blockage of blood vessels, as they tend to adhere to the vessel walls, which can restrict normal blood flow and decrease the delivery of oxygen to body tissues which can lead to severe episodes of pain and stroke. The sickled cells are also destroyed quicker than typical red blood cells, leaving a shortage of red blood cells, or anaemia, which may expose tissues to lower levels of oxygen, or hypoxia.

Figure 1.1 The structure of a normal (A) and a sickled (B) red blood cell. The normal red blood cell has a biconcave structure whereas the sickled cell is more elongated and crescent shaped. Figure generated by thesis author using AutoCAD software.

1.1.3 Symptomatology

Physical symptoms of SCA are not typically observed until a child is about six months old due to the presence of foetal haemoglobin. A child’s own haemoglobin begins to replace the foetal haemoglobin between three and six
months, which is when the symptoms of sickling start to emerge due to the rising levels of abnormal haemoglobin (Smith & Baker, 2010). Symptoms and their severity can vary from one person to another. This patient group becomes more heterogeneous with development however disease complications have become reduced due to advances in medical treatment.

Acute pain due to vaso-occlusive crisis caused by sickling can occur anywhere in the body and is most commonly described to be present in the hands, feet, hips, and abdomen. Pain due to dactylitis, or digit inflammation, is commonly reported in young children with SCA (Rees et al., 2003). Children with SCA are also prone to infection due to compromised immune functioning related in part to damage to the spleen that may result in hypertrophy or infarction. The spleen is sometimes surgically removed and children often receive a daily prescription of penicillin to reduce the risk of infection with Pneumococcus (Al-Salem, 2006; Gaston et al., 1986). Other complications, including pulmonary and cardiac, are commonly seen in children with SCA. There are increased rates of asthma reported in children with SCA as well as a high risk for acute chest syndrome and pulmonary hypertension (Boyd, Macklin, Strunk, & DeBaun, 2006).

Stroke is another serious complication of SCA. Brain regions around the intracranial internal carotid arteries and proximal medial cerebral arteries are most commonly affected (Switzer, Hess, Nichols, & Adams, 2006). Ischaemic stroke occurs due to a restriction in blood supply, and thus oxygen and glucose, to the surrounding brain tissue, and haemorrhagic stroke occurs when a blood vessel ruptures and bleeds into the surrounding brain areas. Stroke due to ischaemia is more commonly observed in children with SCA (Kirkham, 2007). Overt stroke can be readily observed via neurologic examination but covert stroke, or silent cerebral infarct, results in small ischaemic lesions that can only be observed via magnetic resonance imaging (MRI) (Hulbert et al., 2011; figure 1.2). Transcranial Doppler (TCD), which measures cerebral blood flow velocity (CBFV) in the intracranial arteries (figure 1.3), which may be high secondary to the anaemia or in relation to vessel narrowing, has been shown to predict overt stroke (Adams et al., 1998).
and most centres in the USA and Europe now offer screening with regular transfusion for abnormal velocities >200 cm/second.

1.2 Sickle Cell Anaemia and Neurocognitive Functioning

1.2.1 Historical background

The first study to look at the potential effects of SCA on cognition was conducted in the early 1960s on the basis that the potential for an effect of sustained hypoxia on intellectual functioning warranted a systematic study despite no history of stroke (Chodorkoff & Whitten, 1963). However, they found no differences between the SCA patients and sibling controls on measures of general cognition. Despite this, seminal sickle research in the 1980s investigated academic performance in children with SCA and stated that it could be affected by a combination of factors including physical limitations of the disease, subtle deficits in the central nervous system, family functioning, and SES factors (Fowler, Whitt, Lallinger, Nash, Atkinson et al., 1988). Fowler and colleagues reported poorer performance in 28 school age children with SCA who had no evidence of stroke on measures of reading, visuo-motor, and attention when compared with 28 well-matched peers. They also observed that older patients performed poorer than younger children with SCA across these domains, suggesting a potential decline in functioning, and that performance was not related to disease severity measures. Notwithstanding the medical advances in the intervening years, children with SCA remain at an increased risk of a range of physiological, neurological, and neuropsychological consequences of ‘sickled’ cells.

1.2.2 Current research

Up to 40% of children with SCA experience clinical or subtler ‘silent’ stroke before the age of 15 (Armstrong et al., 1996; Bernaudin et al., 2000; DeBaun
et al., 2012). Silent stroke involves brain tissue damage, but unlike clinical stroke, it does not show any sudden observable changes in cognition or behaviour. Figure 1.2 shows examples of MRI scans of adolescents with SCA who have either clinical or silent stroke. Clinical and silent stroke have been directly associated with neurocognitive impairment (Gold, Johnson, Treadwell, Hans, & Vichinsky, 2008). For example, Gold and colleagues found in their retrospective review of 65 patients with SCD that the 40% of their cohort who experienced clinical or silent stroke were performing significantly poorer than the children who had no evidence of infarct on MRI on general cognitive measures. However, even in the absence of neurological abnormalities, neurocognitive deficits have been observed to affect academic performance (Brown, Buchanan, et al., 1993; Daly, Kral, & Tarazi, 2011; Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, & Armstrong, 2001). Children with SCD have been found to have a lower intellectual quotient (IQ) on standardised cognitive assessments whether there are signs of infarct present or not (Steen, Fineberg-Buchner, et al., 2005). Children with no evidence of infarct are typically reported to have IQ scores in the low average range with a gradual decline in overall IQ with increasing age. In addition to a lowered IQ, specific cognitive deficits in processing speed, working memory, and other aspects of EF are frequently reported (Berkelhammer et al., 2007; Brown et al., 2000; Hogan, Pitten Cate, Vargha-Khadem, Prengler, & Kirkham, 2006; Hogan, Vargha-Khadem, Saunders, Kirkham, & Baldeweg, 2006; Marshall et al., 2009; Scantlebury et al., 2011; Schatz, Finke, Kellett, & Kramer, 2002).
Chronic anaemia, covert or ‘silent’ infarction, cerebrovascular abnormality, and higher cerebral blood flow velocity (CBFV) are associated with poor cognitive functioning including lower IQ as well as deficits in specific domains (Armstrong et al., 1996; Hijmans, Grootenhuis, et al., 2011; Prohovnik, Hurlet-Jensen, Adams, De Vivo, & Pavlakis, 2009). High CBFV is an indicator of a greater risk of stroke in patients with SCD. High CBFV velocity occurs in response to the body trying to compensate for low levels of haemoglobin in the bloodflow, and thus an insufficient oxygen supply to the brain. Studies with school-age children have shown an association between elevated CBFV as measured by transcranial Doppler (TCD) imaging (figure 1.3) and performance on attention and EF tasks (Kral et al., 2003). Other related complications of SCA, including acute chest syndrome and pain crises, could potentially contribute to neurocognitive deficits and poor academic functioning due to higher rates of school absences and greater fatigue (Brown, Buchanan, et al., 1993; Gil et al., 2000). A recent emphasis has also been placed on non-disease related factors such as the higher incidence of poorer socioeconomic status and sleep-disordered breathing (SDB) in this population, which are thought to further exacerbate the neurocognitive

**Figure 1.2** MRI scans demonstrating covert ‘silent’ (A) and overt (B) stroke in patients with SCA
sequelae of SCA (Daly, Kral, & Tarazi, 2011; King et al., 2013).

**Figure 1.3** An abnormal or elevated TCD reading indicating a high cerebral blood flow velocity and an increased risk of stroke

Even with no clinical history of stroke or MRI evidence of covert infarction, there is evidence that neuropsychological functioning is abnormal and can decline with age as children with SCA do not develop at the same rate as their peers without SCA (Schatz, Finke, et al., 2002; Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, & Armstrong, 2001). Preliminary research with infants, toddlers, and preschool-age children show that early cognitive delay is detectable in this population (Glass et al., 2012; Hogan, Kirkham, Isaacs, Wade, & Vargha-Khadem, 2005; Schatz, McClellan, Puffer, Johnson, & Roberts, 2008; Tarazi, Grant, Ely, & Barakat, 2007; Thompson, Gustafson, Bonner, & Ware, 2002). Glass and colleagues reported that 17.5% of the 80 infants and toddlers with SCD in their study were performing poorer than two standard deviations below the normative mean on the mental and motor indexes of the Bayley Scales of Infant Development while Schatz et al., (2008) also reported general developmental delay using the Denver Screener in their study of 50 toddlers with SCD. Tarazi et al., (2007) reported that FSIQ scores were in the low average range for their population of 26 children with no stroke. Thompson and colleagues
Downes (2002) followed 89 patients with SCD longitudinally from nine to 36 months and reported a significant decline in cognitive ability on the Bayley Scales. EF deficits have been specifically reported for this patient population; however there has been little emphasis on children younger than school age (Hogan, Telfer, Kirkham, & de Haan, 2012; Tarazi et al., 2007). In the only study to look at EF in children with SCA younger than school age, Hogan and colleagues (2012) reported that infants with SCA (n=14) showed subtle delays on the object retrieval and ‘A not B’ tasks at nine and 12 months old when compared with a control group (n=14), which they interpreted as potential early precursors of poor EF in the patient group. It has been recommended that neuropsychological evaluation of children with SCA should include executive function assessments regardless of stroke occurrence (Daly et al., 2011). However, lack of appropriate measures in younger populations has hindered research into specific domains of EF with studies to date mainly dependent on generalized measures of cognition such as the Wechsler, the Bayley, and the Vineland scales (Glass et al., 2012; Wang, 2011).
Table 1.1 A summary of sickle cell studies that examine executive functioning

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>Description</th>
<th>Age</th>
<th>Battery/Task</th>
<th>Domain(s) of Executive Deficit</th>
</tr>
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<tbody>
<tr>
<td>Brown, Buchanan, et al., 1993</td>
<td>SCD</td>
<td></td>
<td>Sustained attention task</td>
<td>attention</td>
<td></td>
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<tr>
<td>Chua-L, Moore, McCleary, Shan, &amp; Mankad, 1993</td>
<td>HbSS (n=10)</td>
<td>4-6 years</td>
<td>PEER</td>
<td>processing speed</td>
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<tr>
<td>Craft, Schatz, Glauser, Lee, &amp; DeBaun, 1993</td>
<td>HbSS (n=29)</td>
<td>mean age</td>
<td>WISC-R</td>
<td>attention</td>
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<tr>
<td>Goonan, Goonan, Brown, Buchanan, &amp; Eckman, 1994</td>
<td>SCD (n=24)</td>
<td>4-16 years</td>
<td>Computerised vigilance task</td>
<td>attention</td>
<td></td>
</tr>
<tr>
<td>Armstrong et al.</td>
<td>HbSS/HbSC</td>
<td>6-12 years</td>
<td>MFFT</td>
<td>inhibition</td>
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<td></td>
<td></td>
<td></td>
<td>WISC-R</td>
<td>visuomotor/spatial organisation and</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Group(s) Description</td>
<td>Age Range</td>
<td>Test(s)</td>
<td>Domain</td>
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<tr>
<td>Downes et al.</td>
<td>1996</td>
<td>(n=194)</td>
<td>40 years</td>
<td>WJ-R integration</td>
<td></td>
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<tr>
<td>DeBaun et al., 1998</td>
<td></td>
<td>HBSS (n=28), HBSS (n=32)</td>
<td>7-21 years</td>
<td>WJ-R, TOVA, WCST</td>
<td>integration, attention</td>
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<tr>
<td>Watkins et al., 1998</td>
<td>1998</td>
<td>HBSS (n=28), HbSC (n=5)</td>
<td>5.9-16.7</td>
<td>CVLT-C</td>
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<td>Watkins et al., 1998</td>
<td></td>
<td>HbSβ- thalassaemia (n=4)</td>
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<td>attention</td>
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<tr>
<td>Bernaudin et al., 2000</td>
<td></td>
<td>HBSS (n=155), HbSβ0- thalassaemia (n=8)</td>
<td>5-15 years</td>
<td>WCST</td>
<td>shifting</td>
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<td>Brown, 1993</td>
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<td>HbSC (n=7)</td>
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<td>WPPSI-R</td>
<td>perceptual organisation</td>
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<tr>
<td>Buchanan, et al., 1993</td>
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<td>HBSS (n=48), HbSC (n=15)</td>
<td>6.33-17</td>
<td>Cancellation A's task</td>
<td>sustained attention</td>
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<tr>
<td>White, 2000</td>
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<td>SCD with</td>
<td>7-15</td>
<td>Verbal word memory task</td>
<td>working memory</td>
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<tr>
<td>Study</td>
<td>Group Description</td>
<td>Age Range</td>
<td>Measures</td>
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<tr>
<td>Salorio, Schatz, &amp; DeBaun, 2000</td>
<td>SCD (n=20) with no stroke (n=11)</td>
<td>years</td>
<td>WISC-R, VMI, MFFT, impulsivity, WJ-R, DAS Pattern Reconstruction, Judgment of Line Orientation, WISC Block Design, TOVA, WCST</td>
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<tr>
<td>Noll et al., 2001</td>
<td>HbSS (n=15), HbSβ0-thalassaemia (n=1), HbSβ+-thalassaemia (n=6), HbSC (n=9)</td>
<td>9-16 years</td>
<td>WISC-R, VMI, MFFT, impulsivity, DAS Pattern Reconstruction, Judgment of Line Orientation, WISC Block Design, TOVA, WCST</td>
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<tr>
<td>Schatz, White, Moinuddin, Armstrong, &amp; DeBaun, 2002</td>
<td>HbSS (n=64)</td>
<td>10.7 ± 2.6 years</td>
<td>CVLT, CMS, Digit Span, Intrusion errors, Cancellation A's task, Trailmaking test, executive skills, CVLT</td>
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<td>Brandling-Bennett, 2002</td>
<td>HbSS (n=21)</td>
<td>8-17 years</td>
<td>CMS - Digit Span, working memory</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Sample Characteristics</td>
<td>Tests</td>
<td>Cognitive Functions</td>
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<tr>
<td>White, Armstrong, Christ, &amp; DeBaun, 2003</td>
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<tr>
<td>Kral et al., 2003</td>
<td>HbSS (n=60)</td>
<td>6-17 years</td>
<td>CPT-II</td>
<td>attention</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CMS - Numbers Backward, Picture Locations, Trailmaking test</td>
<td>working memory, switching, inhibition, self-monitoring, working memory</td>
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<tr>
<td>Kral &amp; Brown, 2004</td>
<td>HbSS (n=62)</td>
<td>6-17 years</td>
<td>BRIEF</td>
<td>planning</td>
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<td></td>
<td>HbSS (n=20)</td>
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<td>HbSC (n=3)</td>
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<td>Schatz &amp; Roberts, 2005</td>
<td>thalassaemia</td>
<td>6.9-16.3 years</td>
<td>WISC-Processing Instrument, Horn-Cattell Gf-Gc Cognitive Theory</td>
<td>working memory, processing speed, fluid ability</td>
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<td></td>
<td>(n=2)</td>
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<tr>
<td>Kral et al., 2006</td>
<td>HbSS (n=27)</td>
<td>6-16 years</td>
<td>CPT-II</td>
<td>attention</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CMS- Numbers Backward, Picture Locations</td>
<td>visuomotor integration, cognitive flexibility, working memory</td>
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<tr>
<td>Study</td>
<td>Condition</td>
<td>Age Range</td>
<td>Tests Administered</td>
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<tr>
<td>Tarazi et al., 2007</td>
<td>SCD (n=26)</td>
<td>3-5 years</td>
<td>WPPSI-III, NEPSY, DAS, D-KEFS (Colour Trails, Hand movements, Digit Span, Coding, semantic fluency, Bell cancellation, letter-number sequencing)</td>
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<td>Ruffieux et al., 2011</td>
<td>SCD(n=96)</td>
<td>6-24 years</td>
<td>(Conner's CPT), Stop Task, Tower of London, N-back (computerized)</td>
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<td>Hjijmans, Grootenhuis et al., 2011</td>
<td>HbSS (n=30)</td>
<td>mean age 11.8 ± 2.9</td>
<td>Digit Span, Forwards/Backwards, Beery-Buktenica, WISC-III/WAIS-III Digit Span, Letter-Number Sequencing, Coding, Symbol Search</td>
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<td>HbSβ0-thalassaemia (n=4)</td>
<td>2.9 years</td>
<td>Developmental Test of Visual-Motor Integration, Motor Integration</td>
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<td></td>
<td>HbSS (n=11)</td>
<td>mean age 11.67 ± 3.15</td>
<td>Working Memory Index, Coding, Symbol Search</td>
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<td>Scantlebury et al., 2011</td>
<td>HbSC (n=3)</td>
<td>3.15 years</td>
<td>Processing Speed Index, CPT-II</td>
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<td>HbSD (n=1)</td>
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<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Test/Measurements</td>
<td>Executive Functioning/Neurodevelopmental Functioning</td>
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<td>Berg, Edwards, &amp; King, 2012</td>
<td>SCA (n=22)</td>
<td>Control (n=22)</td>
<td>Children's Kitchen Task, D-KEFS, WISC-IV, BRIEF</td>
<td>executive functioning, processing speed</td>
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<td>Hogan et al., 2012</td>
<td>Control (n=14)</td>
<td>SCA (n=14)</td>
<td>A not B, Object Retrieval</td>
<td>executive functioning</td>
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<td>Glass et al., 2012</td>
<td>SCD (n=89)</td>
<td>9m-12m</td>
<td>Bayley Scales</td>
<td>neurodevelopmental functioning</td>
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<td>Ruffieux et al., 2013</td>
<td>SCD (n=96)</td>
<td>3.5 years</td>
<td>Conners’ CPT, D-Kefs</td>
<td>executive functioning, memory, attention</td>
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<tr>
<td>Armstrong et al., 2013</td>
<td>HbSS/ HbSβ0-</td>
<td>7-18</td>
<td>Bayley Scales, VABS</td>
<td>executive functioning</td>
<td></td>
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<tr>
<td>Yarboi et al., 2015</td>
<td>SCD (n=65)</td>
<td>6-16</td>
<td>D-KEFS BRIEF</td>
<td>Executive functioning</td>
<td></td>
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<tr>
<td>Land et al., 2015</td>
<td>SCD (n=38)</td>
<td>8-17</td>
<td>WISC BRIEF</td>
<td>Executive functioning, Processing</td>
<td></td>
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</tbody>
</table>

BRIEF= Behaviour Rating Inventory of Executive Functioning  CPT= Continuous Performance Test  CVLT= California Verbal Learning Test  CMS= Children’s Memory Scale  DAS= Differential Ability Scale  D-KEFS= Delis-Kaplan Executive Function System  MFMT= Matching Familiar Figures Test  NEPSY= A Developmental Neuropsychological Assessment  PEER= Pediatroc Examination of Education Readiness  TOVA= Test of Variables of Attention  VABS= Vineland Adaptive Behaviour Scales  VMI= Beery Visual-
motor Integration  WCST= Wisconsin Card Sort Test  WISC= Wechsler Intelligence Scale for Children  WJR= Woodcock-Johnson Test  WPPSI= Wechsler Preschool and Primary Scale of Intelligence
1.2.3 Sickle cell anaemia and the preschool years

“I hope everybody is going to help to make this world a better place for we the children with sickle cell to live in. ”

-Daniel (aged 6 from Croydon, sicklecellsociety.org)

1.2.3.1 Lack of Awareness

Primary care providers, parents and educators have been found to underestimate the rate of neurocognitive delay in children with SCA (Glass et al., 2012; Schatz, 2004). The presentation of executive deficits in children with SCA can vary according to multiple factors such as socioeconomic status, presence of infarction, and disease severity (Grueneich et al., 2004). This chronic illness is relatively invisible as it is not typically recognized as a ‘brain disorder’ so children often do not receive appropriate special assistance in their school or home environments (Steen, Fineberg-Buchner, et al., 2005). The nature of the deficits that children with SCA present with can sometimes be misinterpreted as a lack of interest or motivation (Dyson, Atkin, Culley, Dyson, & Evans, 2011). This can prevent children from obtaining adequate support and often means that neurocognitive problems go undetected. The current lack of awareness is reflected by higher school drop out and academic failure rates of children with SCA (DeBaun et al., 2012; Schatz, 2004; Smith, Patterson, Szabo, Tarazi, & Barakat, 2013). There is need for a greater emphasis to be placed on the brain-behaviour relationship in developing children with SCA.

1.2.3.2 Early Assessment

As well as providing a baseline for future assessments and painting a picture of current requirements, early neurocognitive assessment can also act as an indicator of future stroke risk (DeBaun et al., 1998; Hill et al., 2006; Hogan, Vargha-Khadem, et al., 2006; Wang et al., 1998). Thus, it is important that adequate neurocognitive assessment and intervention is developed so that
these children can be assessed before they enter the school system (Gold et al., 2008). Assessment at this key period can improve school readiness at an opportune time by highlighting potential problem areas.

The peak time for first clinical stroke occurrence in children with SCA is within the first decade of life (Fullerton, Adams, Zhao, & Johnston, 2004; Kral, Brown, & Hynd, 2001; Kwiatkowski et al., 2009). Stroke incidence is reported to be at its highest between two and five years of age (Adams et al., 1998). The early occurrence of neurological damage during these formative years further emphasizes the significance of early neurocognitive assessment in this age group, both as an indicator of stroke risk and to establish a neurocognitive baseline.

In the absence of stroke, deficits in children with SCA are still reported to appear early in development as well as poorer reported school readiness (Noll et al., 2001; Steen et al., 2002; Tarazi et al., 2007; Thompson et al., 2003). Recent SCA research suggests that neurocognitive deficits emerge in the first 3 years of life and that a relationship between disease severity and neurocognitive function is detectable from nine to 24 months (Hogan, Pit-ten Cate, et al., 2006; Schatz et al., 2008; Jeffrey Schatz, Brown, Pascual, Hsu, & DeBaun, 2001; Thompson et al., 2002; Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, & Armstrong, 2001). Infants with SCA who had lower hemoglobin saturation scores made more errors on classical executive ‘A not B’ and object retrieval tasks (Hogan et al., 2012). Lower cognitive scores in toddlers and early preschoolers were observed to be associated with higher mean CBFV (Schatz et al., 2008). A cognitive gap has been observed to increase during the first three years, with a particular decrease in function between 12 and 24 months where a slower rate of development is observed (Thompson et al., 2002). A recent study also reported some evidence of an even earlier decline in general cognitive functioning between seven and 18 months of age (Armstrong et al., 2013).

There has so far been a lack of neurocognitive research conducted with
preschool children with SCA (Kral et al., 2001). The life expectancy of people with SCD has dramatically increased in the last 40 years and many health problems have become less severe due to new treatments (Platt et al., 1994; Wierenga, Hambleton, Lewis, & Unit, 2001). This means that more emphasis is now placed on the neurocognitive sequelae of the disease and ways in which these can be ameliorated. As measures of EF are sensitive to early executive deficits as well as silent cerebral infarct and risk of future pathology, research in the early years is crucial in order to improve long-term outcomes (DeBaun et al., 1998). Early assessment and intervention in this population could result in improved school readiness, academic attainment, and overall quality of life (Anie, 2005). Currently, however, there is very little known about neurocognitive development and delay in young children with SCA.

1.3 Preschool and the Brain: Executive Development

"Various studies have shown that executive function skills are more important for school readiness than a child's IQ or level of reading and math ability as they enter school."

- Adele Diamond

1.3.1 The development of the executive system

An infant’s ability to control their distress is one of their first great challenges in terms of executive control (Harman, Rothbart, & Posner, 1997). At about 12 months, most infants have developed the ability to inhibit a prepotent response in order to achieve a specific goal. This has been repeatedly demonstrated using the classical A-not-B task (Diamond, 2001). Many other behavioural tasks have shed light on the development of executive control from the second to the third year of life. One study shows the transition from a two year old’s inability to resolve conflict between competing factors of location and identity to a three year old’s successful performance (Gerardi-Caulton, 2000).
Whether the distinct components of EF are already present in preschoolers or emerge from a more undifferentiated system as they develop is still debated in the developmental literature. Some have proposed that distinct executive components are measurable in the preschool years while others have found evidence for a unitary construct which becomes more differentiated over time (Senn, Espy, & Kaufmann, 2004; Wiebe et al., 2011). One group proposes that there are three distinct subsystems of EF that can be discerned prior to five years of age; selective attention, sustained attention, and cognitive control (Atkinson & Braddick, 2012). Specific executive control processes such as inhibition, manipulation, switching, and inhibition have also been reported to develop at different rates (Bunge & Crone, 2009). Evidence suggests that the ability to inhibit responses can increase from 22% to 90% between 36 and 48 months (Jones, Rothbart, & Posner, 2003).

The executive system is responsible for combining different cognitive skills in order to execute cognitive control in high level processes such as making plans and solving problems (Lezak, 1982; Welsh & Pennington, 1988). The major subcomponents of EF have been described as attention, inhibition, self-regulation, working memory, cognitive flexibility, planning, organization, problem-solving, and performance-monitoring skills (Anderson et al., 2008). Theoretical models vary in terms of how they organize these domains and some also include “hot” EFs that encompass the behavioural control of affect while others focus primarily on one specific domain (Baddeley, 2002; Barkley, 1997; Lezak, 1995; Norman & Shallice, 1986; Zelazo, Carter, Reznick, & Frye, 1997). It is widely hypothesized that the executive control system transitions from being a more unified structure to a more differentiated system with age (McAuley & White, 2011; Miyake et al., 2000).

Several developmental models of EF have been proposed based on studies in developmental cognitive neuroscience; however this thesis will draw from Anderson’s model that incorporates four separate but inter-connected general domains of attentional control, cognitive flexibility, goal setting, and information processing, that develop at different rates (Anderson, 2002,
Figure 1.4. Attentional control refers to self-regulation and self-monitoring while inhibiting internal and external distractions so that one can selectively focus on completing the task at hand. A child with deficits in this domain may be described as ‘impulsive,’ failing to complete tasks, might get distracted too easily and may not successfully remember instructions. Cognitive flexibility allows one to divide as well as shift attention between sources, alongside recognizing and appropriately altering behaviour in response to errors. These actions can be described as relying on working memory or the ability to store and alter or adapt information in the short-term and children with deficits in this area may show preservative behaviours as they cannot alter course quickly enough. Goal setting involves three key areas; ‘initiation’ or the ability to start a task, ‘planning’ or the process by which one lays out a series of actions in a sensible way, and ‘organization’ or the ability to arrange information logically in order to reach an end point. These deficits can manifest as poor problem solving and/or conceptual reasoning skills. The final domain is information processing, which is required to attend to a task quickly and efficiently. Deficits in information processing may become apparent through slower completion times, a longer period of time taken to fully understand instructions, and delayed response times. Anderson’s model of EF development proposes that EF domains have different developmental trajectories. Attention control emerges first and forms the foundation for the later emerging domains, including more complex EF skills such as planning and feedback utilization.
Figure 1.4 ‘The executive control system’: a theoretical developmental model of executive functioning as proposed by Anderson (2002).

The development of EFs has received an ever-increasing amount of focus in recent years with most researchers now in agreement that these skills can be successfully assessed from early on in life (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; figure 1.5). Evidence is also accumulating to support the theory that EFs do not directly correspond with general IQ ability (Friedman et al., 2006). Multiple reports have found that EF is a better predictor of school readiness and academic achievement than the more historically studied construct of IQ (Blair & Razza, 2007; Eigsti et al., 2006). Some areas of EF, such as working memory and inhibition, have been researched more extensively than others in the pre-school age range, as these domains are thought to mature at a faster rate than other domains such as goal setting and planning (Best & Miller, 2010).

1.3.2 Impact of disease and environment

EFs have been shown to be highly susceptible to environmental and disease factors (Hughes & Ensor, 2009; Muscara, Catroppa, & Anderson, 2008; Stuss & Alexander, 2000). This may be particularly pertinent to children with SCA.
who have chronically low levels of oxygen, more frequent school absences, and chronic complications including painful episodes, as well as a greater reported incidence of low socioeconomic status and sleep-disordered breathing (Dyson et al., 2010; Gil et al., 2000; Hijmans et al., 2010; King et al., 2013; Salles et al., 2009; van den Tweel et al., 2008). Executive deficits related to frontal lobe functioning are commonly found in children with SCA (Brown et al., 2000; DeBaun et al., 1998; Schatz et al., 2001; Watkins et al., 1998). Brown and colleagues (2000) reported that, based on the performance of their cohort of 63 children with SCA who had silent and overt stroke, developing psychological or medical interventions that focus on executive problems, particularly attention, would improve quality of life due to the pervasiveness of these cognitive problems on day to day living. Evidence for poorer performance on executive tasks in children without overt stroke has been shown by various studies, including Watkins and colleagues (1998), who present findings for patients without overt stroke showing similar risk for EF deficits. DeBaun and colleagues (1998) concluded from their study that poorer functioning on behavioural test of executive functioning could identify or screen for patients that have undetected silent stroke, however they only compared these children with sibling controls rather than patients with SCA with no evidence of silent stroke. Similar to Schatz and colleagues (2001), most studies report specific problems on attention and executive function tasks as compared to other cognitive domains, when a battery of tasks that tap a range of cognitive domains are administered to patients. Executive deficits have even been described as useful indices of progressive cerebral vasculopathy in children with SCA (Kral et al., 2003). Preliminary evidence of early executive deficits has been reported from infancy in young children with SCA, leading researchers to speculate on possible contributing factors other than the impact of clinical stroke (Hogan et al., 2012; Steen et al., 2002; Tarazi et al., 2007; Thompson et al., 2002).

Most research has focused on associations between EF and disease-related factors, such as cerebrovascular injury, cerebral blood flow velocity, and oxygen saturation with executive skills, although emerging research has also
begun to look at the impact of socio-environmental factors (King et al., 2014). Low socio-economic status and poor family functioning have been found to be associated with lower executive skills in typically developing children (Hackman & Farah, 2009). Higher rates of poverty, single parent households, and economic disadvantage have previously been reported in families with SCA (Burlew, Evans, & Oler, 1989; Farber, Koshy, Kinney, & Disease, 1985). Therefore, socio-environmental factors, as well as disease factors, must be considered in the context of executive development in this patient population.

1.3.3 Potential for improvement

Unlike the traditionally well-studied IQ, executive skills show more potential for improvement through intervention (Diamond & Lee, 2011; McHugh, 1943). This is promising as stronger executive skills can provide an important protective factor in children who have lower IQs or deficits in specific areas (Greenberg, 2006). Recent research has shown that executive dysfunction can be remediated by both medical and neuropsychological intervention in the early years (Diamond, 2012; Rueda, Checa, & Cómbita, 2012; Rueda, Posner, & Rothbart, 2005; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009). Preliminary investigations of interventions for improved EF have been explored in older children with SCA (e.g. Marshall et al., 2009); however there have not yet been any interventions aimed at younger children.
1.3.4 Brain-based changes

1.3.4.1 Neural correlates of executive functioning

The protracted development of the prefrontal cortex means that there are changes continuously occurring from early childhood into adolescence and beyond (Casey, Tottenham, Liston, & Durston, 2005; Lenroot & Giedd, 2006). Important functional changes in the prefrontal cortex have been reported to occur in the preschool years (Diamond, 2002). Marked changes in EF are described as occurring between about three and five years of age (Carlson, 2005; Espy, 1997; Kirkham, Cruess, & Diamond, 2003; Munakata & Yerys, 2001; Zelazo et al., 2003). A parallel has been drawn between the maturation of the frontal cortex and the emergence of executive skills (Steinberg, 2005). The frontal cortex controls EF as part of a wider brain network (see figure 1.6). The brain systems underlying rapid executive skill development in the
first few years of life are also amenable to environmental influences (Halperin & Healey, 2011).

Many different structural changes are reported in the prefrontal cortex in the early years. Synaptic density in the prefrontal cortex reaches its peak before five years and gradually decreases into adolescence through a process called pruning whereby the unrequired grey matter connections fade away in order to create a more efficient mechanism (Huttenlocher & Dabholkar, 1997). Neuronal density in layer III of the prefrontal cortex has been shown to decrease dramatically from two to seven years, with one study showing a decrease from 55% to 10% above the mean adult density (Huttenlocher, 1979). These reductions of synaptic and neuronal densities occur alongside
an increase in the growth of dendrites, and white matter volume (Tsujimoto, 2008). Recent neuroimaging research supports a steady increase in grey and white matter volumes in early childhood, reaching a peak about five years old (Giedd et al., 1999; Matsuzawa et al., 2001; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell et al., 2004). Higher rates of cerebral metabolism are seen up to about nine years (Chugani & Phelps, 1991).

The prefrontal cortex does not act in isolation but functions as part of a wider system (Fuster, 2008). Although there is a lot of emphasis on the connections between executive performance and the prefrontal cortex, imaging research shows that a broadly distributed network is required for executive tasks (Luna & Sweeney, 2004; Tamm, Menon, & Reiss, 2002). Different neuronal networks and neuromodulators have been described to subserve the various subcomponents of EF (Posner & Peterson, 1990). Neuroimaging research has provided evidence for a parieto-frontal network that acts as a modulator for other brain areas (Lepsien & Nobre, 2006). Executive tasks also involve many subcortical loops that incorporate structures such as the striatum, the cerebellum, and the thalamus. It has been hypothesized that pathways such as the striatal-thalamus loop may be important in working memory and that the cerebellar-thalamic loop may play a role in inhibition (Stuss & Alexander, 2000). A model for the specific neural circuitry of fractionated EF domains, such as the four domains described in Anderson’s developmental model in the frontal lobes, has been proposed for adults based on neuroimaging and patient research; however a model to describe the specific frontal circuits underlying EFs in young children remains elusive (Stuss, 2011).

Research with children who have extrafrontal pathology shows that they are just as likely to have executive deficits as those with damage in the frontal areas typically associated with EF (Jacobs, Harvey, & Anderson, 2011). This may be because areas outside of the frontal cortex are recruited for EF tasks more during childhood, as the EF systems have not become as specialized or localised as reported for the adult brain. Children with early brain insult have
also been described to ‘grow into’ later emerging EF deficits, whereby impairments are reported to emerge with brain development, and as developmental expectations grow to incorporate higher-order skills such as planning and organisation (Anderson, Northam, & Wrennall, 2014).

Figure 1.7 Developmental processes in the brain. Reproduced from Casey et al. (2005).

1.3.5 Summary

Recent advances in behavioural and neuroimaging techniques have cast some light onto the development of systems underlying specific executive components (Asato, Terwilliger, Woo, & Luna, 2010; Morton, Bosma, & Ansari, 2009). The prefrontal cortex has been implicated in various executive functions and its protracted development is seen to coincide with the emergence of executive skills. Furthermore, different neuronal networks have been shown to subserve the subcomponents of attention and these neuronal networks have been shown to develop at varying rates. The preschool period has been deemed a crucial period of transition for EF due to the magnitude of change occurring during these years (Best & Miller, 2010; Röthlisberger,
Despite this, the lack of appropriate measures leaves a lot to be desired in terms of the normal, and as a result, atypical, development of these executive subsystems.

1.4 Sickle Cell and the Brain: Executive Functioning

1.4.1 Disease-related effects on executive function
Several associations have been demonstrated between disease factors and poorer executive skills in SCD (Berkelhammer et al., 2007).

1.4.2 Frontal lobe involvement
The frontal lobe is the region most likely to sustain pathology linked to SCA as clinical and silent stroke associated with neurocognitive deficits typically involves this region (Brown et al., 2000; Schatz et al., 2001). The frontal lobe is also thought be particularly vulnerable to suboptimal levels of oxygen (Blanié, Vigué, Benhamou, Duranteau, & Geeraerts, 2012). There is evidence of abnormal cerebral blood flow (CBF) in the frontal lobe despite normal MRI (Prohovnik et al., 1995), with global increase in CBF but decreased cerebrovascular reserve, and focal decrease in CBF related to cerebrovascular disease involving the middle and anterior cerebral arteries which supply the frontal lobes. The susceptibility to hypoxia and ischaemia may contribute to an explanation for poorer executive skills in children with SCA (Berg et al., 2012; Daly et al., 2011; Hogan et al., 2012).

1.4.3 Stroke
The incidence of clinically evident stroke and silent cerebral infarct is between 7,000 and 20,000 per 100,000 children within the paediatric sickle cell population (Tullberg et al., 2004). There are direct associations between clinical or silent stroke and extent of executive dysfunction (Gold et al., 2008). Clinical strokes have an obvious and sudden manifestation of symptoms,
including seizures and major changes in motor and sensory functioning. The frontal and parietal cortices supplied by the internal carotid artery and the middle and anterior cerebral arteries are the areas most commonly affected by clinical stroke in children and long-term executive deficits are often observed (Watkins et al., 1998). Most commonly children experience ischaemic strokes due to restricted blood supply but sometimes the rupture of a vessel secondary to aneurysm formation or hypertension can result in an intracerebral haemorrhage (Ohene-Frempong et al., 1998).

Silent strokes involve damaged regions of tissue visible on MRI but without the observable neurological symptoms associated with clinical stroke. Attention and EF measures have been found to be the best means of identifying patients with silent strokes (DeBaun et al., 1998; Hariman, Griffith, Hurtig, & Keehn, 1991; Watkins et al., 1998). TCD screening is now offered in the UK from the age of 2 years and has already reduced the incidence of overt stroke from 10% to <5% (Telfer et al., 2007). However the prevalence of silent infarction is around 25-40% and most children who develop silent infarction will already have done so before their initial MRI screening after the age of 6 years (DeBaun et al., 2012). A recent study found that the volume of white matter hypertensities, the most commonly observed silent lesions in children with SCA (n=38), independently predicted both IQ and processing speed (Van Der Land et al., 2014). Neurocognitive screening may identify young children whose silent infarction will be identified by MRI when they are older.

### 1.4.4 Disease-related effects in absence of stroke

Anaemia severity, abnormal CBFV, and pathological electroencephalogram (EEG) have all been associated with poorer performances in aspects of EF such as attention, processing speed, working memory, and behavioural control (Kral & Brown, 2004; Ruffieux et al., 2013; Schatz & Roberts, 2005). A prolonged lack of oxygen to the frontal cortex has been shown to have effects
on cognitive functioning, even without the influence of clinical stroke (Hijmans, Fijnvandraat, et al., 2011).

The aetiology of neurocognitive deficits in SCA without observable neurological damage is not yet well understood (Armstrong et al., 1996). Despite the presence of focal clinical or silent infarction in some cases, SCA is a model of diffuse brain injury (Steen, Xiong, Mulhern, Langston, & Wang, 1999). Recent findings suggest that there are cognitive deficits in sickle cell patients with normal MRI due to diffuse brain injury and that these deficits tend to increase with age (Ruffieux et al., 2013; Steen, Fineberg-Buchner, et al., 2005). Bilateral white matter density has been found to be less in patients with SCA who have normal MRI compared to controls (Baldeweg et al., 2006). The volumes of the hippocampus, amygdala, pallidum, and cerebellar cortex are significantly reduced bilaterally in children with SCA compared to controls, even without evidence of silent infarction (Kawadler et al., 2013). There have been some findings suggesting associations between greater white matter density, an index of myelination, and faster processing speed in other populations of children including those born pre-term and those at risk for drug use, as well as those who are developing typically (Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006; Silveri, Tzilos, & Yurgelun-Todd, 2008; Soria-Pastor et al., 2009). Scantlebury and colleagues also found potential associations between white matter integrity and processing speed in adolescents with SCA (Scantlebury et al., 2011). Executive deficits could be further exacerbated by chronic hypoxia in SCA (Hill et al., 2006). The increased blood flow may not fully compensate for reduced oxygen levels, which may be particularly damaging for the developing brain. As the brain is deprived of sufficient levels of oxygen, the energy levels in the brain are reduced and this can have an impact on executive performance.

The most rapid period of brain development occurs during the prenatal period and the first couple of years of life. The neurocognitive symptoms of damage sustained during this period are often not be detected until years later.
There is limited MRI evidence from young children with SCA but one study showed that silent frontal infarcts were present in 13% of infants aged 10-18 months of age (Wang et al., 2008). Neurocognitive deficits associated with sickle cell anaemia may emerge at an early stage of development (Daly et al., 2011; Hogan et al., 2012; Thompson et al., 2002; Wang et al., 1998). Delays in the development of EF skills may even be present from the first year of life (Hogan et al., 2012). ERP evidence from older children and infants with SCD has shown some preliminary evidence for differences in cognitive processing at a neural level (Hogan, Vargha-Khadem, et al., 2006).

1.4.5 Indirect disease-related effects

Indirect effects of the SCA disease process such as fatigue, episodes of pain, and number of hospitalisations have also been considered in terms of cognitive and behavioural outcomes (Brown, Buchanan, et al., 1993; Gil et al., 2000; While & Mullen, 2004). Children with SCA have higher rates of absenteeism due to pain episodes that could also have a negative impact on neurocognitive development (Brown, Buchanan, et al., 1993; Ogunfowora, Olanrewaju, & Akenzua, 2005). A UK survey of young people with SCD (N=569) found that 12.5% reported school absences that met the government-defined quota of ‘persistent absence’. Students also reported that they were not helped to catch up after these school absences (Dyson et al., 2010), which means that good EF skills could also act as a protective factor to help compensate for missed days of formal education. A recent study with older children with SCA (N=14; mean age: 13y14m) investigated the relationship between pain and EF, but no associations were found between EF and current reported levels of pain or frequency of pain episodes (Seymour et al., 2012). These findings could be attributed to the small sample size and the subjective nature of pain perception.
1.4.6 Non disease-related factors that affect executive functioning

Recent research has begun to focus on non-disease related factors, including sleep-disordered breathing (SDB), family functioning, and socio-economic status, that are thought to affect the development of EF, particularly in children with SCA (Schatz, Finke, & Roberts, 2004).

1.4.7 Sleep-disordered breathing

Previous research has reported an increased occurrence of SDB due to obstructive sleep apnoea (OSA) in children with SCA (Daniel & Barakat, 2012; Hargrave, Wade, Evans, Hewes, & Kirkham, 2003; Samuels, Stebbens, Davies, Picton-Jones, & Southall, 1992; Wittig, Roth, Keenum, & Sarnaik, 1988). OSA is caused by enlarged tonsils and adenoids that result in a reduction of airflow (Ikävalko et al., 2012; Katz & D’Ambrosio, 2008). As well as sleep fragmentation, OSA results in nocturnal hypoxaemia and hypercarbia, which have been associated with a higher risk of cerebrovascular accidents (Kirkham et al., 2001). As well as low overnight and daytime haemoglobin oxygen saturation, SDB may be associated with compensatory hyperventilation, and abnormal cerebral blood flow (Gavlak et al., 2013; Marshall et al., 2009).

SDB is thought to have a specific impact on the prefrontal cortex, due to its vulnerability to sleep disruption and blood gas abnormalities, resulting in executive dysfunction (Beebe & Gozal, 2002). An association has been observed between executive deficits and SDB in the general population (Gozal & Kheirandish-Gozal, 2007; Yaffe et al., 2011) and in children with SCD (Hollocks et al., 2011). As well as the potential neurocognitive sequelae of the nocturnal physiologic disturbances on the prefrontal cortex, SDB also results in disrupted sleep and daytime tiredness, further contributing to a reduction in a child’s ability to concentrate during the day (Simola et al.,
A recent large-scale proxy-report questionnaire study of SDB in children in the general population (ages 6 months-6 years 9 months; N=12,447) found that children aged 1.5 to 2.5 years were particularly susceptible to snoring and that by 6 years, 25% of children were reported to display some symptoms of SDB (Bonuck et al., 2011). The diagnosis of OSA requires polysomnography, but there are few population-based studies because of the cost. OSA prevalence rates in the general paediatric population vary with age and symptoms but are generally less than 5%, whereas rates as high as 41% have been reported in children aged 4-18 with SCA (Samuels et al., 1992). In a recent study of 1 to 4 year-olds with SCA, 27% were found to have SDB, leading the authors to suggest that all children should be screened for SDB in the preschool years (Dundas et al., 2012).

![Figure 1.8](image1.png)

**Figure 1.8** The OSA prefrontal model illustrating theorised pathway to executive difficulties in children with SDB; reproduced from Beebe and Gozal (2002)

Although the effects of SDB on neurocognitive functioning are well
established in older children, there has been limited research in the preschool population (Walter et al., 2012). Emerging research suggests that an adverse impact of SDB on behaviour and executive control is detectable in the preschool years with inhibition, planning, and working memory being particularly affected (Jackman et al., 2012; Karpinski, Scullin, & Montgomery-Downs, 2008; Scullin, Ornelas, & Montgomery-Downs, 2011). Older children with SCA (N=24; ages 4-18) treated for SDB for six weeks using positive airway pressure therapy showed improvements in processing speed and attention (Marshall et al., 2009). This preliminary evidence suggests that early intervention for SDB in young children with SCA could lead to improved academic performance in the long-term. More research into the effects of SDB in preschool children with SCA could highlight problems at an age where EF is more amenable to intervention.

1.4.8 Family functioning

There is accumulating evidence for the effects of positive family functioning on academic and cognitive outcomes in preschool children (Burchinal et al., 1997; Luster et al., 1992; Molfese et al., 2002). Poor family environment, characterised by conflict and unsupportive or inconsistent environments, may be conducive to stress, which can impact the development of the prefrontal cortex, and has been associated with poorer outcomes in typically developing children (Fishbein et al., 2004). Family functioning encapsulates multiple family dimensions that examine aspects of healthy relationships within the family context, family emphasis on goals and activities, and the degree of organisation or system-maintenance in the home (Kronenberger & Thompson, 1990). Lucia and Breslau (2006) found that family cohesion at six years was predictive of internalizing and attention problems at six and eleven years in typically developing children (n=823). Halpern and colleagues reported that family cohesion and expression served as a protective factor for problem behaviours in typically developing preschool children (Halpern et al., 2004). Sickle cell research has presented some evidence for the psychosocial effects of parenting on cognitive outcomes. Lower family functioning has been
associated with overall disease severity in SCA (Barakat, Patterson, Tarazi, & Ely, 2007). Poorer cognitive functioning in SCA at 24 months has been associated with poorer parenting (Thompson et al., 2002). A learned-helplessness style of parenting was found to have an adverse association with neurocognitive outcomes in young children with SCA (N=89). One study found an association between maternal health and the presence of behavioural issues in children with SCD (N=39)(Kliewer & Lewis, 1995). Another study found that maternal anxiety accounted for over 33% of variance in behavioural problems in 7 to 12 year-olds with SCD (n=91)(Thompson, Gil, Burbach, Keith, & Kinney, 1993).

1.4.9 Socio-economic status

Low socioeconomic status, usually measured through family income and parental education and occupation status, has been reported to have negative implications for health, cognitive, and SES outcomes in children and is known to particularly affect the executive system in comparison to other cognitive domains (Noble, Norman, & Farah, 2005). The role of sociodemographic factors has more recently been taken into consideration in SCA research (King et al., 2013). A recent study looked at first generation immigrant children with SCD (N=68) and found that 72% spoke three languages at home and that 21% spoke two languages (Montanaro et al., 2013). Neurocognitive functioning in children with SCD has been shown to have an association with social class (Brown, Buchanan, et al., 1993). Neurodevelopmental delay was found more likely to occur among children with SCD from 9 months to 3.5 years (N=80) with a lower socioeconomic status (Glass et al., 2012). In a study of 3-5year-olds with SCD and no history of stroke (N=26), disease severity was not significantly related to neurocognitive functioning, while SES was significantly correlated with most domain scores, accounting for 18-47% of variance in neurocognitive functioning (Tarazi et al., 2007). Although there
was no control group or direct measures of attention in this study group, it shows the importance of psychosocial interventions at this early stage.

### 1.4.10 Multiple factor Model

Research suggests that children with SCD have a greater prevalence of executive deficits than their typically developing peers even when there is no evidence of stroke. There remains no clear picture of the factors that contribute to executive deficits in children with SCA, with studies to date showing mixed results. Recent studies in SCA have started to adopt a more biopsychosocial perspective of cognitive development that incorporates socioenvironmental factors as well as disease-related factors (Gustafson et al., 2006; King et al., 2014).

### 1.5 Developing Suitable Measures

#### 1.5.1 Why is there a lack of EF research in preschoolers?

Evaluating EFs has several theoretical, interpretative, and administrative challenges. Specifically in the sickle cell literature, there are mixed neurocognitive findings. This is due to difficulties comparing studies where different cognitive measures have been used, sickle cell subgroups have been divided differently, and different types of control groups used (Berkelhammer et al., 2007; Schatz, Finke, et al., 2002).

The most pertinent issue lays in the lack of studies that focus on younger age populations. There are limited studies with toddler and preschool populations. In the sickle cell literature, general IQ measures and parent-reports of functioning have been widely used, however the reliable assessment of EF in the preschool years is important for the early identification and remediation of deficits (Mahone, 2005).

The lack of research in preschool-age children is largely due to two main barriers. Firstly, there is a lack of reliable and standardized measures for this
age population. In terms of the sickle cell literature, this provides us with limited information in regards to the early development and delay of specific EFs, such as processing speed, which are affected in older children and adolescents. The more widely reported general IQ or developmental scores in the younger population offer minimal information for use in developing early interventions and delivering individualised support for potential EF deficits (Berg et al., 2012). A relation between EF and IQ has been reported to exist between some specific aspects of EF and IQ, such as working memory, but not for other domains, such as inhibition and shifting, so IQ measures alone are not sufficient to capture EF deficits (Friedman et al., 2006).

The second barrier, despite many advances in the past decade, is the unsuitability of many measures for ease of use with preschool age children (Johnson, Halit, Grice, & Karmiloff-Smith, 2002; Scerif, Kotsoni, & Casey, 2006). Imaging protocols that look at functional activity during a cognitive task require the participant to stay still inside the scanner for long periods, proving a practical barrier to applying this technique in younger children. Commonly applied neuroimaging techniques in older children, such as functional magnetic resonance imaging (fMRI), are largely reserved for those over six years as they can be seen as invasive and require the participant to remain still, a request which many know poses a great challenge to preschool age children (de Haan & Thomas, 2002; Hajnal et al., 1994; Tsujimoto, 2008). One recent study applied fMRI in an investigation of the posterior parietal cortex of typically developing four-year-old children but no other investigations using fMRI have been made involving other crucial areas such as the prefrontal cortex in this young age group (Cantlon, Brannon, Carter, & Pelphrey, 2006). Functional near-infrared spectroscopy is emerging as a more appropriate and child-friendly neuroimaging technique, with researchers beginning to apply it as a measure to investigate the neural development of EF, particularly working memory, in young children (Buss, Fox, Boas, & Spencer, 2014; Perlman, Huppert, & Luna, 2015). However, no paradigms to measure attention development at this early stage of development have yet been developed.
There are several potential avenues in terms of the intervention and the improvement of executive skills in SCA in order to improve school readiness and to address the gaps that have been found in older children before they become problematic. Potential avenues include medical, neuropsychological, and educational interventions. For those who experience sleep-disordered breathing as well as SCA, sleep interventions could show potential for improving executive skills. However, as it is currently difficult to measure EF and specific neurocognitive functions in preschool children, it would be challenging to test the impact of interventions focused on improving executive skills. Recent research has emphasized the need for developmentally sensitive measures that can be reliably applied in the preschool population (Carlson, 2005; Garon, Bryson, & Smith, 2008; Zelazo & Müller, 2010). More specifically, a strong weight has been placed on the demand for measures that can assess executive skills (Espy, Kaufmann, Glisky, & McDiarmid, 2001).

1.5.2 Developing suitable measures for three to five year olds

It is a great challenge to develop tasks that are suitable for use across a range of ages and ability levels. However, the preschool years pose a particularly demanding task for researchers due to the rapid development of executive skills from three to six years (Espy, Kaufmann, McDiarmid, & Glisky, 1999). The variable nature of constructs such as attention in the preschool years makes for poorer reliability across different measures (Anderson, 2002; Mahone, 2005). Task instructions used for older children can be too linguistically demanding, which is why most standardised measures of EF are designed for use with children over six years.

A commonly held misconception is that executive skills cannot be adequately assessed at this early stage of development (Anderson & Reidy, 2012). Previous research has found that performance in an established measure of infant functioning, such as the Bayley Infant Neurodevelopmental Screener,
can be a poor predictor of later cognitive skills (Hack et al., 2005). However recent research suggests that from infancy and the early preschool years, performance in executive tasks can be predictive of future functioning (Cuevas, Hubble, & Bell, 2012; Kraybill & Bell, 2012; Nakagawa & Sukigara, 2013). Moffitt and colleagues found that executive skills in childhood are predictive of physical health, substance abuse, socioeconomic status, and criminal record in early adulthood, even when controlling for socioeconomic status and IQ in childhood, showing the extent of the potential impact of EF on a child’s future outcomes (Moffitt et al., 2011). Unfortunately, most studies in the preschool age range are not well documented, which means that tasks are not well replicated and findings are often not comparable across studies.

An important route for future research is the development of a combination of behavioural measures of distinct EFs, as well as more ecologically valid tasks. A second necessary route is the design and application of event-related potential (ERP) studies. These methods have been widely used with infant populations and older children and show potential for adaption to pre-school age populations. The advantage of these methods is that they can circumnavigate some of the linguistic, attention, and motor limits of younger children and so their methodological issues are not as constraining as other biophysical measures of cognition such as fMRI.
Table 1.2 Current measures of executive function used in the preschool literature (WM=working memory; RI=response inhibition)
<table>
<thead>
<tr>
<th>Task</th>
<th>Brief Description</th>
<th>Age range</th>
<th>Component</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed response</td>
<td>Find hidden object after delay</td>
<td>4m+</td>
<td>Simple wm</td>
<td>Diamond &amp; Doar, 1989</td>
</tr>
<tr>
<td>Digit/Word span</td>
<td>Repeat list of digits/words</td>
<td>3yr+</td>
<td>Simple wm</td>
<td>Gathercole, Pickering, Ambridge, &amp; Wearing, 2004</td>
</tr>
<tr>
<td>Corsi block span</td>
<td>Child repeats tapping sequence</td>
<td>3yr+</td>
<td>Simple wm</td>
<td>Orsini et al., 1987</td>
</tr>
<tr>
<td>Stationary pots</td>
<td>Avoid re-checking pots</td>
<td>15m+</td>
<td>Complex wm</td>
<td>Ewing-Cobbs, Prasad, Landry, Kramer, &amp; DeLeon, 2004</td>
</tr>
<tr>
<td>Spinning pots</td>
<td>Pots moved</td>
<td>15m+</td>
<td>Complex wm</td>
<td>Hughes, 1998</td>
</tr>
<tr>
<td>Self-ordered pointing</td>
<td>Select picture not yet shown</td>
<td>3yr+</td>
<td>Complex wm</td>
<td>Hongwanishkul, Happaney, Lee, &amp; Zelazo, 2005</td>
</tr>
<tr>
<td>Invisible displacement</td>
<td>Large/small containers</td>
<td>15m+</td>
<td>Complex wm</td>
<td>Gopnik &amp; Meltzoff, 1984</td>
</tr>
<tr>
<td>Backwards digit span</td>
<td>Repeat digits/words backwards</td>
<td>3yr+</td>
<td>Complex wm</td>
<td>Carlson, 2005</td>
</tr>
<tr>
<td>Delay of gratification</td>
<td>Waits for larger treat</td>
<td>2yr+</td>
<td>Simple RI</td>
<td>Arend, Gove, &amp; Sroufe, 1979</td>
</tr>
<tr>
<td>(snack/gift)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Object retrieval</td>
<td>Detour transparent box</td>
<td>6m+</td>
<td>Simple RI</td>
<td>Diamond, 1991</td>
</tr>
<tr>
<td>Anti-saccade</td>
<td>Rewarded for producing saccade contralateral to cue</td>
<td>4m+</td>
<td>Simple RI</td>
<td>Johnson, 1995</td>
</tr>
<tr>
<td>Task</td>
<td>Description</td>
<td>Age</td>
<td>Complexity</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Bear and dragon</td>
<td>Act on bear, inhibit dragon</td>
<td>3yr+</td>
<td>Complex RI</td>
<td>Reed, Pien, &amp; Rothbart, 1984</td>
</tr>
<tr>
<td>Tower</td>
<td>Take turns with E</td>
<td>22m+</td>
<td>Complex RI</td>
<td>(Gerardi – Caulton, 2000)</td>
</tr>
<tr>
<td>Simon says</td>
<td>Game rules</td>
<td>4yr+</td>
<td>Complex RI</td>
<td>Reed et al., 1984</td>
</tr>
<tr>
<td>Shape stroop</td>
<td>Must point to small fruit</td>
<td>22m+</td>
<td>Complex RI</td>
<td>Kochanska, Murray, &amp; Harlan, 2000</td>
</tr>
<tr>
<td>Reverse categorisation</td>
<td>Big blocks/small bucket</td>
<td>24m+</td>
<td>Complex RI</td>
<td>Carlson, Mandell, &amp; Williams, 2004</td>
</tr>
<tr>
<td>Baby stroop</td>
<td>Baby spoon/big cup</td>
<td>2yr+</td>
<td>Complex RI</td>
<td>Hughes &amp; Ensor, 2009</td>
</tr>
<tr>
<td>Grass-snow</td>
<td>Point to white for ‘grass’</td>
<td>3yr+</td>
<td>Complex RI</td>
<td>Simpson &amp; Riggs, 2009</td>
</tr>
<tr>
<td>Day-night</td>
<td>Respond ‘night’ to sun</td>
<td>3yr+</td>
<td>Complex RI</td>
<td>Gerstadt, Hong, &amp; Diamond, 1994</td>
</tr>
<tr>
<td>Spatial conflict</td>
<td>Screen-matching target key</td>
<td>2yr+</td>
<td>Complex RI</td>
<td>Gerardi – Caulton, 2000</td>
</tr>
<tr>
<td>Hand game</td>
<td>Must oppose E gesture</td>
<td>3yr+</td>
<td>Complex RI</td>
<td>Hughes, 1998</td>
</tr>
<tr>
<td>Knock-tap</td>
<td>Knock when E taps</td>
<td>3yr+</td>
<td>Complex RI</td>
<td>Klenberg, Korkman, &amp; Lahti-Nuutila, 2001</td>
</tr>
<tr>
<td>A-not-B</td>
<td>Object hidden at B</td>
<td>6m+</td>
<td>Response shifting</td>
<td>Diamond, 1990</td>
</tr>
<tr>
<td>Test Name</td>
<td>Description</td>
<td>Age Range</td>
<td>Function(s)</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Multilocation search</td>
<td>Object visibly changed w/ 10 s delay</td>
<td>24m+</td>
<td>Response shifting</td>
<td>Zelazo, Reznick, &amp; Spinazzola, 1998</td>
</tr>
<tr>
<td>DCCS</td>
<td>Sort acc to dimension</td>
<td>3yr+</td>
<td>Attention shifting</td>
<td>Frye &amp; Zelazo, 2003</td>
</tr>
<tr>
<td>Teddy bear task</td>
<td>Must deduce rule from feedback</td>
<td>3yr+</td>
<td>Attention shifting</td>
<td>Hughes, 1998</td>
</tr>
<tr>
<td>Preschool Vigilance Task (CPT)</td>
<td>Bird on tree, varying ISI, 14.5mins</td>
<td>4-6</td>
<td>Inhibition, reaction time</td>
<td>Harper &amp; Ottinger, 1992</td>
</tr>
<tr>
<td>Zoo runner (CPT)</td>
<td>Auditory/visual *rates of omission errors @ 3, ceiling after 5.5yrs</td>
<td>3-6</td>
<td>Sustained attention</td>
<td>DeWolfe, Byrne, &amp; Bawden, 1999</td>
</tr>
<tr>
<td>CPTP (CPT)</td>
<td>8.5mins, high commission/omission rate for 3yr group</td>
<td>3-5</td>
<td>Sustained attention</td>
<td>Corkum, Byrne, &amp; Ellsworth, 1995</td>
</tr>
<tr>
<td>C-CPT (CPT)</td>
<td>3 tasks x 5mins (easier but high omission/commission rate in 3y/o)</td>
<td>3+</td>
<td>Sustained attention</td>
<td>Kerns &amp; Rondeau, 1998</td>
</tr>
<tr>
<td>ACPT-P (CPT)</td>
<td>Go/no-go, minimize 3yo</td>
<td>3-6</td>
<td>Sustained attention</td>
<td>Mahone, Pillion, &amp;</td>
</tr>
<tr>
<td>Test Name</td>
<td>Description</td>
<td>Duration</td>
<td>Task Type</td>
<td>Validated With</td>
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</tr>
<tr>
<td>ECVT (CPT)</td>
<td>*only preschool attention task validated with ERP, 7mins, no motor req., video coding</td>
<td>7.5mins, mouse click, space bar</td>
<td>2+</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>K-CPT (CPT)</td>
<td></td>
<td>4-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDTP-R</td>
<td>Pictures instead of letter/number cancellation tasks, bingo stamper,</td>
<td>3-5</td>
<td>Selective attention</td>
<td></td>
</tr>
<tr>
<td>MFFTpPV</td>
<td>Latency to first choice/no. of errors recorded</td>
<td>3+</td>
<td>Impulsivity</td>
<td></td>
</tr>
<tr>
<td>NEPSY</td>
<td></td>
<td>4-5, 3-6</td>
<td>Visual attention, Inhibition</td>
<td></td>
</tr>
<tr>
<td>Go/no-go</td>
<td>Press button for particular picture</td>
<td>3-6</td>
<td>RI</td>
<td></td>
</tr>
<tr>
<td>Boxes task</td>
<td>Jack-in-the-box search task</td>
<td>3-6</td>
<td>WM</td>
<td></td>
</tr>
<tr>
<td>Boy-girl stroop</td>
<td>Say opposite sex</td>
<td>3-6</td>
<td>inhibition</td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>Description</td>
<td>Age</td>
<td>Function</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
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<td>------------------------------------------------</td>
</tr>
<tr>
<td>Border version of the DCCS</td>
<td>Organise by border/no border</td>
<td>3-6</td>
<td>Shifting attention</td>
<td>Zelazo, 2006</td>
</tr>
<tr>
<td>Tower of Hanoi</td>
<td>Monkeys and trees</td>
<td>3-6</td>
<td>Planning</td>
<td>Kerns et al., 2001</td>
</tr>
<tr>
<td>Self-ordered pointing test</td>
<td>pictures of familiar objects or hard-to-verbalise abstract designs</td>
<td>5-11</td>
<td>Working Memory</td>
<td>Cragg &amp; Nation, 2007</td>
</tr>
<tr>
<td>Shape School Task</td>
<td>Storybook format: 4 conditions (control, inhibit, switch, both)</td>
<td>3-6</td>
<td>Inhibition, switching</td>
<td>Espy, 1997</td>
</tr>
<tr>
<td>Whisper</td>
<td>Whisper familiar cartoon names</td>
<td>3+</td>
<td>Inhibition</td>
<td>Kochanska, Murray, Jacques, Koenig, &amp; Vandegeest, 1996</td>
</tr>
<tr>
<td>Pinball</td>
<td>Wait until “Go”</td>
<td>3+</td>
<td>Inhibition</td>
<td>Reed et al., 1984</td>
</tr>
<tr>
<td>Count and Label</td>
<td>One shoe, two key</td>
<td>3+</td>
<td>WM</td>
<td>Carlson, Moses, &amp; Breton, 2002</td>
</tr>
<tr>
<td>KRISP</td>
<td>Match shape</td>
<td>3+</td>
<td>impulsivity</td>
<td>Carlson &amp; Moses, 2001</td>
</tr>
<tr>
<td>Forbidden Toy</td>
<td>Wait 5 mins</td>
<td>3+</td>
<td>inhibition</td>
<td>Lewis, Stanger, &amp; Sullivan, 1989</td>
</tr>
<tr>
<td>Disappointing Gift</td>
<td>Neutralise expression</td>
<td>3+</td>
<td>inhibition</td>
<td>Saarni, 1984</td>
</tr>
<tr>
<td>VExP task</td>
<td>Eye tracker</td>
<td>24m+</td>
<td>Processing speed</td>
<td>Haith, Hazan, &amp; Goodman, 1988</td>
</tr>
<tr>
<td>Task Name</td>
<td>Description</td>
<td>Age Range</td>
<td>Measure/Function</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Continuous familiarization task</td>
<td>Testing continued until infants showed a consistent preference for the new photo</td>
<td>24m+</td>
<td>Encoding speed</td>
<td>Rose, Feldman &amp; Jankowski, 2009</td>
</tr>
<tr>
<td>Look duration</td>
<td>How long stimulus is fixated</td>
<td>24m+</td>
<td>attention</td>
<td>Rose, Feldman, Jankowski, &amp; Rossem, 2005</td>
</tr>
<tr>
<td>Shift rate</td>
<td>Four measures of shift rate</td>
<td>24m+</td>
<td>switching</td>
<td>Rose et al., 2005</td>
</tr>
<tr>
<td>KiTAP Battery</td>
<td></td>
<td>6-10</td>
<td>Attention/EF</td>
<td>Zimmermann, Gondan, &amp; Fimm, 2002</td>
</tr>
<tr>
<td>TEA-Ch</td>
<td>Sustained, selective, executive control</td>
<td>6 years+</td>
<td>attention</td>
<td>Manly et al., 2001</td>
</tr>
<tr>
<td>ECAB Battery</td>
<td></td>
<td>3-6</td>
<td>Attention/EF</td>
<td>Breckenridge, Braddick, &amp; Atkinson, 2012</td>
</tr>
<tr>
<td>Hide and Seek, Tricky Box, Flap Book</td>
<td>Three measures of working memory, shifting, inhibition</td>
<td>1.5-5</td>
<td>WM, shifting, inhibition</td>
<td>Garon, Smith, &amp; Bryson, 2014</td>
</tr>
<tr>
<td>Missing Scan Task</td>
<td>Which animal is missing?</td>
<td>3-6</td>
<td>WM</td>
<td>Roman, Pisoni, &amp; Kronenberger,</td>
</tr>
</tbody>
</table>
CPT = Continuous Performance Test; DCCS = Dimensional Change Card Sort; ECAB = Early Childhood Attention Battery; ECVT = Early Childhood Vigilance Test; K-CPT = Conners' Kiddie Continuous Performance Test; KiTAP = The Test of Attentional Performance for Children; KRISP = Kansas Reflection-Impulsivity Scale for Preschoolers (KRISP); M = months; MFFTpPV = Matching Familiar Figures Tests-preschool version; PDTP-R = Picture Deletion Test for Preschoolers; WM = working memory; RI = response inhibition; TEA-Ch = Test of Everyday Attention for Children; VexP = visual expectation paradigm; yr = years
1.5.3 Behavioural measures

1.5.3.1 Behavioural measures for ease of use with preschool children

Valid assessment of executive skills can be achieved using performance-based assessments in this age range as long as appropriate vigilance is used in the design and development process (Mahone, 2005). There has been interest in executive skills in the early years over the past decade, with both new tasks being developed and tasks from other age ranges being modified to be more age appropriate to account for shorter attention spans, as well as less dependent on language and motor fluency (see Table 1.2). Important design characteristics need to be considered when developing or adapting measures for ease of use with preschool children (Garon et al., 2008). These include response modality, language requirements, length of task, ease of use, and novelty (Isquith, Crawford, Espy, & Gioia, 2005). To date, most tasks have not been well documented and so replications are not consistent, making it difficult to build upon existing research. Well-documented and clearly designed tasks that build upon existing research should be explored and modified further in order to develop sensitive tasks that can be used across different research groups for consistency (Carlson, 2005).

1.5.3.2 Ecologically valid assessments

Preschool assessments that rely on summary scores to indicate performance levels are considered to be questionable as an accurate indicator of cognitive abilities in this age group (Carlson, 2005). It has been suggested that ecologically valid measures which adopt a micro-analytic approach incorporating quantitative and qualitative scoring systems would better represent specific skills developing at various rates (Pritchard & Woodward, 2011).
Ecologically valid measures are important and necessary to inform both the cognitive and behavioural implications of executive difficulties in daily life (Anderson, 2002). A greater emphasis on ecologically valid measures has seen an increase in the application of behavioural assessments that incorporate various components of EF. However, many tasks in the preschool age range are aimed at measuring specific skills rather than EF in a more general and ecologically valid sense. In regards to intervention, it is important to understand what specific cognitive deficits are present, but also to have an understanding of the amount and type of general guidance and support a child requires in a typical school setting (Henry & Bettenay, 2010). Many clinical tests are a good indicator of how a child is struggling with a specific skill, but this does not inform their guardians or teachers of how much interaction they need when participating in a typical activity. Tasks in everyday life require the integration of executive functions, unlike the artificial separation of cognitive domains that often occurs in neurocognitive assessments.

Ecological validity refers to using cognition in real-life social environments. It is reflected in classroom behaviour where children must cooperate with their teacher and classmates in novel learning situations. Thus, assessments that closely resemble everyday life should be an important part of neurocognitive testing (Chan, Shum, Touloupoilou, & Chen, 2008). The Children's Kitchen Task Assessment (CKTA) is a task that aims to detect executive dysfunction during the performance of a novel task (Rocke, Hays, Edwards, & Berg, 2008). It is a cue-based task where children have to follow step-by-step instructions with as little help as possible. This type of task helps us to identify how much support is needed for an individual child and when this support may be needed. Using the CKTA, lower EF was found among eight to 12 year-olds with SCD (Berg et al., 2012).

Preschool assessments of EF often use pass/fail or summary scores of performance that cannot be considered an accurate representation of a child’s
ability (Carlson, 2005). More ecologically valid tasks for younger children, such as a downward extension of the CKTA, would provide a useful measure in terms of detecting executive difficulties in preschool children with SCA, by focussing on where things go wrong and how much support is required, rather than an uninformative summary score.

1.5.4 Biophysical measures

1.5.4.1 ERP methodology

Event-related potentials (ERP) could be particularly useful in the detection of difficulties in attention and information processing at a neural level (Knapp et al., 2013). These are deficits that are widely cited in the sickle cell literature and may lend some insight into the development of these processes in the early years where standardised neuropsychological assessment is restricted due to factors such as language and motor constraints. An advantage of ERP is that it can be carried out passively without the requirement of an overt response and is relatively resistant to motion (Casey & de Haan, 2002).

ERP is the averaging of an on-going EEG recording that is time-locked to a stimulus. It measures the response of groups of neurons during sensory or cognitive processes (Taylor & Baldeweg, 2002). ERPs are frequently used to investigate the development and dysfunction of processes such as attention, processing speed, memory, language, and social skills. There is ERP evidence of delayed neurocognitive functions, such as visual and auditory attention, in preschool-age children with a history of prematurity, autism, ADHD, epilepsy, phenylketonuria, and specific language impairment (de Sonneville, Huijbregts, Licht, Sergeant, & van Spronsen, 2011; Mikkola et al., 2007; Myatchin, Mennes, Wouters, Stiers, & Lagae, 2009; Overtoom et al., 1998; Salmond, Vargha-Khadem, Gadian, de Haan, & Baldeweg, 2007; Stevens, Sanders, & Neville, 2006).
Although patients with SCA share commonalities with these other groups, there has been a dearth of research into the development of neurocognitive functions using ERP methodology (Hogan, Vargha-Khadem, et al., 2006). This is despite recent research that has found associations between EEG correlates and EF among patients with SCD (Ruffieux et al., 2013). One ERP study from our group found that frontal lesions in young people with SCD (N=11) affected performance monitoring on a response task as compared to sickle cell patients without lesions (N=11) and sibling controls (N=11). They also found signs of slower processing speed in the P3 latency for both sickle cell groups but these results did not reach significance (Hogan, Vargha-Khadem, et al., 2006). Another recent study also found a delayed response in children with SCA with no observable neurological damage (N=12) in response to auditory stimuli, along with the activation of altered neural networks when compared to a comparison group (Colombatti et al., 2014).

Recent preliminary ERP data examining auditory attention in a group of children with SLI suggests that executive skills may be amenable to intervention, with observable changes in neurological correlates (Darves, Sanders, Stewart, & Neville, 2005). Thus, ERP methodology could be used to investigate whether current medical interventions such as blood transfusion or hydroxyurea therapy lead to improved functioning at a neural level (Puffer, Schatz, & Roberts, 2007). ERP research has shown that children as young as three years can actively participate in behavioural EEG tasks (Sanders, Stevens, Coch, & Neville, 2006). One recent study showed that lower SES groups showed reduced selective attention in neural processing specifically related to a reduced ability to filter irrelevant information (Stevens, Lauinger, & Neville, 2009). Future studies incorporating similar task designs may also be relevant to the sickle population, considering the high rates of low SES in this population.
1.6 General Discussion

1.6.1 Future Directions
Seminal studies in typically developing young children are already showing the positive benefits of interventions that are aimed at both general and more specific EF skills (Diamond, 2012). However, due to the lack of research into executive development during the preschool period, there is a lack of available measures for assessing these skills in preschool children (Garon, Smith, & Bryson, 2013). As executive skills have been described as a protective factor, and can be successfully trained, an emphasis must be placed on developing assessment strategies in the early years in order to further our understanding of the developing brain-behaviour relationship and future functional outcomes (Johnson, 2012a). This is particularly relevant to preschool children with SCA who may benefit from early identification and intervention. Emerging research suggests that executive deficits can have an impact on both academic attainment and social functioning in children with SCA (Hensler et al., 2014). This further emphasizes the need for further research into EF development in the preschool years in this patient population.

1.6.2 Conclusions

1.6.2.1 There is a current lack of valid assessments of executive functioning for preschool children.
The information reviewed above shows that there is a lack of measures of EF for children in the preschool years. This is particularly pertinent to children with SCA who are known to have executive deficits, although the timing and magnitude of which they emerge and become problematic remain unclear. Thus, a range of assessments that can capture a child’s level of functioning before they enter the school system would be invaluable in the development of appropriate interventions and in informing policy. A combination of methods that access specific cognitive
components with ecologically valid measures that simultaneously integrate various components will paint a more holistic picture of a child’s abilities and how best to support them.

1.6.2.2 Little is currently known on the early development, and potential dysfunction, of executive functioning in children with SCD.

A neurodevelopmental profile of young children with SCD that accounts for both disease-related and environmental factors must be established so that parents and care providers can be provided with more informed support.

1.6.3 Aims

This thesis aims to contribute to the current understanding of the development and delay of executive functions in young children with SCD. The current literature reviewed in the introduction emphasises the need to assess executive skills and to determine what may contribute to the disruption of their development in young children with SCA. First, new reliable means of assessing executive skills in preschool age children require design and development. Second, it needs to be established whether specific executive deficits are observable in preschool children with SCA in comparison to their peers at this early stage. Additionally, the potential contribution of disease and environmental factors to the development of executive skills in children with SCA needs to be investigated. These aims are further outlined below.

1.6.3.1 To develop a valid battery of executive functioning measures for preschool children

I planned to develop a battery of EF measures that will provide a holistic picture of EF in preschool-age children. The design criteria (listed below) for the development of this battery of tasks are based on a review of the preschool and sickle cell literatures, as discussed in the above literature.
review. The development of a multidimensional battery of tasks allows the opportunity to measure executive functions on a biophysical (ERP), behavioural (tasks that tap specific skills), and ecological (tasks that look at how executive deficits may present in a normal setting) level. In this way, we can better understand how executive deficits manifest as the child develops and how easily they can be observed.

1.6.3.1.1 Design Criteria for Executive Battery Development

- A battery of tasks that measure executive deficits previously identified in older populations of children with SCA.
- A battery of tasks that is developmentally appropriate for preschool-age children, overcoming some current task restrictions by minimizing additional demands that make tasks inappropriate for younger children.
- A battery of tasks that can be administered from thirty-six to seventy-two months, without floor or ceiling effects.
- The development of executive tasks that are valid and reliable.
- The development of executive tasks that are grounded in the current literature.
- The development of executive tasks that are well documented and replicable.
- The development of an age-appropriate event-related potential measure of executive function.
- The development of an ecologically valid measure of executive function.
- The inclusion and development of behavioural measures of executive function that tap specific executive domains.

1.6.3.1.2 How Aim 1 will be addressed in this thesis:

The Methodology Section (Chapter 2) will introduce and describe all assessments whilst the Validation Section (Chapter 3) will further expand on
the validity and reliability of behavioural tasks. The ERP measure will be reported in Chapters 7. Chapter 8 (General Discussion) will summarise the addressed aims.

1.6.3.2 **To establish whether there are observable executive deficits in preschool children with SCA and the potential impact of disease-related and other relevant factors**

We already know that children with SCA tend to develop executive deficits by school age and adolescence. We do not, however, know the extent to which deficits may be present in the early years or when they first begin to emerge. The novel battery of executive tasks will help us better understand the developmental trajectory of EF in SCA in terms of how, when, and where potential specific deficits may be identified. This study aims to build a neuropsychological profile of children with SCA that will help to inform how, when and where potential interventions could be applied. Alongside the executive battery, I will use other neuropsychological and medical measures, based on a review of the SCA literature, to explore the impact of disease and environmental factors on executive development in order to gain a greater understanding of which patients may be at a greater risk of developing executive deficits, as well as gaining an insight into the complex and dynamic relationship between SCA and executive dysfunction.

1.6.3.2.1 How Aim 2 will be addressed in this thesis:
Chapters 4 and 5 (General Functioning and Executive Functioning) will describe EF of the SCA group based on behavioural task performance in the context of their general functioning. Chapter 6 will look at the relations between executive performance and disease and non-disease related factors. Chapter 7 will look at the neurophysiological profile of patients with SCD. Chapter 8 (General Discussion) will summarise all of the addressed aims.

1.6.4 **Research Questions and Hypotheses**
Specific research questions and predictions are outlined in the table below and at the beginning of each of the experimental chapters. Findings are summarised in the General Discussion.
Table 1.3 List of study predictions divided by chapter

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3: The development and validation of measures of EF for three to five year olds</td>
<td>To develop tasks that validly and reliably assess aspects of EF from 36 to 72 months</td>
</tr>
<tr>
<td>4: An investigation of the children with SCA in the current study with a particular focus on factors known to have a potential impact on executive development</td>
<td>Factors relevant to EF other than disease status may be different in the children and the matched comparison group</td>
</tr>
<tr>
<td>5: Investigating the early development of EF in children with SCA using measures that tap specific components as well as measures that look at EF in a more ecologically-valid way</td>
<td>Children with SCA will show poorer performance on executive tasks as observed in studies of older children</td>
</tr>
<tr>
<td>6: An investigation of factors that contribute to poorer EF in preschool children with SCA</td>
<td>Poorer parent-reported family functioning and more sleep problems in children with SCA will have more of an influence on executive outcomes than markers of disease severity.</td>
</tr>
<tr>
<td>7: A neurophysiological investigation of selective auditory attention, an early emerging and foundational executive skill, in preschool children with SCA</td>
<td>1: Children with SCD will show diminished neural modulation with attention. 2: Children with the poorest executive scores on behavioural tasks will show less controlled EFP responses and less differentiation between the</td>
</tr>
</tbody>
</table>
attended and unattended conditions.

3: Poorer SES and less positive family functioning will be associated with less mature ERP responses but there will be no relation with markers of disease severity.
Chapter 2: Methodology

Studying executive functioning in the preschool years using neurophysiological and behavioural methods
2 General Methodology

2.1 Ethical Approval and Study Design

2.1.1 Ethical Approval

The researcher obtained ethical approval from the NHS Research Ethics Committee (13th August 2013), the UCL Institute of Child Health R&D committee (23rd August 2013), and Barts Heath NHS Trust R&D committee (13th February 2014). A substantial amendment was approved by the NHS Research Ethics Committee (3rd October 2014), and the UCL Institute of Child Health R & D committee (20th November 2014). See appendix 1 for approval letters.

2.1.2 Study Design

This current study was designed and set-up by the researcher with two main objectives in mind. The first aim was to develop an appropriate battery of EF measures for three to five year olds and the second aim was to use these measures to investigate whether executive deficits, largely noted in older children and adolescents in the literature, are already present and detectable at this early stage in children with sickle cell anaemia. The mixed-methods study incorporated behavioural, neurophysiological and proxy-report measures and spans three phases of testing.

The first phase, henceforth described as phase one, involved the piloting and development of executive tasks that the researcher developed or adapted with preschool-age children.

The second phase (phase two) involved the norming and validation of one of the piloted tasks in a larger cohort of children, taking testing from the laboratory to the classroom.
The final phase of the study (phase three) looked at executive development in children with sickle cell anaemia using both novel (developed from phase one and two) and standardized measures of EF. A matched comparison group was also recruited in order to control for ethnic and socioeconomic factors.

2.2 Participant Recruitment

The study consent and recruitment documents are attached in appendix 2. The recruitment documents included ethically approved Internet and email advertisement formats, poster advertisement, brochures, and information sheets for each group.

2.2.1 Phase one: Typically developing participants

Twenty-eight pilot participants between three and five years were recruited in order to develop the ERP paradigm and experimental behavioural measures of EF for pre-school age children. Pilot children were recruited through a number of methods:

- Poster advertisements in libraries, crèches, preschools, and parent groups throughout central London.
- Brochures available in community centres, libraries, play groups and schools.
- On-line advertisement on parent blogs, newsletters, and websites such as “Bloomsbury Babies.”
- Email advertising to staff and students at UCL, GOSH, and Barts NHS Trust.
- School and preschool newsletters.
- The researcher also gave science engagement talks at local parent groups where study was further advertised.
The inclusionary criterion was that the child must be aged between 36 and 72 months. Exclusionary criteria included a child having a history of a developmental, a psychiatric, or a neurological disorder, as well not being fluent in English. The researcher orally obtained this information from the parent or guardian at first contact.

2.2.2 Phase two: Participants for norming of executive task

Over a hundred nurseries and schools across London were contacted by email/letter and/or phone. Contact details for the schools were found on-line and emails and letters were addressed to the principal or vice principal. Schools were sent copies of the information sheet and consent form (see appendix 9.1) as well as an explanatory cover letter from the researcher. Two schools and one nursery were able to participate in the study. In one case, this was because the school had a teacher who had allocated hours to help coordinate external research projects. The main reasons for non-participation were recent change of principal or classroom teacher for reception or nursery class or not able to commit the time with no response in many cases. Of the three participating educational centres, one was in East London, one in Central London, and one in South London with 120, 38, and 260 children respectively registered within the age range. The two schools were mainstream state schools with both nursery and reception classes whilst the nursery was fee-paying with a free early education entitlement scheme. The researcher delivered information packs to the site, which the teachers sent home for parents who wished to consent for their children to participate. Parents who wished to participate had up to three weeks to return packs, including consent form and behavioural questionnaires, to the school before the testing week. Any packs returned after testing dates were not included in analysis.

Exclusionary criteria included a history of a developmental, a psychiatric, or a neurological disorder, as well as not being fluent in English.
2.2.2 Phase three: Participants with sickle cell anaemia

Patients were recruited through sickle cell clinics at the Royal London Hospital (Barts and the London Hospitals NHS Trust). The majority of patients attending this hospital for treatment were from Central and East London. The researcher attended approximately 50 morning or afternoon transcranial and sickle cell clinics on Wednesdays, Fridays, and Saturdays, where patients were seen by two paediatric haemotologists, Dr Paul Telfer and Dr Banu Kaya. If a patient met the study criteria listed below, the clinicians informed them of the project:

- aged between 36 and 72 months
- HbSS genotype
- no other developmental or psychiatric disorders
- no history of overt stroke\(^1\)
- not being fluent in English

If the family wanted to hear more about the project then the clinician introduced them to the researcher in a separate quiet space where they could learn more about participation. If the families were interested after the researcher provided the relevant information, then the researcher provided them with the study information pack and took their contact information so that they could be contacted within one week.

\(^1\) Silent stroke cannot be definitively ruled out without an MRI scan, however we plan to follow up this cohort in mid childhood at an age when they can undergo scanning.
2.2.3 Phase three: Comparison participants without sickle cell anaemia

Matched comparison children were recruited in order to control for socio-economical, ethnic, and cultural factors. The importance of recruiting children closely matched for age, sex, ethnicity, and socioeconomic status has been previously emphasized in the sickle cell literature (Richard & Burlew, 1997). Matched children were recruited in a number of ways, and areas in East London were particularly targeted, as this is where the majority of the patient group resided:

- Siblings and cousins of children with sickle cell were recruited through sickle cell clinics, sickle cell coffee mornings, and sickle cell charities.
- On-line advertisements with African heritage websites
- Brochures and posters targeted community places such as libraries in East London
- Schools in East London were sent information packs

Exclusionary criteria included a history of a developmental, a psychiatric, or a neurological disorder, as well as English as a second language or not being ethnicity matched. The researcher orally obtained this information from the parent or guardian at first contact.

2.3 Participation Rates

2.3.1 Phase one: Typically developing participants

In total, 28 children were recruited and assessed by the researcher at the London Babylab during the development phase. In further sections, the
number of children completing each task may vary due to some tasks changing during the development phase.

2.3.2 Phase two: Participants for norming of executive task
One hundred and thirty nine children were recruited through the three education centres. Parent consent rate was consistent with previously quoted norms for similar studies at 19/38 (50%), 46/120 (38%), and 82/260 (32%) with an overall response rate of 35% (L. Cohen, Manion, & Morrison). Eight packs were returned too late and thus not included in testing or analysis.

2.3.2 Phase three: Participants with sickle cell anaemia

There were 110 cases of HbSS registered on the Barts NHS Trust database within the required age range. Some of these were lost to follow-up or attended the Royal London Hospital for scheduled annual reviews only. Of those registered for more regular review (typically biannual transcranial Doppler scans), poor attendance was not uncommon. Though the exact rate of non-attendance is not known for these particular clinics, a recent audit of a similar institution, North Middlesex University Hospital, discussed how the high rates of non-attendance to paediatric SCD clinics contributed to the hospital not meeting all of its targets for UK national standards for SCD care (Hann, Roberts-Harewood, Yardumian, & Wilkey, 2012). No clinical or demographic information is available for those who did not participate in the current study.

Of those eligible for the study and referred to the researcher in clinic, the participation rate was approximately 85%. Reasons for non-participation included unavailability or, when re-contacted by the researcher, lack of response. The researcher was available for testing seven days a week so that children did not necessarily have to miss any school days in addition to hospital appointments and illness days. However, some parents worked irregular shifts at the weekend and/or attended church so found it difficult to
schedule the time. Some families changed their mind or cancelled before the date scheduled for the testing protocol (N=2) or did not attend on the day with no response (N=1). One child was retrospectively excluded as he had been diagnosed with specific language impairment between recruitment and assessment. A second child was retrospectively excluded from the majority of analysis as he was erroneously referred to study and had another sickle cell genotype (HbSC) which typically has a less severe disease presentation. Despite this, 23% of the children actively followed up on the Barts NHS Trust database with the HbSS genotype in this age range were included in the final analysis (see figure 3.1). Additionally, it is likely that a number of the children on the database who were not included in the study would not have met all of the study criteria (e.g. no evidence of stroke or co-morbid developmental disorder or English as a second language).
Figure 2.1 Flowchart of recruitment from current 3.00 to 5.99 year old HbSS patients (born between 15 March 2008 – 15 October 2011) registered on medical database of the Royal London Hospital.

2.3.3 Phase three: Comparison participants without sickle cell anaemia

Thirteen age, gender, socio-economic status, IQ and ethnicity-matched participants were recruited and assessed at the London Babylab during phase three. One child was excluded, as she was born very pre-term (before 32 weeks) and it is well established in the literature that children born extremely and very preterm commonly experience executive problems later on in
development. Two of the Phase one comparison children and 11 of the Phase two (3.3.2) children were also ethnicity-matched (Black British) and matched for age, gender, IQ, and SES. These children were included in matched comparisons with patient group where possible. In these instances, there were 26 children in the matched control group. Other children from phase one who were age, sex, socio-economic status, and IQ matched, but not ethnicity-matched, were included in the Neurophysiological chapter only.

2.4 Design, Development and Piloting of Protocol

The aim of phase one was to design, develop, and pilot a battery of tasks appropriate for investigating executive functions in preschool-age children. Established measures were combined with new measures that were developed based on the existing literature for testing different aspects of EF in young children. All executive measures were chosen to robustly measure different aspects of EF in line with the Anderson model of EF (figure 3.2). Non-executive measures were included to control for IQ as well as factors that have been previously flagged as important in the sickle cell and general preschool literature, such as sleep, family functioning, temperament, and pain. An electrophysiological paradigm was also developed in order to directly investigate correlates of EF in lieu of the constraints found in behavioural and questionnaire methods.
2.4.1 Established Questionnaire Measures used in Testing Protocol

Parent-report questionnaires were chosen to measure aspects of family functioning, behaviour, EF, sleep, and pain. As well as questionnaires, further demographic information was collected from the parent: age, ethnicity, handedness, and gender of child, mother’s education, postcode, and if the child could speak more than one language, as well as information on the child’s developmental and neurological history, if the child had any special requirements, and if there was a history of SCD in the family.

Despite the participants’ fluency in English, English was not the first language of many of the parents of the patients and the ethnicity matched children in the study due to immigration to the United Kingdom in their adult years. Thus, the researcher was available to assist in the case of any potential questionnaire statements that were not clearly understood at the beginning, the middle and at the end of the testing protocol and encouraged the parent to
mark any unclear statements so that they could be explained better. The researcher read sample items at the start of the study session and explained their meaning to reduce the likelihood of alternative interpretation of questionnaire items due to dialectical rules (McNicol & Armour-Thomas, 2001).

2.4.1.1 Family Environment Scale (FES)

Research has shown that family factors, such as cohesion and expression, can have an impact on neurocognitive development (Schroeder & Kelley, 2010). Family environment has been specifically highlighted in the sickle cell literature as a factor to take into consideration when looking at cognitive development (Barakat et al., 2007; Brown, Buchanan, et al., 1993; Drazen, Abel, Gabir, Farmer, & King, 2015; Thompson et al., 1999). The relationship between environment and executive development is complex. However, there is emerging evidence for the role of family functioning in executive development with it even being reported as a mediator for socio-economic status and other external factors. Associations have been observed for family functioning and behavioural development in older children with sickle cell disease. Some research has found environmental factors to be more predictive of neurocognitive outcomes than disease severity in young children with sickle cell (Tarazi et al., 2007). Family functioning could be a potential target for intervention with the goal to promote executive development.

Parents completed the Family Environment Scale (FES) (Moos, 1990), a 90-item true-false, measure of family functioning that is widely used in the literature. The FES contains 10 subscales and measures three underlying dimensions of family environment: relationships, personal growth, and system maintenance. It has been used in previous studies that look at the effects of environmental factors on cognitive development in children with SCA. Previous studies in the sickle cell literature have found that the 10 subscales cluster into three empirically-derived factors of supportiveness, conflicted, and controlling (Kronenberg & Thompson, 1990; Thompson Jr, Gustafson, Gil, Kinney, & Spock, 1999). Further research in families of children who are
chronically ill led to the development of a total FES composite score where higher scores indicate more positive home environments (Perrin, Ayoub, & Willett, 1993). Previous research has shown a decline in cognitive functioning over time in toddlers with SCD that has been associated with both parenting risk and the HbSS phenotype (Thompson et al., 1999). Thus, it has been proposed that the family environment may be a salient target for intervention in terms of fostering adaptation to this chronic illness, as well as having a potential impact on neurocognitive development.

The questionnaire layout was modified during the pilot phase on the basis of feedback from parents so that it would be easier to understand and complete. This meant that the true/false response was placed under each individual statement rather than on a corresponding response box at the back of the booklet.
Table 2.1 Description of domain areas of the Family Environment Scale

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Sample Item*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohesion</td>
<td>degree of commitment, help and support</td>
<td>Family members really help and support one another.</td>
</tr>
<tr>
<td>Expressiveness</td>
<td>family members are encouraged to express their feelings</td>
<td>Family members often keep their feelings to themselves.</td>
</tr>
<tr>
<td>Conflict</td>
<td>amount of openly expressed anger and conflict</td>
<td>We fight a lot in our family.</td>
</tr>
<tr>
<td>Independence</td>
<td>family members are assertive, self-sufficient and make their own decisions</td>
<td>We don't do things on our own very often</td>
</tr>
<tr>
<td>Achievement Orientation</td>
<td>how much activities (such as school and work) are cast into an achievement-oriented or competitive framework.</td>
<td>We feel it is important to be the best at whatever you do.</td>
</tr>
<tr>
<td>Intellectual-cultural Orientation</td>
<td>level of interest in political, intellectual and cultural activities</td>
<td></td>
</tr>
<tr>
<td>Active-recreational Orientation</td>
<td>amount of participation in social and recreational activities</td>
<td></td>
</tr>
<tr>
<td>Moral-religious emphasis Organisation</td>
<td>emphasis on ethical and religious issues and values</td>
<td></td>
</tr>
<tr>
<td>Organisation</td>
<td>degree of importance of clear organization and structure in planning family activities and responsibilities.</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>how much set rules and procedures are used to run family life</td>
<td></td>
</tr>
</tbody>
</table>

*Only five sample items allowed for copyright reasons (see appendix 3 for approval letter)
2.4.1.2 BRIEF-Preschool

The BRIEF-Preschool (Gioia, Espy, & Isquith, 2003) is sensitive to atypical variations in EF development (Isquith et al., 2005). It measures neurocognitive functions that are purportedly subserved by frontal systems and thus, should be a useful index related to recognized pathology, including silent cerebral infarction and raised cerebral blood flow velocity in children with SCA (DeBaun et al., 2014; Kral et al., 2003). It is the most commonly used screener questionnaire for executive dysfunction. It consists of 63 items relevant to a preschool-age child’s everyday EF. It is comprised of five subscales (Inhibit, Shift, Working memory, Plan/Organize, and Emotional Control) that create three broader indexes (Flexibility, Emergent Metacognition, and Inhibitory Self-Control) and an overall summary score (General Executive Composite). Higher scores indicate poorer EF. Preliminary findings in older children without SCD showed an association between snoring, increased CBV and BRIEF scores (Hill et al., 2006). A trend has also been observed between TCD values and BRIEF scores (Kral et al., 2003).
Table 2.2 Description of BRIEF-Preschool subdomains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit</td>
<td>To inhibit or control his/her behaviour</td>
</tr>
<tr>
<td>Shift</td>
<td>To move from one activity or context to another flexibly</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>Ability to modulate emotional reactions</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Ability to keep information in mind during multi-step activities</td>
</tr>
<tr>
<td>Plan/Organise</td>
<td>Ability to anticipate future events and to order information or materials</td>
</tr>
<tr>
<td>Inhibitory Self-Control Index</td>
<td>Created from Emotional Control and Inhibit subscales. Ability to modulate behavior.</td>
</tr>
<tr>
<td>Flexibility Index</td>
<td>Created from Shift and Emotional Control subscales. Ability to move flexibly between events and behaviours.</td>
</tr>
<tr>
<td>Emergent Metacognition Index</td>
<td>Created from working memory and plan/organize subscales. Ability to solve problems and make plans.</td>
</tr>
<tr>
<td>Global Executive Composite</td>
<td>Summary score of all five subscales.</td>
</tr>
</tbody>
</table>

Shaded rows are composite scores; non-shaded rows are individual domains.
2.4.1.3 Children's Behaviour Questionnaire-short

The Children's Behaviour Questionnaire (CBQ-S; Putnam, 2006) is frequently used to look at temperament in 3 to 8 year olds. It involves 94 items that form 13 dimensions including impulsivity, inhibitory control, focusing attention, shyness, sadness, anger/frustration, and activity levels. Parents are asked to answer, on a scale of 1 (extremely untrue) to 7 (extremely true), how true each statement is for their child. It has been reported to be a reliable assessment of reactive or self-regulative behaviours in preschool children (Rothbart, Ahadi, Hershey, & Fisher, 2001). Deficits in EF are a risk factor for behavioural problems (Utendale & Hastings, 2011). It was proposed that children who displayed poor executive task performance would score higher on the inhibitory control, and attentional focusing subdomains of the CBQ. The short version of this questionnaire was chosen due to the volume of questionnaire responses that were required from parents.
### Table 2.3 Description of domain areas of the CBQ-S (domains of interest in italics)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Sample Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity Level</td>
<td>Higher score reflects more gross motor activity.</td>
<td>Seems always in a big hurry to get from one place to another.</td>
</tr>
<tr>
<td>Anger/Frustration</td>
<td>Higher score reflects more negative affectivity in relation to interruptions or blocking of goals.</td>
<td>Gets angry when told s/he has to go to bed.</td>
</tr>
<tr>
<td>Attentional Focusing</td>
<td>Higher score reflects greater ability to maintain focus on task at hand.</td>
<td>When practicing an activity, has a hard time keeping her/his mind on it.</td>
</tr>
<tr>
<td>Discomfort</td>
<td>Higher score reflects more negative affect related to sensory stimulation.</td>
<td>Is not very bothered by pain.</td>
</tr>
<tr>
<td>Falling Reactivity/Soothability</td>
<td>Higher score reflects faster recovery from distress or excitement.</td>
<td>Has a hard time settling down after an exciting activity.</td>
</tr>
<tr>
<td>Fear</td>
<td>Higher score reflects negative affectivity or nervousness.</td>
<td>Is afraid of burglars or the &quot;boogie man.&quot;</td>
</tr>
<tr>
<td>High Intensity Pleasure</td>
<td>Higher score reflects greater enjoyment to stimulating events.</td>
<td>Likes going down high slides or other adventurous activities.</td>
</tr>
<tr>
<td>Domain</td>
<td>Description</td>
<td>Sample Item</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Higher score reflects more impulse responses.</td>
<td>Usually rushes into an activity without thinking about it.</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td><em>Higher score reflects greater capacity to plan and to suppress inappropriate responses.</em></td>
<td><em>Can wait before entering into new activities if s/he is asked to.</em></td>
</tr>
<tr>
<td>Perceptual Sensitivity</td>
<td>Higher score reflects greater detection of low-level stimuli from the external environment.</td>
<td>Notices it when parents are wearing new clothing.</td>
</tr>
<tr>
<td>Sadness</td>
<td>Higher score reflects lower mood.</td>
<td>Cries sadly when a favourite toy gets lost or broken.</td>
</tr>
<tr>
<td>Shyness</td>
<td>Higher score reflects greater discomfort in social context.</td>
<td>Seems to be at ease with almost any person.</td>
</tr>
<tr>
<td>Smiling/Laughter</td>
<td>Higher score reflects greater positive affect in response to environmental stimuli.</td>
<td>Enjoys funny stories but usually doesn't laugh at them.</td>
</tr>
</tbody>
</table>
2.4.1.4 *Children's Sleep Habits Questionnaire*

An adapted version of the Children’s Sleep Habits Questionnaire (Goodlin-Jones, Sitnick, Tang, Liu, & Anders, 2008; Owens, Spirito, & McGuinn, 2000) was used to look at the child’s sleeping behaviour. The adapted version was previously used in another multicentre study with children who have SCD and asthma (Rosen et al., 2014) in order to gain more information on symptoms of sleep disordered breathing. This sleep questionnaire includes variables such as snoring and other clinical symptoms of upper airways obstruction. Previous studies have found that children with sleep-disordered breathing score significantly lower in executive tasks (Kheirandish & Gozal, 2006; O’Brien et al., 2004). Possible compound effects of SCA and SDB on neurocognitive functioning have been found in older children. SDB has been related to SES and SCD complications (Daniel, Grant, Kothare, Dampier, & Barakat, 2010). This is a potential early medical avenue for intervention.

Sleep-disordered breathing is associated with increases in cerebral blood flow in children without SCA (Hill et al., 2006). There has been a reported increased prevalence of sleep apnoea in SCA (Khatwa, Bazzy-Asaad, & Kothare, 2012; Rosen et al., 2014; Salles et al., 2009). Thus, it is hypothesized that the combined influence of sleep breathing problems (identified by the CSHQ and polysomnography data where available) and SCA will exacerbate executive difficulties in attention and processing speed in the patient population.

As well as descriptive variables, the researcher created a sleep composite score based on previous research. The composite score was created from 20 questions relating to snoring, enuresis, and other sleep problems. The ratings ranged from 0 (never) to 5 (always) for each question and a combined weighted score of all questions comprised of the overall sleep score. A higher score was indicative of poorer sleep quality.
<table>
<thead>
<tr>
<th>Current Nighttime Symptoms</th>
<th>(a) never</th>
<th>(b) not often ( &lt;1 night week)</th>
<th>(c) sometimes (1-2 nights week)</th>
<th>(d) often (3-5 nights week)</th>
<th>(e) always (6-7 night/s week)</th>
<th>(f) don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snores</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Difficulty breathing while asleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Stops breathing during sleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Noisy breathing</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Restless sleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sweating when sleeping</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Nightmares</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sleep walking</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sleep talking</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Screaming in his/her sleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kicks or jerks legs in sleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Uncomfortable feelings in his/her legs; creepy/crawly before falling asleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Resists going to bed at bedtime</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Trouble falling asleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Feels like s/he can’t move arms or legs when falling asleep</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Wakes up at night</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gets out of bed at night</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Trouble staying in his/her bed at night</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Grinds his/her teeth</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Wets the bed</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Figure 2.3** Nighttime symptom questions, as presented in the adapted Children’s Sleep Habits Questionnaire, used to create sleep composite score.
2.4.1.5 *Faces Pain Scale-Revised*

The Faces Pain Scale-Revised (Hicks, von Baeyer, Spafford, van Korlaar, & Goodenough, 2001) was used to measure a child’s current pain experience. The child was instructed to point to what they are feeling on the scale. This scale has been previously described as appropriate for pre-school children so was administered during phase one to gauge the child’s understanding of instructions before being delivered to patients (Hunter, McDowell, Hennessy, & Cassey, 2000). Chronic pain affects cognitive function in children but the degree of the effects on cognitive development is not yet clear (Dick & Riddell, 2010).

![Figure 2.4 Faces pain scale-revised](image)

**Figure 2.4** Faces pain scale-revised

![Figure 2.5 Summary of questionnaire measures administered to parents](image)

**Figure 2.5** Summary of questionnaire measures administered to parents (faces pain scale administered directly to participant)
2.4.2 Established Cognitive/Behavioural Tasks

2.4.2.1 Wechsler Preschool and Primary Scale of Intelligence

The Wechsler Preschool and Primary Scale of Intelligence or WPPSI-III-UK (Wechsler, 2002) is a standardized and well-established (intellectual quotient) IQ measure. Verbal and performance IQ can be obtained as well as overall full-scale IQ. This measure was used to control for IQ in the interpretation of task performance, to ensure that comparison children were matched for IQ, and to determine that each child had the language proficiency to understand task instructions in the executive tasks. Separate forms are used for three year olds and four/five year olds. Subtest differences for each age group can be seen in Table 2.4.

<table>
<thead>
<tr>
<th>Subtests</th>
<th>Information</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Block Design</td>
<td>Word Reasoning</td>
</tr>
<tr>
<td></td>
<td>Receptive Vocabulary</td>
<td>Vocabulary</td>
</tr>
<tr>
<td></td>
<td>Object Assembly</td>
<td>Matrix Reasoning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Block Design</td>
</tr>
<tr>
<td>Age Range</td>
<td>2:6-3:11 years</td>
<td>Picture Concepts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coding</td>
</tr>
</tbody>
</table>

Table 2.4 WPPSI-III-UK subtests as administered to children based on age

2.4.2.2 NIH Toolbox: Attentional Control and Processing Speed

The NIH Toolbox (Gershon et al., 2010) is a newly developed, computerized battery of measures of neurological and behavioural function. It has been normed and validated from ages three to 85 years, and contains executive measures as part of its early cognitive domain. Each task takes about three to five minutes to administer. The battery also contains a processing speed task appropriate for the current age range, which is not readily available.
elsewhere. This battery was employed as the tasks are reliable and valid measures, but also short and interactive, as well as usable across different cultures and ages, important requirements for the current study (Weintraub et al., 2013). The computerized tasks were used to validate and/or complement the behavioural measures of EF administered as part of the current study. Table 3.5 shows the tasks piloted within the toolbox during phase one and also illustrates the tasks discontinued for phase three. Two of the discontinued tasks were removed due to inattention in young children when completing prolonged periods in front of a computer, and the third task was later used in its tabletop version as it more successfully engaged children during the piloting session (see section 3.4.4.6).

**Executive function-inhibitory control and attention (Zelazo et al., 2013)**

The original and well-known Flanker task (Eriksen, 1995) was adapted from the Attention Network Test (Rueda, Fan, et al., 2004) to be usable across different age ranges. It requires the participant to press the arrow button that corresponds with the direction that the middle fish on the screen is facing. The middle fish is “flanked” by two fish on either side and sometimes it is congruent, or swimming in the same direction, whereas other times it is incongruent, or swimming in the other direction. The resulting score is based on the correct responses during incongruent trials. The test phase is preceded by a practice phase and if the child performs well, they continue to higher levels where they must press the arrow that corresponds with the digital on-screen arrow.

**Pattern Comparison Processing Speed (Carlozzi, Tulsky, Kail, & Beaumont, 2013)**

The NIH toolbox version of this task is based on Salthouse’s Pattern Comparison Task (Salthouse, 1996). The child is instructed to choose a smiley face when two pictures are the same and a sad face when two pictures differ. The pictures that differ are either in a different colour or have a feature added or taken away. They are required to make the choice as quickly as they can. The score is a summary of correct answers (of a possible 104) that a child completes in 90 seconds.
**Table 2.5** Status of validated computerized tasks used from the Early Cognitive Domain of the NIH toolbox

<table>
<thead>
<tr>
<th>Early Cognitive Domain Tasks</th>
<th>Domain</th>
<th>Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flanker</td>
<td>Inhibitory Control and Attention</td>
<td>Included</td>
</tr>
<tr>
<td>Pattern Comparison</td>
<td>Processing Speed</td>
<td>Included</td>
</tr>
<tr>
<td>Dimensional Change Card Sort</td>
<td>Shifting</td>
<td>Change to tabletop DCCS task (see DCCS section below)</td>
</tr>
<tr>
<td>List Sorting</td>
<td>Working Memory</td>
<td>Removed-Session too long, task not priority</td>
</tr>
<tr>
<td>Picture Sequence</td>
<td>Episodic Memory</td>
<td>Removed-Session too long, task not priority</td>
</tr>
</tbody>
</table>

*Status = description of whether task was used in experimental battery after piloting study*
2.4.2.3 *EF Scale for Early Childhood: Cognitive Flexibility*

The DCCS was included in the current battery as a measure of cognitive flexibility. Two target pictures are presented that vary in two dimensions (shape and colour). Participants were asked to match a series of test pictures to the target pictures, first according to one dimension (e.g., colour) and then, after a number of trials, has to switch to new sorting rules (e.g., shape). “Switch” trials require the participant to change the dimension that is matched. The adult version of this task has been shown to be sensitive to silent infarcts of the frontal lobes in older children and adults (DeBaun et al., 1998; Jeffrey Schatz et al., 2001). One study, using near infra-red spectroscopy in children without SCA, found that both three year olds and five year olds who were able to flexibly change between rules, showed an increase in oxygenated haemoglobin in the ventrolateral PFC, whilst three year olds who failed to switch between rules, did not show this response (Moriguchi & Hiraki, 2009). Initially, this task was used in its computerized format as part of the NIH toolbox battery but it was found that the younger children had difficulty staying on task and the tabletop task version was used in its stead (Carlson &
The child is required to take the card and to put it in the correct box. This more interactive format leads to more successful task completion rate. Deficits in cognitive flexibility or ‘switching’ have been found in older children and adults with SCA (Brown et al., 2000; DeBaun et al., 1998; Watkins et al., 1998).

2.4.3 Design and development of ERP paradigm: Attentional Control

2.4.3.1 Background
An ERP task was designed in order to investigate whether children with SCA showed neurophysiological differences on a measure of auditory EF.

2.4.3.1.1 An Introduction to the Event-Related Potential
Electroencephalography (EEG) is the measurement of continuous electrical activity in the brain. An event-related potential (ERP) is a voltage change that is time-locked to a specific stimulus (Taylor & Baldeweg, 2002) and is acquired by averaging multiple trials so that the EEG signal of interest can be isolated from other brain activity (Luck, 2005). ERP components are averaged waveforms that have been attributed to a certain cognitive or sensory process and researchers are often interested in the information that the amplitude and latency of a component relays. ERP methodology is a useful neuroimaging tool for application in young children as it allows for some movement and can be applied in a child-friendly way, making it more feasible than other methods such as functional magnetic resonance imaging (de Haan, 2007).

2.4.3.1.2 ERP studies of executive functioning in Sickle Cell Disease
ERP methods have been widely used to investigate the development of executive skills in typically developing children and children with executive dysfunction (de Sonneville et al., 2011; Mikkola et al., 2007; Myatchin et al., 2009; Overtoom et al., 1998; Salmond et al., 2007; Stevens et al., 2006). Only two published studies have previously used ERPs to look at EF in older children with SCD (Colombatti et al., 2014; Hogan, Vargha-Khadem, et al., 2006). Hogan et al., (2006) looked at ERP components related to
performance monitoring in children between the ages of 11 and 23 and found that children with SCA showed some electrophysiological evidence for executive deficits even in the absence of stroke. Colombatti and colleagues investigated the P300 in 12 children with SCD (ages 6 to 15) and found that two patients did not evidence the P300 response and that the response was more protracted in the frontal areas and more variable than in comparison children, with differences in the cortical sources (Colombatti et al., 2015). The current study focused on components related to attentional control, as this domain is thought to both develop at a faster rate and to influence the development of other executive domains, including performance monitoring (Anderson, 2002). Thus, it is particularly suitable to study in younger children.

2.4.3.1.3 Previous ERP investigations of Selective Auditory Attention in Preschool Children

In 1973, Steven Hillyard first identified the ERP index of selective auditory attention in adults, who typically show an early positivity (P1) followed by a negative component (N1) at approximately 100ms (Hillyard & Kutas, 1983). He found that adults showed greater amplitudes in response to attended versus unattended stimuli. This “attention effect” is also present in children; however, the underlying component differs in terms of morphology, amplitude, and latency. In children, a broad positivity is seen at about 100ms and can extend to approximately 300ms depending on the developmental stage (Sanders et al., 2006). Children as young as three years old can successfully attend to one of two simultaneously presented auditory streams, when provided with sufficient cues (Sanders et al., 2006). ERP studies using binaural attention tasks have shown that preschool-age children with language impairments, dyslexia, and poor socio-environmental backgrounds show deficits in the selective attention process (Stevens et al., 2009; Stevens et al., 2006). These deficits are either due to a reduced ability to filter irrelevant information or “probes” in the unattended channel (Stevens et al., 2009) or a reduced amplification of the neural response to probes in the attended channel (Stevens et al., 2006). Information on what aspect of the
selective attention process is delayed can be invaluable in terms of improving school readiness and providing more focused interventions.

2.4.3.2 Methodological Considerations
There are several methodological considerations to be cognizant of when designing, analyzing, and interpreting an ERP experiment for young children (DeBoer, Scott, Nelson, & de Haan, 2007; Taylor & Baldeweg, 2002). This amplifies the importance of having well-crafted ERP paradigms that ask specific questions and build upon established research.

2.4.3.2.1 Design Issues
One issue concerning the design of an experimental paradigm is for it to be sufficiently engaging in order to retain a young child’s attention, but still rigorous enough to measure the construct of interest (DeBoer, Scott, Nelson, & de Haan, 2007). A second design challenge is to strike a balance between conducting enough trials to get enough clean and analyzable data and not losing a child’s interest if the experiment is too long. Pre-school children have relatively short attention spans and are not typically used to sitting quietly for long periods of time; this is specific concern for the present study, where children with SCA were hypothesized to have poor attention. A third challenge during the design process is to devise an experiment that does not rely on language and motor skills. This is particularly pertinent to pre-school age children as a button-press response task may not be truly reflective of their performance if reliant on motor processing, and a task that contains dense language may cause a young child to lose interest if they cannot follow the story or instructions.

2.4.3.2.2 Analysis and Interpretation Issues
ERP data tends to be ‘noisier’ in younger populations, due to increased movement, decreased trials, and changes in underlying substrates. There is no general consensus on data reduction or analysis methods in ERP studies so researchers must follow best practice guidelines and published research during their analysis (DeBoer, Scott, Nelson, & de Haan, 2007). ERP components in young children are not as clearly identifiable as adult ERP
components and there is a greater degree of variability within and between participants, which places more emphasis on maximising the signal-to-noise ratio during data collection (DeBoer et al., 2007).

The researcher must also be aware that the relationship between ERP components and behaviour is associative and not causal (Hood, 2001) and so caution must be taken in the interpretation of apparent relations. A second interpretative issue is the rate of developmental change in this age period. There are many underlying neurobiological changes in the early years, including changes in synaptic density and myelination, that may affect amplitudes and latencies (Casey et al., 2005; Lenroot & Giedd, 2006). It has been recommended that age ranges are kept as narrow as possible to reduce the impact of these developmental processes on data interpretation (Taylor & Baldeweg, 2002). A third issue lies in the current knowledge gaps in this relatively new area that is described as developmental neurophysiology. These gaps concern how neurophysiologic activity in a young child’s brain propagates to the scalp (where the data is acquired), how functional networks develop, and precise developmental trajectories of specific ERPs (DeBoer et al., 2007).

2.4.3.2.3 Choosing an ERP Paradigm

An appropriate binaural attention task design was chosen and developed based on four main criteria. A task to investigate the neural correlates of selective attention was chosen that required:

- Low receptive language demands
- No motor demands
- Relatively short and interactive
- Previously successfully applied with preschool-age children

The current task design was chosen, as it is more appropriate for application in young children than alternative tasks such as the classical auditory oddball paradigm and it required more executive control of attention. It was developed based on similar paradigms that have been successfully
implemented with children from three years (Sanders et al., 2006; Stevens et al., 2009). Studies have also shown that interventions can improve the neurophysiological response (Darves et al., 2005) and the neurophysiological response has also been associated with other executive measures in children (Lackner, Santesso, Dywan, Wade, & Segalowitz, 2013). These characteristics and evidence base means that the chosen paradigm fit the criteria required for investigating attention deficits in young children with SCA but that it also offers the opportunity to investigate brain-behaviour relations and a potential means to measure impact of future interventions if deficits were found.

2.4.3.3 Design and development of ERP paradigm

2.4.3.3.1 Age-appropriate parameters

In accordance with previous modifications applied to make this task more age-appropriate (Sanders et al., 2006), several measures were taken to assist children in understanding the task and allocating their attention. This included:

- The design of a training and practice phase
- The creation of custom static low-detail visual cues for on-screen presentation to match to story to be attended
- The inclusion of arrows on screen to help child attend to the correct ear and reduce memory load
- The adaption of stories so that the language was more age and content appropriate
- The recording of all stories in a male and a female voice so that the child was always attending to a male and a female voice concurrently, further helping them to differentiate between the two auditory streams and attend to the required one

2.4.3.3.2 Stimulus design

Stories: Fifteen short stories from Aesop’s classical fables (www.librivox.org) were edited to make the language and content more appropriate for younger children and were re-recorded in both a male and female voice. The sound recordings were edited using a program called Audacity
(http://audacity.sourceforge.net) to remove gaps longer than 100 ms and to compress the files in order to make them comparable in terms of loudness. During the recording sessions, the narrators were instructed to keep their tone and pitch at a consistent level throughout each story. These steps were taken to ensure that some stories were not more appealing than others and so that they only differed in timbre. Each story was up to one minute in duration.

Probes: Pure tone burst of white noise with a length of 500ms were randomly inserted into the attended and unattended streams and were the same loudness as the story being attended. The inter-stimulus-interval was 1.5 seconds to ensure no overlap between trials.

On-screen images and arrows: Images on the screen corresponded with the story that the child was instructed to listen to with an arrow that pointed in the direction of the channel that they should have been tuning in to. Custom images were generated using a drawing application to match each story.

2.4.3.3.3 Stimulus presentation
Stimuli were presented through age-appropriate adjustable headphones. Tests showed that the headphones did not induce electrical artefacts above background noise. The auditory and visual task stimuli were presented using a script programmed via Matlab 2012 R2012b (The MathWorks, MA) using Psychtoolbox V3 (Kleiner et al., 2007). Stimuli were presented on a Dell Optiplex (Dell Inc., TX) computer screen running Windows XP. Auditory stimuli were transmitted via a Creative Sound Blaster Express sound card with a low latency driver. The offset latency for auditory stimuli was measured to be 23ms on average using an EGI latency-testing device.

2.4.3.3.4 Recording and Set-up
The EEG session took place in the London Babylab at the Wolfson Assessment Centre, UCL Institute of Child Health. Data was obtained and recorded using NetStation V4.1.2 (Electrical Geodesics Inc., OR) on Mac OS 10.3.9 software. A NetAmps 200 amplifier and HydroCel Geodesic Sensor Nets were used (Electrical Geodesics Inc., OR). These sensor nets provide advantages over alternative sensor net models, as they do not require
washing the child's hair afterwards or scalp abrasion so the process is less invasive and they are quicker to apply (Johnson et al., 2001). Sensor nets were prepared in saline solution in accordance with the Electrical Geodesics instructed method. EEG was recorded from 128 electrodes and digitized at 250 Hz with a bandwidth of 0.1-100 Hz. The vertex electrode (Cz) was used as an online reference (data were later re-referenced offline using an average reference). The amplifier was calibrated and impedances were measured in each session. Channels with impedances greater than 50kΩ were adjusted where necessary and appropriate to levels below 50kΩ. In young children, a balance needs to be maintained by the researcher between acquiring good impedances across the scalp (by using a pipette with potassium-chloride solution or moving hair out of way) and sustaining the compliance of a child who may grow frustrated during an extended period of preparation time. An electro-oculogram was recorded for the detection of eye-related artefacts during the analysis stage.

2.4.3.4 Task Protocol

The full session, including net preparation, typically lasted thirty minutes. The head circumference for each participant was measured in order to choose an appropriately sized sensor net. Measures were taken with the child to allow them to become comfortable with the apparatus. The researcher allowed the child to feel the net and also measured the parent’s or guardian’s head to see who had the biggest head. Other measures included getting a parent to try on a larger net if the child showed hesitance in terms of wearing this ‘strange hat.’ The sensor nets were soaked for approximately ten minutes in a saturated potassium-chloride solution. The child was sat on a comfortable seat behind a divider (to minimize distractions) and the parent typically left the room during the session to minimize noise in the data collected. Lights were dimmed and the blind and room door were closed. The child watched a cartoon as the electrodes were being correctly positioned and impedances were obtained. This was followed by a training session where the researcher
interacted with the participant in order to gauge their understanding of ‘Left’ and ‘Right.’ An arrow sign was used and the child was instructed to touch the ear that corresponds with the side that the arrow was pointing towards (an understanding of direction is not necessary as long as the child understands that they are to listen to the ear that the arrow points towards).

After the initial training phase, the child undertook a practice session with two popular nursery rhymes and the researcher asked him or her questions about the song that they were cued to listen to. Once the researcher was satisfied that the child understood the rules, the testing session began. Participants were cued to selectively attend to one of two simultaneously presented stories that differed in location (left/right), voice (male/female), and content. There were up to 14 story blocks. At the beginning of each story the child heard “Are you ready?” and the researcher pressed a key for the session to proceed. After each story the child was asked questions relating to the attended story. Once the researcher had established whether the child was attending to the correct story, a button was pressed and the task was continued. The researcher noted story answers and bad trials (e.g. observed excessive movement, removal of headphones/sensor net) on a response sheet. If the child expressed a request to end the testing session after a period of time, the researcher asked if they would like to do one more story and then terminated session if the child did not agree.

2.4.3.5 ERP Processing Pipeline

2.4.3.5.1 Pre-processing steps
The EEG recordings were exported from Netstation for processing and analysis in EEGLAB (Delorme & Makeig, 2004). “Bad” story trials (where the child was not participating in the task, was moving excessively, or was attending to incorrect side) were manually removed.

2.4.3.5.2 Filtering
Filtering is applied to reduce the level of noise in an EEG signal. The EEG was digitally filtered with finite impulse response (FIR) filters rather than infinite impulse response (IIR) filters due to FIR being more typically applied in
the literature as they are considered to have more phase stability, thus not altering the signal. Data was filtered at a high-pass frequency of 0.1Hz and a low-pass frequency of 30Hz in EEGLAB 11.0.3 (Delorme et al., 2011).

2.4.3.5.3 Epoching
The EEG signal was epoched at 200 milliseconds before the stimulus event (allowing for a 200 millisecond baseline) to 600 milliseconds after for a total trial segment of 800ms.

2.4.3.5.4 Threshold Rejection
Threshold rejection was set so that automatic epoch rejection of bad epochs occurred at plus or minus 100 microvolts.

2.4.3.5.5 Baseline Correction
The data were baseline corrected to remove noise from the segments that was unrelated to the voltage change in response to the stimulus. The average voltage of the 200 milliseconds segment before stimulus onset was set as the baseline. This segment represents ‘zero voltage’ and is subtracted from every channel in the epoch.

2.4.3.5.6 Manual artefact rejection
Artefact is a term used in EEG research to describe unwanted noise in the EEG signal which may be caused by many sources (DeBoer et al., 2007). Visual inspection was used to remove artefacts such as eye blinks, saccades, muscle activity, and skin potentials (Luck, 2005).

2.4.3.5.7 Re-referencing
The data were re-referenced from the vertex reference to an ‘average reference’ montage. The average reference is the average voltage of all the electrodes and is preferable to the vertex reference for further processing, as the vertex reference does not have a true value of zero. The average reference is thought to be a closer approximation of zero due to the dipolar nature of neural activity (Junghöfer, Elbert, Tucker, & Braun, 1999) and is particularly recommended for studies that use high-density arrays (Junghöfer, Elbert, Leiderer, Berg, & Rockstroh, 1997).
2.4.3.5.8 Minimum Trial Criteria

It has been recommended that studies with young children should include at least ten to twenty trials per condition (DeBoer et al., 2007). The current study required a minimum of 25 trials for each condition in all datasets in order to reduce noise and to obtain a reliable estimation of the ERP component under investigation (Cuevas, Cannon, Yoo, & Fox, 2014). The child completed up to 14 sessions so children had up to 160 events (12 to 15 per story session) before processing. Children were reminded to fixate on the screen and to sit still between each story in order to maximize the number of artefact-free trials and were offered a teddy bear to hold “so he could also watch the images appearing on the screen’ if they struggled to stop movement.

2.4.3.5.9 Averaging

The trials were averaged together to acquire a single averaged segment for the *ignore* and *attend* condition for each participant.

2.4.3.5.10 Channel Groupings

For further improvement of signal-to-noise ratio, several channels were combined for channel-level analyses based on previous reports (Coch, Sanders, & Neville, 2005; Sanders & Zobel, 2012; Strait, Slater, Abecassis, & Kraus, 2014). Electrode groupings were based on research into relevant studies looking at similar constructs and age ranges (see figure 2.7).
Figure 2.7 The Geodesic Sensor Net 128 channel layout in accordance to the 10-20 system of electrode placement. The four channel cluster sites are located over the mid frontal, left frontal, right frontal, and central sites and are illustrated in black, green, orange, and purple respectively. Channel selection was based on previous research using similar age range and paradigm (Sanders & Zobel, 2012).

2.4.3.5.11 Time Window
The time window of interest (100 to 300 milliseconds) was chosen based on a review of the relevant literature for this age range in similar tasks (Sanders et al., 2006; Sanders & Zobel, 2012; Stevens et al., 2009) and examination of the current data.
2.4.3.5.12  Grand averaging

The averages of each condition for both the patient and the comparison groups were analyzed. Grand averages were also computed for three year olds, four year olds, and five year olds separately in order to ensure that the expected developmental trends were observed.

Figure 2.8 The ERP paradigm and example of physical set-up. Ethical consent for use of photos in thesis was obtained.
2.4.3.6 Pilot Studies
The ERP paradigm and processing pipeline was piloted with 10 adults and two preschool children in order to ensure that the stimuli scripts were working correctly and that the data obtained was showing the expected ERP component (P-N-P response for adults and early frontal positivity for children). The pilot studies also allowed for further developments in term of child-friendliness and ease-of-use with the researcher before being administered to children in phase one of data collection. Further practical modifications, such as the addition of child-friendly headphones and the use of a teddy bear to be held to limit movement and fussiness were also made (see figure 3.5).

2.4.4 Design, Development and Piloting of Behavioural Tasks
Where no existing tasks were available, the researcher developed or adapted existing measures based on the current literature. The following tasks were developed as part of phase one in order to measure different aspects of EF in preschool-age children.

2.4.3.7 Doggie Deletion Task for Preschoolers (DDTP): Attention Control and Processing Speed

2.4.3.7.1 Task Development
Cancellation tasks have been used with older children with SCA to show improvements in poor attention and processing speed post-intervention (Marshall et al., 2009). The following task was developed based on a task used to measure attention in preschool-age children (Corkum et al., 1995). The researcher contacted the original authors in April 2013 for information on their task design and was encouraged to develop the task further in order to create a version that could be successfully applied across the preschool age range. The task was developed and piloted with phase one participants. Custom dog stimuli were designed to vary only in position. The child undergoes a teaching phase and a practice phase with shapes before the testing phase. This is to ensure that they can hold and use the bingo stamper.
successfully and can understand the task instructions. The aim is to stamp the target stimuli as cued by the image on the top of the page. The original design of the task was not suited to typically developing 3 year-old pilot children. The task was also modified so that the examiner could cue if a child remained off-task for greater than a 20 second block and terminate the task if a child remained off-task for greater than a 20 second block on a second occasion. Omission/commission errors and time to completion or termination are coded. A motor phase at the end of the task, requires children to stamp every stimulus on the presented page, and is used to control for motor speed. The task instructions are attached in appendix 4.

2.4.3.7.2 Design
Training phase: The preschooler is taught to identify the target pictures and to use a washable, self-inking bingo stamper to mark each target (in a 2 × 6 array).
Practice phase: This is continued until the preschooler accurately identifies all targets and makes no errors of commission. This phase consists of two pages upon which the target ([30]: triangle) and distracter ([90]: circle, square, diamond, and octagon) are arranged in a 10 × 6 array. After successful completion of the training phase, the child can continue onto the test phase.
Test Phase: This contains 8 pages; each page consisted of a 10 × 6 array of targets (N=120 standing dogs) and distracters (N=360 four identical dogs varying in position only). The target picture is located at the top and centre of each page for the child’s reference. The pictures are randomly organized on each page, with 15 targets and 45 distracters in each array.
Motor Speed Phase: This phase is to be administered last. The child is asked to start at the top left side dog and to stamp all the dogs until the end, going as fast as they possibly can.
Figure 2.9 Participant completing the DDTP task with bingo stamper. Ethical consent for use of photos in thesis was obtained.

2.4.3.7.3 Administration and Scoring
Please see appendix 4 for administration instructions developed for this task. The amount of omissions, commissions, and time to completion should be coded for each phase along with whether cues were offered or not during the testing phase. The motor phase time is also coded.

In cases where a child does not complete the task to end during test phase, the examiner still codes the omissions, commissions, and time to completion but adjusts scores by dividing by number of lines and pages attempted (judging by last line stamped).

Analysis of task findings is described in the Validation chapter (Chapter 3).

2.4.3.8 Preschool Executive Task Assessment (PETA): Ecologically valid task of Executive functioning/Goal Setting

2.4.3.8.1 Task Development
This task was developed in order to obtain an ecologically valid assessment of a preschool child’s EF. An ecologically valid assessment is a task that is designed to closely resemble the demands of an everyday task and reflects real-life performance (Chan et al., 2008; Chaytor & Schmitter-Edgecombe, 2003). Two tasks were developed for this age range; the caterpillar task (initial design idea by Christine Berg, Washington University, St. Louis, USA) and the banana split task. The latter was found to be too easy for the older children
and not as rich in terms of the information that is collected relating to aspects such as self-reflection, safety, and judgment. The emphasis for this assessment is on the amount and type of support required to proceed to end of the task rather than accuracy or speed. As the caterpillar task was more informative and required fewer modifications, it was further piloted during phase one and later normed in a larger population (phase two). The task is recorded so it can be coded at a later time. The examiner delivers a pre-task questionnaire and post-task questionnaire, times task completion, and follows a set protocol with regards to administering cues. The researcher developed the manual for this task and piloted and developed procedure with children in the laboratory. This was followed by a large study based on school sites to norm and validate task further. See Section 3.4 for validation and norming data and appendix 5 for manual and score sheets.

Figure 2.10 Two potential ecological measures developed and explored at initial pilot phase

2.4.3.9 Bear & Dragon Task: Inhibition of a prepotent response

This task is analogous to the Go/No-Go paradigm as it involves suppressing or initiating an activity in response to a stimulus (Reed et al., 1984). It is has been reported to be highly correlated with parent reports and other inhibition tasks (Kochanska et al., 1996). An association has been drawn between effortful control in the bear and dragon task and adaptive functioning in preschool children (Murray & Kochanska, 2002). Research with preschool children diagnosed with ADHD found an association between ADHD, conduct
problems, and inhibition on the Bear & Dragon task (Sonuga-Barke, Dalen, Daley, & Remington, 2002).

2.4.3.9.1 Task Development
This task is similar to the well-known game of ‘Simon says.’ The child undergoes a screener with the examiner in order to determine that they understand all the instructions that bear/dragon will give. The examiner asks the child to point to a list of body parts and on successful completion; the examiner begins recording responses as the practice phase begins. The child is told to perform all actions (i.e. ‘Touch your nose!’ or ‘Touch your tummy!’) asked by the “nice” bear puppet but to ignore the directions of the “naughty” dragon puppet (figure 2.11a), in an alternating fashion. The examiner hides behind a screen. Once it is established that the child understands the rules, the testing phase begins with six inhibition (Dragon: No-go) trials and six activation (Bear: Go) trials in a predetermined order.

2.4.4.4 Circle Tracing Task: Inhibition of an on-going response
This task allows direct measurement of inhibition of an ongoing, or continuous, response (Scheres et al., 2003). It has been found that more impulsive participants find it difficult to slow down when tracing the circle for the second time (Bachorowski & Newman, 1990). It has been used with older children and adults to study the effects of ADHD (Avila, Cuenca, Félix, Parcet, & Miranda, 2004).

2.4.3.9.2 Task Development
The task had not been previously implemented with preschool-age children younger than six years. The task was adapted from previous studies (e.g. Scheres et al., 2003) with simple instruction and examiner demonstration. The task is administered under two conditions: neutral (“trace the circle with your finger like this”) and inhibition (“trace the circle again, but this time as slowly as you can”). The circle is 50.80 cm in diameter, drawn on a plastic square (child-friendly materials that can be cleaned and rolled away), and covered with clear film (see figure 2.11b). A maximum of 12 minutes is allowed for both tracing conditions. The dependent variable is ‘inhibition time’ or the time
taken to trace the circle in slow condition minus time taken to trace circle in neutral condition. A greater inhibition time indicates a greater ability to inhibit the continuous response.

![A](image1) ![B](image2)

**Figure 2.11** Pilot participant demonstrating (A) puppets from Bear & Dragon task and (B) the circle-tracing task. Ethical consent for use of photos in thesis was obtained.

### 2.4.3.10 Scrambled Boxes Task: Working memory

Working memory deficits have been identified in older children with SCA with stroke but seem to be relatively preserved in older children with no history of stroke (W. Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, Armstrong, et al., 2001). The current task aims to explore the functioning of working memory in preschool-age children with SCA for the first time.

#### 2.4.3.10.1 Task Development

This visual working memory task was adapted from previous studies that investigated working memory in preschool-age children (Griffith, Pennington, Wehner, & Rogers, 1999). Boxes are scrambled according to a predetermined protocol during a ten second delay between trials while the child is distracted. A maximum of 20 trials are administered, until the child finds all of the toys or makes five consecutive errors. Initially, the task was piloted with 6 boxes but it
was found that a substantial minority of the children (5/13) were successfully obtaining all of the toys in the lowest amount of ‘gos’ so 3 more boxes were added to make a total of 9 boxes (ceiling effects were not seen for the remaining pilots; N=7). The increased number of boxes increases the amount of information retained in working memory and thus makes the task more challenging for the older children where ceiling effects were observed with six boxes. Figure 2.12 shows the six-box version of the task being completed by a child in phase one.

Figure 2.12 Scrambled boxes task. Ethical consent for use of photos in thesis was obtained.

Analysis of task findings is described in the Validation chapter (Chapter 3).

2.4.5 Additional measures applied with children with sickle cell anaemia

A combination of direct medical measures and medical chart review were used to investigate relevant disease factors.

2.4.4 Medical measures

2.4.4.1 Medical Measures collected on day of assessment

In the patient population, daytime oxygen saturation (SpO₂), haemoglobin concentrations (SpHb), pulse rate (PR), and perfusion index (PI) were measured non-invasively for two minutes on the right middle finger using a
pulse oximeter (Masimo Pronto 7). End-tidal carbon dioxide (EtCO$_2$) was measured non-invasively for two minutes using a capnograph monitor with a small tube close to the nose while the child watched a short video (figure 2.13).

**Figure 2.13** EtCO$_2$ readings being taken as child observes video on screen

2.4.4.2 **Medical Chart Review**

Transcranial Doppler (TCD) velocities, number of hospital admissions in past year, and other medical history events associated with disease severity were reviewed for each patient at the Royal London Hospital after consent was received on the day of their testing session. Any available polysomnography data from available infant sleep studies was also reviewed.

2.4.5 **Procedure**

The whole testing session typically lasted for one morning or afternoon, lasting up to four hours, with breaks. The order of administration of tasks by the researcher can be seen in figure 2.14.
2.4.6 Statistical Analysis

2.4.6.1 General Approach

Statistical analyses were conducted using SPSS for Mac version 21.0. Details for the statistical techniques employed are outlined in each chapter.
2.4.6.2 Power Calculation

The Power and Sample Size Calculation (PS) software was used to estimate the sample size required for Phase three in consultation with Deborah Ridout from the Statistical Support team at UCL Institute of Child Health (Dupont & Plummer, 1990). A study with 22 patients and 22 controls was planned. The sample size estimation was based on a similar study that used executive measures with young children with sleep disordered breathing as there have been no studies that have looked at EF in patients with SCA in this age range with a control group and it was expected that similar EF difficulties will be observed in otherwise typically developing preschool children with SCA (Hill et al., 2006). In a previous study the response for processing speed (17 mild SDB, 14 controls) and the general EF (21 mild SDB, 17 controls) on the BRIEF-P within each subject group (aged 3 to 7 years old) was normally distributed with a standard deviation of 14 and 13, respectively. If the true difference in the experimental and control means was 11.3 and 16 respectively, I would have been able to accept or reject the null hypothesis that the population means of the experimental and control groups were equal with power between .80 and .98 (80 to 98%) on the executive measures of interest. The Type I error probability, $\alpha$, associated with this test of the null hypothesis was 0.05.

2.4.6.3 Missing Data

As is the nature of testing with young children, clinical populations, and mixed methods, some children did not complete all measures. Reasons for non-completion of full battery of tasks were typically due to technical errors, time restrictions or non-compliance in the case of the ERP task. Reasons for missing data are described in each section.

2.4.7 Thesis Population Description

This section provides a summary of the participants recruited and assessed at the London Babylab during this thesis. Over 190 children were recruited and assessed by the researcher as part of this thesis. All of the patients were assessed at the London Babylab. However, only 41 of the typically developing
children were assessed at the London Babylab (as part of phase one and three) while the rest were assessed on school sites (phase two). The Validation Chapter includes typically developing children from phase one, two, and three. The General Functioning and EF Chapters include the patients with sickle cell anaemia and typically developing ethnicity-matched control children (Black British) from phase two and phase three. The Predictors Chapter includes the patients from phase three only. The Neurophysiological Chapter includes the patients and typically developing children from phase one and phase three.

2.4.8 Demographic and Descriptive measures

Parents reported general information, such as age, ethnicity, additional languages and handedness, at the start of the testing session. Children with SCA have been described as being at a “double disadvantage” (Hijmans, Grootenhuis, et al., 2011). Many children with SCA in Europe come from families who have recently immigrated and have a lower socio-economic status, which highlights the importance of employing matched control groups. Socio-economic status was based on postcode to estimate total weekly house income on a scale from one (up to £520) to five (over £791). Office for National Statistic website data was used to analyse SES (e.g. Nation, Cocksey, Taylor, & Bishop, 2010). Parents provided information on the highest level of maternal education. Information for IQ and other domains of interest was collected on the assessment day. The relevant demographic and descriptive data are presented for each group in the respective chapters. Additional information for the patient population of children with SCD presented in this thesis, including the incidence of patients with disease-related complications, is described in Table 2.6 and Table 2.7.
Table 2.6. Summary of descriptive data for patients recruited and assessed during this thesis work

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total Number of Patients tested</td>
<td>25*</td>
</tr>
<tr>
<td>Genotype</td>
<td>24 HbSS; 1 HbSC**</td>
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<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Second Language</td>
<td></td>
</tr>
<tr>
<td>Can understand some or few spoken words:</td>
<td></td>
</tr>
<tr>
<td>Nigerian</td>
<td>2</td>
</tr>
<tr>
<td>Ghanian</td>
<td>1</td>
</tr>
<tr>
<td>French</td>
<td>1</td>
</tr>
<tr>
<td>Ethnic Origin</td>
<td>All Black British</td>
</tr>
</tbody>
</table>

African Heritage (Parents mostly identified as from Nigeria, Ghanian, Congo, Angola)

Patient Current Pain Rating (n=12)***

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<tbody>
<tr>
<td>Some pain</td>
<td>9</td>
</tr>
<tr>
<td>Highest level of mother’s education</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Postgraduate</td>
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</tr>
<tr>
<td>Undergraduate</td>
<td>9</td>
</tr>
<tr>
<td>Secondary School</td>
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</tr>
<tr>
<td>No information</td>
<td>2</td>
</tr>
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</table>

<table>
<thead>
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<td>£591-670</td>
<td>9</td>
</tr>
<tr>
<td>£521-£590</td>
<td>5</td>
</tr>
<tr>
<td>up to £520</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th>Mean Haemoglobin****</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Range</td>
<td>6.4-13</td>
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### Table

<table>
<thead>
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<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
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<td>3.05-5.91</td>
</tr>
<tr>
<td>Birth weight (Kg; n=10)</td>
<td>3.29</td>
<td>2.3-3.91</td>
</tr>
<tr>
<td>Number of hospitalizations in previous year</td>
<td>1</td>
<td>0-4</td>
</tr>
</tbody>
</table>

*Mean Haemoglobin****
<table>
<thead>
<tr>
<th></th>
<th>Mean SpO₂</th>
<th>Mean CO₂</th>
<th>Mean Tamm (max TCD velocity at most recent hospital visit)</th>
<th>Sleep Composite Score</th>
<th>FES Summary Score (n=24)</th>
<th>BRIEF GEC</th>
<th>WPPSI Full Scale IQ</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>97.1</td>
<td>37.4</td>
<td>155</td>
<td>21.6</td>
<td>114</td>
<td>53.2</td>
<td>98.8</td>
<td>99.7</td>
<td>98</td>
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<td></td>
<td>91-99</td>
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<td>120-216</td>
<td>5-47</td>
<td>68-173</td>
<td>36-78</td>
<td>81-116</td>
<td>78-133</td>
<td>79-128</td>
</tr>
</tbody>
</table>

*Including child with diagnosis of specific language impairment who was not included in analysis **Child with HbSC trait was included in neurophysiological chapter only to increase power ***Pain rating scale was discontinued to lack of understanding in younger children ****Measure taken on day used if recent clinical reading (<3 months) not available
Table 2.7. Incidence of illness-related factors reported for 22 SCA patients recruited and assessed during this thesis work

<table>
<thead>
<tr>
<th>Illness-related factors</th>
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</thead>
<tbody>
<tr>
<td>Dactylitis</td>
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<tr>
<td>Splenic Sequestration</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Splenomegaly</td>
<td>1</td>
</tr>
<tr>
<td>Aplastic Crisis</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Adenotonsillectomy</td>
<td>2</td>
</tr>
<tr>
<td>Regular Transfusion Treatment</td>
<td>5</td>
</tr>
<tr>
<td>Iron Chelation</td>
<td>1</td>
</tr>
<tr>
<td>Hydroxyurea Treatment</td>
<td>4</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>0</td>
</tr>
<tr>
<td>Other disorder</td>
<td>1 *</td>
</tr>
</tbody>
</table>

*This child was recently diagnosed with Specific Language Impairment and excluded from study analyses
Chapter 3: Validation

The development and validation of measures of executive functioning for three to five year olds
3 Validation

3.1 General Introduction
Executive functioning (EF) domains have been described as attention, inhibition, self-regulation, working memory, cognitive flexibility, planning, organization, problem-solving, and performance-monitoring skills (Anderson et al., 2008). Confirmatory factor analysis studies have reported that executive functions may have more of a unified structure in the early years (Hughes & Ensor, 2009) with some researchers suggesting that certain EF domains, like working memory, may develop earlier than others (Garon et al., 2008). Recent research has disproven the notion that executive skills are not measurable, or indeed informative, in the early years (Diamond, 1990). Performance on executive tasks in infancy and the early preschool years has been shown to be predictive of future EF (Cuevas et al., 2012; Kraybill & Bell, 2012; Nakagawa & Sukigara, 2013). In comparison to IQ, executive skills show more potential for malleability with intervention (Diamond & Lee, 2011) and can provide an important protective factor for children who have deficits in other areas (Greenberg, 2006). Executive skills are a good indicator for school readiness and academic achievement, which emphasizes the importance of having a variety of measures for the holistic assessment of EF in pre-school aged children (Blair & Razza, 2007).

3.1.1 Measuring executive functioning in the preschool years
In order to understand the structure of EF in the early years and the foundation it lays for the years to come, it is imperative that we develop appropriate and robust ways of assessing these skills. The preschool years pose a particularly demanding challenge for researchers due to the rapid development of executive skills from three to five years (Espy et al., 1999). The variable nature of constructs such as attention in the preschool years makes for poor reliability across different measures (Anderson, 2002; Mahone, 2005). Task instructions used for older children can be too linguistically demanding, which is why most behavioural measures of EF are
standardized for use with children over five years (Delis, Kramer, Kaplan, & Holdnack, 2004; Visu-Petra, Benga, & Miclea, 2007).

Valid assessment of executive skills can be achieved using performance-based assessments in this age range as long as appropriate vigilance is used in the design and development process (Mahone, 2005). There has been a growing interest in preschool executive skills over the past decade, with both new tasks being developed and tasks from other age ranges being modified to be more age appropriate to account for shorter attention spans, as well as less language and lower motor fluency (Garon et al., 2008). Important design characteristics need to be considered when developing or adapting measures for ease of use with preschool children. These include response modality, language requirements, length of task, ease of use, and novelty (Isquith et al., 2005). To date, most tasks have not been well documented so replications are inconsistent, making it difficult to build upon existing research (Carlson, 2005).

3.2 Validation Aims
The lack of research in preschool assessment presents a real problem for clinicians who want to characterise executive deficits in order to determine whether early interventions can prevent later difficulties. This chapter aims to contribute to current research by validating tasks that have been developed based on previous research. The Preschool Executive Task Assessment (PETA), an ecologically valid measure of EF, the Doggie Deletion Task for preschoolers (DDTP), a measurement of attention control and processing speed, the Scrambled Memory task, an assessment of working memory, and two inhibitory control tasks, the Circle Tracing task and the Bear & Dragon task, are compared with standardised measures in order to establish their validity as preschool tasks of EF.
3.3 Validation Methodology

There is some overlap between the following sections in terms of the population and the standardized measures used for the validation of each task. A general overview of the overall population and the standardized measures typically used in the validation process are described below.

3.3.1 Participants

In total, 40 typically developing children (mean age = 4.4 years, SD = .92; mean IQ = 109, SD = 13.5) were tested by the researcher at the London Babylab during phase one and phase three, and the researcher recruited and assessed a further 139 children (mean age = 4.5 years, SD = .79; mean IQ = 101, SD = 16.7) on school sites for the validation and norming of the PETA in phase two (3.4). The inclusionary criterion was that the child was aged between 36 and 60 months and the exclusionary criteria included a history of a developmental, a psychiatric, or a neurological disorder, as well as English as a second language.

Information on age, ethnicity, and gender was collected for every child from parents. IQ was obtained for every child using the WPPSI-III-UK (Wechsler et al., 2002). Socio-economic status was based on the provided home postcode to estimate total house income on a scale from the UK Office for National Statistics for children attending the London Babylab, while school postcode was used for children assessed on school sites (Nation, Cocksey, Taylor, & Bishop, 2010).

All of the children did not complete all of the tasks that were validated in the current chapter. Some of the tasks from phase one were discontinued for phase three and some of the tasks were developed or altered during phase one, so that all children did not complete the final version of the task. Population descriptions for each task being validated in this chapter are described in further detail in the individual sections.
3.3.2 Standardised Measures

3.3.2.1 BRIEF-Preschool
The BRIEF-Preschool (Gioia et al., 2003) or BRIEF-P is sensitive to atypical variations in EF development (Isquith et al., 2005). It is the most commonly used screener questionnaire for executive dysfunction. It consists of 63 items relevant to a preschool-age child’s everyday EF. It is comprised of five subscales (Inhibit, Shift, Working Memory, Plan/Organize, and Emotional Control) that create three broader indexes (Flexibility, Emergent Metacognition, and Inhibitory Self-Control) and an overall summary score (General Executive Composite). Higher scores indicate poorer EF (mean=50; SD=10).

3.3.2.2 Children's Behaviour Questionnaire-short
The Children’s Behaviour Questionnaire-short (Putnam & Rothbart, 2006) or CBQ is frequently used to look at temperament in 3-7 year olds. Deficits in EF, particularly the reduced ability to inhibit a dominant action, are a risk factor for behavioural problems (Utendale & Hastings, 2011). Children with poorer self-regulation are hypothesized to have lower scores on the inhibitory control (mean score= 4.71, SD=0.92) and attention domains (mean score =4.92, SD=.081).

3.3.2.3 WPPSI-III-UK
The WPPSI-III-UK (Wechsler, 2002) is a standardized and well-established IQ measure used to control for performance IQ (PIQ) and verbal IQ (VIQ). For three year olds, the full WPPSI form was administered but for four and five year olds, two verbal subtests (Information and Vocabulary) and two performance subtests (Block Design and Matrix Reasoning) were used to prorate PIQ and VIQ.

3.3.2.4 NIH Toolbox task of Inhibitory Control and Attention
This NIH Toolbox task (Gershon et al., 2010) is a computerised measure based on the classical Flanker task that is standardised for three years and
upwards. Children have to press the arrow button that is pointed in the same direction as the on-screen stimulus.

3.3.2.5 NIH Toolbox task of Processing Speed
In the NIH toolbox task of processing speed (Carlozzi et al., 2013), the child is instructed to choose a smiley face as quickly as they can when two pictures are the same and a sad face when two pictures differ. The dependent variable is a summary of correct answers (of a possible 104) that a child completes in 90 seconds. Higher scores indicate better attention control (mean standardised score =100, SD=15).

3.4 Validation and Norming of the Preschool Executive Task Assessment (PETA): An Ecologically Valid Task of Executive Functioning

3.4.1 Abstract
In order to investigate the development of EF in young children in a meaningful way, it is important to look at how they perform in a situation that mirrors an everyday task. In this section I introduce the Preschool Executive Task Assessment (PETA), which aims to assess executive skills on a more ecologically valid level than tasks typically used in this age range, as well as providing a comprehensive way to measure executive skills in pre-school age children. It investigates a child’s ability to maintain attention, follow through on tasks, and remember instructions. It reflects real-life situations that a child may encounter at home with a guardian or at school with a teacher. Successful completion of this task involves the integration of several executive skills. Healthy three to five year old children (N=166) were recruited and assessed in London nursery and school settings as well as the UCL London Babylab. VIQ and PIQ as well as parent and teacher reports of EF were collected. A subgroup of children also completed the NIH Toolbox Inhibitory Control and Attention Task. Encouragingly, task performance improved significantly with age and was related to proxy-reports of EF and behavioural performance on the NIH Toolbox task. It is concluded that the
PETA can successfully be used to measure EF in an ecologically valid way in children from 36 to 60 months.

3.4.2 Introduction

3.4.2.1 Developing an ecologically-valid measure of executive functioning

Preschool assessments that rely solely on summary scores to indicate performance levels are considered to be questionable as an accurate indicator of cognitive abilities in this age group (Carlson, 2005). Whether specific executive skills are already established in preschoolers or emerge from a more undifferentiated system with development is still debated. Some have proposed that distinct executive skills are measurable in preschoolers while others have found evidence for a unitary construct that becomes more differentiated over time (Senn, Espy, & Kaufmann, 2004; Wiebe et al., 2011). Thus, in addition to summary scores, it is important to assess the differentiation of these skills over the preschool period.

It has been suggested that ecologically valid measures which adopt a micro-analytic approach incorporating quantitative and qualitative scoring systems would better represent specific skills developing at various rates than tasks that tap specific EF skills (Pritchard & Woodward, 2011). Ecological validity is the extent to which performance on a cognitive task reflects real-life performance and can be measured by a task’s verisimilitude and veridicality (Chaytor & Schmitter-Edgecombe, 2003). Verisimilitude concerns the similarity between a task’s cognitive demands and the participants’ everyday task demands, while veridicality is the strength of association between task performance and measures of everyday functioning.

Ecologically valid measures that reflect real-life tasks are important and necessary to inform both the cognitive and behavioural implications of executive difficulties in daily life (P. Anderson, 2002). Many clinical tests are a
good indicator of how a child is struggling with a specific skill but this does not inform their guardians or teachers of how much support they need when participating in a typical activity. Tasks in everyday life require the integration of executive functions, unlike the artificial separation of cognitive domains that often occurs in neurocognitive assessments. Thus, assessments that closely resemble everyday life should be an important part of neurocognitive testing (Chan et al., 2008).

The Children's Kitchen Task Assessment (CKTA) is a task that aims to detect executive dysfunction in eight to 12 year olds during the performance of a novel task (Rocke et al., 2008). The task is novel in the sense that the child would not have completed this specific task before but it is similar in concept to tasks that a child would be expected to do on an everyday basis. It is a cue-based task where children have to follow step-by-step instructions with as little help as possible. This type of task helps us to identify how much support is needed for an individual child and when this support may be needed. Using the CKTA, lower EF was found among eight to 12 year-olds with SCD, a population who are known to have deficits in EF (Berg et al., 2012).

Preschool assessments of EF often use pass/fail or summary scores of performance that cannot be considered an accurate representation of a child’s ability (Carlson, 2005). An ecologically valid task for younger children, such as a downward extension of the CKTA, would be useful for assessing executive development in preschool-age children.

There are currently no other tasks that focus on EF or self-regulation in a more general and practical sense. The Preschool Executive Task Assessment (PETA) has been developed to investigate a young child’s ability to listen, maintain attention, follow through on tasks, and remember instructions. Thus it reflects real-life situations that a child may encounter at home with a guardian or at school with a teacher. It also incorporates pre- and post-task questionnaires, which allow a child to reflect on their performance. The task was developed based on ecological assessments developed for older children.
with executive problems and adults with brain injuries (Rocke et al., 2008). It has been adapted from the CKTA so that the child is following a picture rather than a written recipe and that motor, linguistic, and hearing difficulties can be taken into consideration. The task focuses on the process rather than an end point and there is no time cut-off. In this way, the task can be successfully completed by children as young as three years. The task was designed in such a way so that all levels of functioning can be accommodated and scored, allowing for a wider range of abilities than a typical pass/fail task.

3.4.2.2 Development of the PETA

This task was developed to measure the construct of EF in an ecologically valid way (Burgess et al., 2006; Schmuckler, 2001). This emphasizes the importance of a naturalistic setting and a type of task that is typical for a pre-school child. Other task requirements during task design and development included a task that is not dependent on linguistic ability or motor speed and accuracy, and a focus on process rather than accuracy so that a young child’s executive skills could be appropriately captured. For example, the child could receive support from the examiner during steps that involve bimanual coordination such as to open the glue stick and containers and to cut the page without being penalised (Birtles et al., 2011). It is important for the task to be novel in the sense that the child will not have completed a similar task, and that it is multi-step so that the child can engage various executive skills.

The task can be scored both quantitatively and qualitatively for different dimensions of interest and is not time limited. Unlike most bottom-up tasks of EF, the PETA does not solely focus on what a child cannot do; rather the task helps to identify what they can do as well as identifying areas where they may need additional support in real-life situations. The purpose of the combined cueing system is to highlight a specific child’s strengths and weaknesses as well as creating an objective and standardised way to reflect upon where a child’s overall performance lies in comparison to their peers (see Table 3.1). A pre- and post-task questionnaire helps to gage an idea of the child’s self-awareness and judgment of their performance, giving the examiner an
opportunity to build a rapport and to ensure that the task is introduced to each child in the same way.

The PETA codes whether a child engages in self-talk. There is some evidence for a potential link between executive performance and the use of self-talk in the preschool years (Alarcón-Rubio, Sánchez-Medina, & Prieto-García, 2014; Aro, Poikkeus, Laakso, Tolvanen, & Ahonen, 2014; Fernyhough & Fradley, 2005; Winsler, Carlton, & Barry, 2000) so it is important to determine the role of self-talk in individual children when performing everyday tasks. Finally, there have been some reports on a marginal gender difference in executive tasks in preschool children (Anderson, 2002) and on the potential impact of socio-economic status (SES) on EF in this age group (Noble, Norman, & Farah, 2005; Ponitz et al., 2008; Sarsour et al., 2011), domains that should be taken into consideration when validating a new task.

Figure 3.1 Participant proudly displaying completed caterpillar at end of task. Ethical consent for photo use in thesis obtained.

3.4.2.3 Aim

The primary aim of this study is to validate the PETA, examining rater reliability, developmental changes in performance, as well as the convergent and discriminant validity of the PETA. Given that previous research using executive tasks has found gender, SES, and engagement in self-talk, to play an important role in the emergence of executive skills in the preschool years, a secondary aim of this study is to investigate the potential influence of gender, SES, and self-talk on task performance.
3.4.3 Method

3.4.3.1 Participants
Testing occurred on-site in nurseries and schools and in the London Babylab. Sixty schools and nurseries across London were contacted. Two schools and one nursery were able to participate in the study. Reasons for non-participation were typically a change of principal or classroom teacher or inability to make a sufficient time commitment. Of the three participating educational centres, one was in East London, one in Central London, and one in South London with 120, 38, and 260 children respectively registered within the age range. The two schools were mainstream state schools with both nursery and reception classes whilst the nursery was fee-paying with a free early education entitlement scheme. The study was also advertised on-line and at sites throughout London in order to recruit families to visit the London Babylab.

3.4.3.2 Measures

3.4.3.2.1 Preschool Executive Task Assessment
The PETA is an engaging tabletop task that is administered one-to-one to a child with minimal input from the examiner. The task, which can be easily assembled, involves using an 'ingredients' box with pre-prepared materials, a recipe book, a timer, cueing/scoring sheets, and a video camera (see figure 3.2). The child follows a picture recipe book step-by-step, using the supplied materials, to make the final picture. The examiner delivers a pre-task questionnaire and post-task questionnaire, times task completion, and follows a set protocol with regards to administering cues (see Table 3.1). Children receive a total weighted score (total summary score; TS) that is the combination of the amount and level of cues required to complete task, as well as completion time, highest level required during task, total number of cues required (TC), and cues required to initiate, sequence, and complete task. Qualitative scores for working memory, distractibility, organization, and emotional control are also noted by examiner at end of task as well as other qualitative scores based on task performance (see Table 3.2).
Table 3.1. Weighted cueing levels used for each step of the PETA. Each cue level is delivered twice when the participant is not following or engaged in the task. There is a 10 second delay between every cue, with the exception of cases where a child is distressed or in danger.

<table>
<thead>
<tr>
<th>Cue (Level)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cues (Level 0)</td>
<td>The participant is able to complete step without support.</td>
</tr>
<tr>
<td>General verbal cue (Level 1) x 2</td>
<td>Participant requires prompting with open-ended question that will help him/her proceed with the step. E.g. “What is the next step?” or “What else do you need?”</td>
</tr>
<tr>
<td>Gestural cue (Level 2) x 2</td>
<td>Administrator may move his/her hand to demonstrate without words (e.g. demonstrating how to open ink pad) or use pointing (e.g. point to where the participant may find the item, point to the recipe book picture, or point to the appropriate place on the paper). However, the administrator does not handle any of the items or participate physically.</td>
</tr>
<tr>
<td>Direct verbal cue (Level 3) x 2</td>
<td>The participant requires a direct one-step instruction. E.g., “The recipe shows that the red circle is over here” “You need the timer for this part” or “You need the scissors to cut the grass”</td>
</tr>
<tr>
<td>Physical assistance (Level 4) x 2</td>
<td>The administrator physically assists the participant with a single part of the step. E.g. Retrieve a necessary item from the box or put glue on back of circle and wait for participant to stick in correct position.</td>
</tr>
<tr>
<td>Do for participant (Level 5) x 1</td>
<td>The administrator completes the step that the participant is demonstrating difficulty with using self-talk, and then waits for the participant to proceed to next step.</td>
</tr>
</tbody>
</table>
Table 3.2. Task Score Descriptions

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Summary Score (TS)</strong></td>
<td>Total score is a weighted score based on the number and level of cues required throughout task.</td>
</tr>
<tr>
<td><strong>Total Cues (TC)</strong></td>
<td>Total number of cues required throughout whole task.</td>
</tr>
<tr>
<td><strong>Completion Time (Time)</strong></td>
<td>Time taken to complete the task.</td>
</tr>
<tr>
<td><strong>Highest Cue Level</strong></td>
<td>Highest level of cue required during task (5 levels as per Table S1).</td>
</tr>
<tr>
<td><strong>Initiation</strong></td>
<td>Number of cues required to independently start task.</td>
</tr>
<tr>
<td><strong>Learning</strong></td>
<td>An improvement in the number of cues required for part A and part C in a section that repeats the same step three times can be informative of an individual child’s learning process.</td>
</tr>
<tr>
<td><strong>Sequencing</strong></td>
<td>Number of steps without any cues required.</td>
</tr>
<tr>
<td><strong>Meta-Cognition</strong></td>
<td>Number of cues required to figure out that the timer is required to time for one minute whilst blowing on the ink</td>
</tr>
<tr>
<td><strong>Judgment/Safety</strong></td>
<td>Number of safety cues required throughout whole task.</td>
</tr>
<tr>
<td>Trait</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Completion</td>
<td>Number of cues required to finish task/realize task is completed.</td>
</tr>
<tr>
<td>Working Memory</td>
<td>The child can be rated from 1 (poor working memory) to 3 (superior working memory) with 2 denoting a child who is observed to have typical working memory for their age-based on manual guidance.</td>
</tr>
<tr>
<td>Organisation</td>
<td>The child can be rated from 1 (low organisation skills) to 3 (highly organised) with 2 denoting a child who is observed to have organisational skills as typical for their age-based on manual guidance.</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>The child can be rated from 1 (very emotionally labile) to 3 (low lability) with 2 denoting a child who is observed to have emotional reactions as typical for their age-based on manual guidance.</td>
</tr>
<tr>
<td>Distractibility</td>
<td>The child can be rated from 1 (very distractible) to 3 (not distractible) with 2 denoting a child who is observed to typical levels of distractibility for their age-based on manual guidance.</td>
</tr>
<tr>
<td>Pre-task self-judgment</td>
<td>A child’s judgment or prediction of their own ability to complete</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Post-task self-judgment</strong></td>
<td>A child’s judgment of how much help they received to complete task.</td>
</tr>
<tr>
<td><strong>Post-task self-review</strong></td>
<td>A child’s judgment of how good a job they did during task</td>
</tr>
<tr>
<td><strong>Self-talk</strong></td>
<td>Coded as Yes or No.</td>
</tr>
</tbody>
</table>
Validation Measures

The validation measures in this study included the BRIEF-P (Gioia et al., 2003), the CBQ-S (Putnam & Rothbart, 2006) and the NIH Toolbox task of Inhibitory Control (Gershon et al., 2010). Further task descriptions can be seen in section 3.1.

3.4.3.3 Procedure

Ethical approval was obtained from the local NHS ethics committee and UCL Institute of Child Health. Parental consent and child assent was obtained in advance of testing. For the schoolchildren, the researcher delivered information packs to the site, which the teachers sent home for parents who wished to consent for their children to participate. Three testers administered all tests. The researcher trained two assistant researchers using observation, video coding, and pilot participants. All children in school settings were administered the WPPSI followed by the PETA. The subset of children in the laboratory setting completed the NIH Toolbox task of Inhibitory Control and Attention with the WPPSI always being completed first followed by a combined order of the PETA and the NIH toolbox Task. The whole testing procedure typically lasted approximately one 40-45 minute session. Ten sessions were videotaped in order to determine the inter- and intra-rater reliability. Parents or guardians filled out the CBQ and the BRIEF-P was completed by the classroom teacher or by the parent/guardian in the case of the children who were tested at the London Babylab.
3.4.3.4 Statistical Analysis
Data analyses were conducted using SPSS for Mac version 21. One-way random intraclass correlation coefficient (ICC) was obtained for rater reliability analyses. Multivariate analysis of variance (MANOVA), chi-square and linear regression were used to look at the association between age and performance. Pearson’s bivariate correlations were used to investigate associations between PETA performance and age and other executive tasks. One-way ANOVA was used to investigated group differences for self-talk (yes/no), gender (male/female), and SES (low/high). Post hoc comparisons were conducted using Tukey HSD.

3.4.4 Results

3.4.4.1 Participation rate and demographics
One hundred and sixty six children were recruited and assessed (mean age=4.5 years; range=3.0-6.0). Figure 3.3 illustrates the recruitment flow for the participants included in the final study. Parent consent rates at schools were consistent with previously quoted norms for similar studies at 19/38 (50%), 46/120 (38%), and 82/260 (32%) with an overall response rate of 35%. Nine school children were consented by parents but were not tested either due to not giving assent (N=5) or school timetable/unavailability (N=4). All children tested completed the PETA. Seven CBQs and 44 BRIEF-Ps were not completed or returned. Seven school packs were returned to the study too late and thus not included in the testing/analysis. Participant demographics and task descriptives are seen in Tables 3.3 and 3.4. Mean ranges and standard deviations for PETA domains are in Table 3.5 while frequencies for more qualitative domains can be seen in Table 3.6. Table 3.7 shows participant self-ratings and Table 3.8 shows strong intercorrelations between the different PETA scores.
Figure 3.3. Flowchart for recruitment and assessment of children who completed the PETA and were included in the validation analysis.
**Table 3.3** Total group demographics and separated for each age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>3 year olds</th>
<th>4 year olds</th>
<th>5 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants tested (N)</td>
<td>166</td>
<td>45</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Male (N, %)</td>
<td>87 (53%)</td>
<td>23</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>White British (N, %)</td>
<td>99 (60%)</td>
<td>23</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Black British (N, %)</td>
<td>24 (15%)</td>
<td>7</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Other Ethnic Minority (N, %)</td>
<td>41 (25%)</td>
<td>15</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>
Table 3.4. Task descriptives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Mean</th>
<th>3 year olds</th>
<th>4 year olds</th>
<th>5 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>PIQ</td>
<td>101.6 (15.9)</td>
<td>103.9 (15.5)</td>
<td>102.0 (16.3)</td>
<td>99.1 (14.7)</td>
</tr>
<tr>
<td>VIQ</td>
<td>107.7 (16.5)</td>
<td>106.2 (18.0)</td>
<td>107.3 (16.6)</td>
<td>108.5 (16.1)</td>
</tr>
<tr>
<td>BRIEF GEC a</td>
<td>48.3 (10.4)</td>
<td>49.2 (9.6)</td>
<td>48.7 (11.0)</td>
<td>47.5 (10.4)</td>
</tr>
<tr>
<td>BRIEF EMI a</td>
<td>49.3 (10.8)</td>
<td>49.9 (11.3)</td>
<td>50.0 (10.6)</td>
<td>48.6 (10.0)</td>
</tr>
<tr>
<td>BRIEF ISCI a</td>
<td>47.4 (8.7)</td>
<td>48.9 (7.6)</td>
<td>47.4 (9.1)</td>
<td>46.3 (9.2)</td>
</tr>
<tr>
<td>BRIEF FI a</td>
<td>45.8 (8.7)</td>
<td>45.6 (8.6)</td>
<td>45.1 (5.9)</td>
<td>46.3 (10.4)</td>
</tr>
<tr>
<td>CBQ Attention b</td>
<td>4.9 (0.94)</td>
<td>4.68 (.85)</td>
<td>4.89 (.94)</td>
<td>5.04 (.94)</td>
</tr>
<tr>
<td>CBQ Inhibitory Control b</td>
<td>4.9 (0.8)</td>
<td>4.69 (.73)</td>
<td>4.98 (.80)</td>
<td>4.92 (.8)</td>
</tr>
<tr>
<td>NIH Toolbox Attention/Inhibition c</td>
<td>102.9 (19.9)</td>
<td>101.3 (5.7)</td>
<td>110.2 (25)</td>
<td>98.5 (22.2)</td>
</tr>
</tbody>
</table>

a BRIEF-P missing for 44 children
b CBQ missing for seven children
c Age-adjusted standard scores for 26 children (3 year olds: N=8; 4 year olds: N=8, 5 year olds: N=10)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Mean, SD (range)</th>
<th>3 year olds</th>
<th>4 year olds</th>
<th>5 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Summary Score</td>
<td>46.6 38.3 (4-202)</td>
<td>84.7 42.2 (20-202)</td>
<td>41.8 26.6 (4-139)</td>
<td>22.85 18.2 (4-84)</td>
</tr>
<tr>
<td>Total Cues</td>
<td>26.3 15.8 (4-73)</td>
<td>41.8 14.7 (12-73)</td>
<td>25.3 11.8 (4-59)</td>
<td>15.5 9.3 (4-44)</td>
</tr>
<tr>
<td>Completion Time</td>
<td>13.96 3.9 (6-26)</td>
<td>16.7 4.0 (7.5-26)</td>
<td>13.9 3.4 (7-25)</td>
<td>11.9 2.8 (6-17.5)</td>
</tr>
<tr>
<td>Initiation</td>
<td>2.6 (0-9)</td>
<td>4.1 (0-9)</td>
<td>2.7 (0-9)</td>
<td>1.4 (0-9)</td>
</tr>
<tr>
<td>Sequencing</td>
<td>1.87 (0-7)</td>
<td>0.80 (0-6)</td>
<td>1.8 (0-6)</td>
<td>2.7 (0-7)</td>
</tr>
<tr>
<td>Meta-Cognition</td>
<td>4.27 (0-9)</td>
<td>5.84 (2-9)</td>
<td>4.42 (1-9)</td>
<td>2.9 (0-7)</td>
</tr>
<tr>
<td>Judgment/Safety</td>
<td>43 (0-5)</td>
<td>.53 (0-5)</td>
<td>.46 (0-5)</td>
<td>.32 (0-5)</td>
</tr>
<tr>
<td>Completion</td>
<td>1.1 (0-6)</td>
<td>1.4 (0-6)</td>
<td>1.1 (0-5)</td>
<td>0.7 (0-3)</td>
</tr>
</tbody>
</table>
Table 3.6. Data for qualitative PETA domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>%</th>
<th>Domain</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td><strong>Distractibility</strong></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>11</td>
<td>Poor</td>
<td>13</td>
</tr>
<tr>
<td>Typical</td>
<td>51</td>
<td>Typical</td>
<td>46</td>
</tr>
<tr>
<td>Very Good</td>
<td>38</td>
<td>Very Good</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Organisation</strong></td>
<td></td>
<td><strong>Highest Level of Support</strong></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>17</td>
<td>Verbal Guidance</td>
<td>4.9</td>
</tr>
<tr>
<td>Typical</td>
<td>38</td>
<td>Gestural Guidance</td>
<td></td>
</tr>
<tr>
<td>Very Good</td>
<td>45</td>
<td>Direct Verbal</td>
<td>19.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical Assistance</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Examiner Completes</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td><strong>Emotional Lability</strong></td>
<td></td>
<td><strong>Self-talk</strong></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>6</td>
<td>No</td>
<td>51.1</td>
</tr>
<tr>
<td>Typical</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Very Good</td>
<td>62</td>
<td></td>
<td>48.8</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.7. PETA Self-ratings

<table>
<thead>
<tr>
<th>How much help do you think you will need?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>30%</td>
</tr>
<tr>
<td>A little</td>
<td>44%</td>
</tr>
<tr>
<td>A lot</td>
<td>26%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How much help did you need?</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>A little</td>
</tr>
<tr>
<td>A lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you think you did a good job?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>
Table 3.8 Inter-correlations between quantitative PETA domains

<table>
<thead>
<tr>
<th></th>
<th>PETA TS</th>
<th>PETA TC</th>
<th>Initiation</th>
<th>Sequencing</th>
<th>Meta-Cog</th>
<th>Judgment</th>
<th>Completion</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETA TS</td>
<td>-</td>
<td>.972**</td>
<td>.639**</td>
<td>-.618**</td>
<td>.717**</td>
<td>.170*</td>
<td>.265**</td>
<td>.691**</td>
</tr>
<tr>
<td>PETA TC</td>
<td>.972**</td>
<td>-</td>
<td>.662**</td>
<td>-.703**</td>
<td>.731**</td>
<td>.205**</td>
<td>.319**</td>
<td>.738**</td>
</tr>
<tr>
<td>Initiation</td>
<td>.639**</td>
<td>.662**</td>
<td>-</td>
<td>-.465**</td>
<td>.481**</td>
<td>.018</td>
<td>.177*</td>
<td>.540**</td>
</tr>
<tr>
<td>Sequencing</td>
<td>-.618**</td>
<td>-.703**</td>
<td>-.465**</td>
<td>-</td>
<td>-.534**</td>
<td>-.146</td>
<td>-.305**</td>
<td>-.574**</td>
</tr>
<tr>
<td>Meta-cog</td>
<td>.717**</td>
<td>.731**</td>
<td>.481**</td>
<td>-.534**</td>
<td>-</td>
<td>.158*</td>
<td>.243**</td>
<td>.574**</td>
</tr>
<tr>
<td>Judgment</td>
<td>.170*</td>
<td>.205**</td>
<td>.018</td>
<td>-.146</td>
<td>.158*</td>
<td>-</td>
<td>.068</td>
<td>.118</td>
</tr>
<tr>
<td>Completion</td>
<td>.265**</td>
<td>.319**</td>
<td>.177**</td>
<td>-.305**</td>
<td>.243**</td>
<td>.068</td>
<td>-</td>
<td>-.369**</td>
</tr>
<tr>
<td>Time</td>
<td>.691**</td>
<td>.738**</td>
<td>.540**</td>
<td>-.574**</td>
<td>.574**</td>
<td>.118</td>
<td>.369**</td>
<td>-</td>
</tr>
</tbody>
</table>

*p<.05  ** p<.01  *** p<.005
Table 3.9. Correlations between PETA domains and age

<table>
<thead>
<tr>
<th>PETA Domains</th>
<th>TS</th>
<th>TC</th>
<th>Initiation</th>
<th>Sequencing</th>
<th>Meta-Cog</th>
<th>Judgment</th>
<th>Completion</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.631***</td>
<td>-0.652***</td>
<td>-0.431***</td>
<td>-0.336***</td>
<td>-0.559***</td>
<td>-0.049</td>
<td>-0.212***</td>
<td>-0.481***</td>
</tr>
</tbody>
</table>

***p < .005
<table>
<thead>
<tr>
<th></th>
<th>PETA TS</th>
<th>PETA TC</th>
<th>Initiation</th>
<th>Sequencing</th>
<th>Meta-cog</th>
<th>Judgment</th>
<th>Completion</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRIEF-P GEC</strong></td>
<td>.181*</td>
<td>.196*</td>
<td>.280***</td>
<td>-.144</td>
<td>.141</td>
<td>.085</td>
<td>-.005</td>
<td>.183*</td>
</tr>
<tr>
<td><strong>BRIEF-P EMI</strong></td>
<td>.186*</td>
<td>.193*</td>
<td>.307***</td>
<td>-.099</td>
<td>.115</td>
<td>.101</td>
<td>-.028</td>
<td>.181*</td>
</tr>
<tr>
<td><strong>BRIEF-P ISCI</strong></td>
<td>.205*</td>
<td>.208*</td>
<td>.174</td>
<td>-.177</td>
<td>.186*</td>
<td>.128</td>
<td>.077</td>
<td>.192*</td>
</tr>
<tr>
<td><strong>BRIEF-P FI</strong></td>
<td>.152</td>
<td>.167</td>
<td>.174</td>
<td>-.183*</td>
<td>.109</td>
<td>.044</td>
<td>-.015</td>
<td>.181*</td>
</tr>
<tr>
<td><strong>CBQ Attention</strong></td>
<td>-.220***</td>
<td>-.224***</td>
<td>-.129</td>
<td>.205**</td>
<td>-.193*</td>
<td>-.122</td>
<td>-.023</td>
<td>-.172*</td>
</tr>
<tr>
<td><strong>CBQ</strong></td>
<td>-.187*</td>
<td>-.192*</td>
<td>-.086</td>
<td>.130</td>
<td>-.218***</td>
<td>-.091</td>
<td>-.052</td>
<td>-.229***</td>
</tr>
</tbody>
</table>

**Inhibitory Control**

|               |         |         |            |            |         |         |            |        |
| **NIH Attention and Inhibition** | -.554***| -.599***| -.474*     | .265       | -.337   | -.458*   | -.281      | -.267  |
| **WPPSI Block Design**  | -.149   | -.194*  | -.174      | .114       | -.15    | -.059    | .000       | -.132  |
| **WPPSI Information**   | -.159   | -.186*  | -.215**    | .047       | -.138   | -.052    | -.079      | -.092  |

*p<.05  ** p<.01  *** p<.005
Table 3.11. Mean BRIEF-P subdomain scores for the children divided into groups based on examiner rating during PETA administration as poor, typical, or very good on the four categorical PETA domains (Organisation, Distractibility, Working Memory, Emotional Lability). There were no significant group differences on the BRIEF-P subdomains relevant to each PETA domain. However, there is a trend for mean scores going in the correct direction for the four domains (i.e. the poor groups obtaining the highest scores on the relevant BRIEF-P subdomains).

<table>
<thead>
<tr>
<th>PETA Examiner Category Rating</th>
<th>BRIEF-P Plan/Organize $^a$</th>
<th>BRIEF-P Inhibit $^b$</th>
<th>BRIEF-P Working Memory $^c$</th>
<th>BRIEF-P Emotional Control $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>53.2</td>
<td>48.6</td>
<td>54.9</td>
<td>46.8</td>
</tr>
<tr>
<td>Typical</td>
<td>48.3</td>
<td>47.9</td>
<td>49.4</td>
<td>46.6</td>
</tr>
<tr>
<td>Very Good</td>
<td>47.1</td>
<td>46.5</td>
<td>49.1</td>
<td>46.2</td>
</tr>
</tbody>
</table>

$^a$ As rated for the PETA Organisation domain  
$^b$ As rated for the PETA Distractibility domain  
$^c$ As rated for the PETA Working Memory domain  
$^d$ As rated for the PETA Emotional Lability domain
3.4.4.2 Intra- and Inter-rater reliability

To test rater reliability, ten testing sessions were coded by three testers with a strong inter-rater reliability (ICC = .93) and re-coded at least a week later showing evidence for strong intra-rater reliability (ICC = .88 to .98).

3.4.4.3 PETA Performance and age

Age was strongly related to performance on all quantitative domains of the PETA, except for Judgment/Safety (Table 3.9). Differences in the Total Summary Score by age group were investigated with a univariate ANOVA. Post hoc tests showed that performance significantly increased with age in line with the rapid development of executive skills reported during this age period (F_{2,164} = 58.39, p < .001; figure 3.4). A linear regression found that chronological age predicted 40% of Total Summary Score performance (F_{1,162} = 42.9, p < .001, R^2 = .398). Younger children required higher levels of examiner support to complete the task with a chi-square showing that three year olds tended to require higher levels of cues (e.g. level 4-physical assistance) in comparison to four and five year olds. Only a small number of five year olds required physical assistance and none requiring examiner step completion on any of their steps (p < .001). Chi-square analysis showed significant developmental trends for better performance with age in the qualitative domains of Working Memory (p = .003), Organisation (p = .01), and Emotional Lability (p = .02), with older children receiving higher scores from the examiner for their performance in each of these domains. A non-significant trend for examiner rated improvements in distractibility with age was also observed (p = .055).
Figure 3.4. Typical Performance for (a) Total Number of Cues, Total Summary Score, and (b) highest level of support required during task based on age range. Higher scores in the Total Number of Cues and Total Summary Score indicate poorer performance in 2(a). Five year olds required less cues and support than the three and four year olds.
3.4.4.4 PETA Convergent and Discriminant Validity

The convergent validity of PETA scores was investigated by comparing with proxy-report domains of EF and performance on the NIH Toolbox Task of Inhibition Control and Attention. Mild to moderate correlations between quantitative PETA scores and scores on the BRIEF-P and CBQ executive domains provide evidence for the convergent validity of the PETA. Additionally, moderate to strong correlations were observed between PETA scores and performance on the NIH Toolbox Task of Inhibition Control and Attention. The associations between the PETA scores and the BRIEF-P, CBQ domains, and the NIH task were stronger in the four and five year olds when investigated separately, but became non-significant for the three year olds.

Discriminant validity was investigated by comparing the PETA domains with the hypothetically unrelated constructs of the Block Design and Information WPPSI-III-UK subtests (Table 3.10). Evidence for some influence of IQ subtest performance can be observed.

The qualitative PETA domains were investigated using one-way ANOVAs to determine whether the experimenter categorization of ‘poor’, ‘typical’, and ‘very good’ corresponded to teacher ratings on the approximate domains of the BRIEF-P. Although the model was not significant, examiner ratings of Organization during the PETA task showed that, in general, the poor group obtained the poorest scores on the BRIEF-P Plan/Organize domain, followed by the typical group, and the very good group. Distractibility categorization was compared with scores on the BRIEF-P Inhibit subdomain with a trend for mean scores going in the correct direction, but again the model was not significant. The model for Working Memory was also not significant, although the poor group had lower mean scores than the other two groups. There were no differences between the Emotional Lability groups on the Emotional Control BRIEF-P domain (potentially due to the small number of children rated as poor; see Table 3.6 and Table 3.11).
3.4.4.5 Influence of self-talk, gender, and socioeconomic status on performance

The influence of self-talk, gender, and SES were investigated separately for the Total Summary Score, Total Number of Cues, and Completion Time. Overall, the use of self-talk had no influence on Completion Time ($F_{1,134} = .282, p = .596$) but those who engaged in self-talk obtained a better Total Summary Score ($M=35.26$, $SD=23.6; M=47.51$, $SD=40.5; F_{1,134} = 4.52, p = .035$) and showed a trend for a difference in Total Number of Cues ($M=22.14$, $SD=11.3; M=26.7$, $SD=17.5; F_{1,134} = 3.14, p = .079$). There were no differences in the rates of self-talk between age-ranges. When investigated further, self-talk had no effect on performance for the four- and five-year-olds but the three-year olds who did not engage in self-talk were found to require more support to complete the task (Total Number of Cues, $t(133)=1.77, p = .004$; Total Summary Score, $t(133)=2.13, p = .003$) but no group difference for Completion Time. A non-significant trend for gender differences showed that girls tended to receive less cues overall ($M=23.8$, $SD=14.8; M=28.4$, $SD=16.3; t(162)=-1.71, p = .06$) and a lower Total Summary Score ($M=41.2$, $SD=36.2; M=51.4$, $SD=39.7; t(162)=-1.90, p = .09$), but there was no difference for Completion Time. Poorer performance in the “lower SES” group (N=47) was observed for Total Number of Cues ($M=30.5$, $SD=18.9; M=24.5$, $SD=13.9; t(162)=-2.4; p = .04$), Total Summary Score ($M=58$, $SD=46.5; M=42.1$, $SD=33.7; t(162)=-2.1; p = .05$), and longer Completion Time ($M=14.9$, $SD=4.2; M=13.5$, $SD=3.2; t(162)=2.0; p = .04$).

3.4.5 Discussion

The PETA paints a rich picture of a preschooler’s ability to use executive skills to carry out everyday tasks, offering parents and teachers a more real-life perspective in terms of where, when, and how much or what type of support
their child requires. Children who showed better executive control on the behavioural and proxy-report measures required less assistance to complete the PETA. Additionally, the qualitative and quantitative subdomains of the PETA shed further light on where performance breaks down for individual children in comparison to their peers (normative data for individual domains are provided in the supplementary section). This task complements current questionnaire and pass/fail measures for preschool children by providing a Total Summary Score to describe general executive performance, while also indicating where the child is falling down in the task and where their strengths lie. In this way, a profile is created that can be used by educators to directly inform interventions and the provision of targeted support systems. The utility of the PETA scoring system is the ability to capture children who may perform well on brief standalone tasks that focus on one specific skill but may show performance break-down in the PETA due to the combination of steps, similar to everyday life. In contrast, the PETA could also identify children who may perform poorly on existing laboratory measures that are time-limited.

The PETA aims to bridge some of the measurement gap that currently exists in the assessment of young children with suspected executive difficulties (Beck, Schaefer, Pang, & Carlson, 2011; Carlson, 2005). Few executive measures are validated for this age range (Delis et al., 2004; Korkman, Kirk, & Kemp, 2007) and the proxy-report screeners and specific executive tests that are widely used are limited in terms of gauging the impact of their deficits on everyday life and informing potential interventions (Isquith et al., 2005; Isquith, Gioia, & Espy, 2004). This study presents preliminary evidence for both the reliability and validity of this task as a useful tool for looking at executive development in both clinical and research settings. Inter- and intra-rater reliability is high in trained examiners and task performance improves with age showing a significant increase between three and five years in line with the current understanding of executive development in preschool-age children (Anderson, 2002).
The PETA also aims to address the lack of ecological measures currently available in the literature (Burgess et al., 2006), due in part to the theoretical and methodological difficulties of validating an EF task (Rabbitt, 2004). The authors are not aware of any other performance-based ecologically valid tasks that are available for preschool aged children, despite the importance of EF for social skills and school readiness at this crucial transition period for young children (Anderson & Reidy, 2012). This task has the potential advantage over existing measures to provide a more holistic and multi-faceted picture of a child’s EF (Espy, 1997).

The lack of validated measures currently available for application across this age range was a limitation for this study. The BRIEF-P is designed for parent or teacher respondents and for practical reasons, parents rather than teachers, who may have shown response bias towards their own children, filled out a subset of the BRIEF-Ps. A further limitation is the low to moderate correlations between the PETA domains and the proxy-report domains on the BRIEF-P and the CBQ; however this is typical for validation of similar measures in the literature (Dias & Seabra, 2012; Ponitz et al., 2008) and low correlations have previously been found between parent-report measures of EF and performance based tasks (Mahone et al., 2002). To some degree, these correlations may be impacted by differences in task constructs as well as the rater reliability for the BRIEF-P and the CBQ. In addition, these associations were not observed for the three year olds and were stronger in the other age ranges when investigated separately. This may be due to more variability in the behaviour of younger children and the small number of three year olds who completed the NIH task (N=8). However, the higher association with the NIH task in comparison to the non-executive tasks corroborates the construct validity of the PETA. Further validation for the PETA can also be observed in the relationship between self-talk and performance in the younger children (Winsler, Carlton, & Barry, 2000), the trend for girls performing slightly better than boys (Ponitz et al., 2008; Wiebe, Espy, & Charak, 2008), and the impact of poorer SES on performance (Noble, Norman, & Farah,
2004; Sarsour, Sheridan, Jutte, Nuru-Jeter et al., 2011). However, the influence of SES needs to be further studied, as the crude two-category approach adopted in the current study, due to lack of postcode data and other indicators of SES, is limited in terms of interpretation. Nevertheless, the potential influence of these variables on PETA performance further substantiates reports in the EF literature, and illustrates the importance of controlling for these variables in future studies.

In conclusion, results of this study suggest that the PETA is a valid measure of EF for preschool aged children and can be used to complement existing questionnaires and more fractionated performance-based measures (Toplak, West, & Stanovich, 2013). Children apply a multitude of executive skills in everyday tasks that may not be adequately measured when diluted in a non-natural context. To further elucidate the external validity of the task, further research is required to establish how patient groups with known executive deficits, such as children with attention deficit disorder, autism spectrum disorder, and SCD, perform on this ecological assessment. If the PETA is a valid assessment for EF it should be able to discriminate between atypical and typically developing groups. Another aim is to develop more elaborate and informative PETA profiles for future clinical and research use as well as to develop and validate the subdomains of the PETA further. As the PETA demonstrated, executive skills develop rapidly over the preschool period so it would be useful to develop norms for narrower age bands in order to provide a more precise picture of development. Although some of the children tested were turning six years, no child reached ceiling (where no cues would be required) so further thought about potential modifications to bridge the age gap between the current norming of the PETA for three to five year olds and the CKTA (Rocke et al., 2008) which is available for eight to twelve year olds would be useful. A final important avenue for the future is to develop a comparable novel task for preschoolers that could be used as alternative version of the PETA in order to maintain task novelty enabling assessment of executive development over time and the impact of interventions.
3.4.5.1 **Future development of the PETA: A brief update**
Funding from the Grand Challenges Fund has been secured to develop a training video for the task. Alongside the manual and normed data, this will be made freely available on-line as a low-cost, high quality tool for other research groups and clinicians to access and develop further. A second grant has been submitted to develop an alternate version of the PETA over the next few years.

3.5 **Doggie Deletion Task for Preschoolers (DDTP): Attentional Control and Processing Speed**
To investigate the development of attention and inhibitory control in young children, it is important that a task is sufficiently repetitive or uninteresting so that these constructs are tapped, but is also accommodating enough for children to complete, particularly a child with executive deficits. In this section I introduce the Doggie Deletion Task for Preschoolers, which has been developed and refined to tap into these behaviours in children from three to five years. It measures a child’s ability to sustain attention, inhibit distractors, and speed of processing. Healthy three to five year old children (N=26) were recruited and assessed at the UCL London Babylab. Intellectual ability and behavioural task performance on executive tasks of the NIH Toolbox as well as parent reports of EF were collected. Task performance was related to behavioural performance on the NIH Toolbox but there was no association with proxy-reports of inhibition on the BRIEF-P. I conclude that the DDTP can successfully be administered to measure executive skills in preschool children, however there are some limitations in the current task design as further described in the discussion.

3.5.1 **Introduction**
This measure was developed based on a cancellation task used to measure attention control in preschool aged children (Corkum et al., 1995). The initial
version of the Picture Deletion Task was modified in these studies in order to develop a more preschool-friendly assessment. The task identified differences between preschool children with ADHD and typically developing children, with all three studies finding that children with ADHD had a higher rate of commission errors. Children with ADHD required more examiner support to complete the task but the researchers did not provide a description of what or how much support was offered, which leaves open the question of how objective the task was (DeWolfe et al., 1999). One study used the Picture Deletion Task Revised version of the task on a population (N=33) of Australian children aged four and five years and found that the task was appropriate for typically developing preschool children but that it may not be suitable for children with disorders that affect executive development, despite the fact that the objective of this task is to illustrate difficulties in these children (Parker, 2005). Parker (2005) concluded that further work was required to standardize the administration in order to make the task a more reliable and valid source of information. The main modifications of the task in the current study from the original Picture Deletion Task-Revised version include updated stimuli, an updated and more in-depth script and examiner instructions, and the addition of objective instructions to administer “cues” to participants who go off-task for upwards of 20 seconds, as well as instructions for scoring incomplete assessments (Byrne et al., 1998).

3.5.2 Aims
To examine the utility and validity of the task with preschool aged children
To investigate whether rates of omissions and commissions, and time to completion, are associated with task performance on the NIH Toolbox Task of Inhibitory Control and Attention and the Inhibit domain of the BRIEF-P.
To investigate associations between motor speed and the NIH Toolbox Task of Processing Speed.
3.5.3 Method

3.5.3.1 Measures

3.5.3.1.1 Doggie Deletion Task for Preschoolers (DDTP)

The four dependent variables of this task are commission errors, omission errors, time to completion, and motor speed. Inattention is thought to relate to the rate of omissions (targets not stamped) while commission errors (stamped distractors) are postulated to be an indicator of impulsivity or hyperactivity (Halperin, Wolf, Greenblatt, & Young, 1991). The task was piloted with five pre-school age children, from three to five years, before the final version was administered, in order to ensure there were no floor or ceiling effects, the instructions were easily understood, and the amended script and cueing system were easily implemented and scored by the examiner. See appendix 4 for the newly developed task forms, manual, and score sheet.

Figure 3.5 Child using bingo stamper to mark target stimuli

3.5.3.1.2 Validation Measures

Further task descriptions for the below tasks can be observed in section 3.2.2.

- NIH Toolbox task of Inhibitory Control and Attention (Zelazo et al., 2013)
- NIH Toolbox task of Processing Speed (Carlozzi, Tulsey, Kail, & Beaumont, 2013)
- BRIEF-P (Gioia et al., 2003)
3.5.3.2 Participants

Twenty-six typically developing children were administered the picture-deletion task for pre-schoolers (Mean age 4.7; 3.00-6.00 years). Twenty-two children passed phase one (the training phase). The four children who did not pass the training phase were between 3.25 and 3.75 years of age. One child finished the task on the first page of the test phase, but the data could not be included because over two pages were required to compute pro-rated or estimated scores. One child did not complete the task to the end, only completing five pages so their score was pro-rated. The final version of the motor phase was only administered to eleven children as the motor phase was altered after piloting. Ten of the group were males and the mean IQ was 110.88 (13.04). Twelve of the children were Black British, 10 were White/White British and four children were identified as Asian British or mixed ethnicities. Two of the questionnaires were excluded due to non-completion. Five children did not complete the NIH Toolbox tasks due to technical issues.

3.5.4 Results

3.5.4.1 Task Completion

As expected, the younger children made more omissions ($r=-.746$, $p=<.001$) and were slower in motor speed ($r=-.811$, $p=.002$), but there were no developmental effects observed for commissions or time to complete task. Associations remained significant on removal of outliers (figure 3.6).
3.5.4.2 Associations with Standardized Measures

Correlations were computed between the omission, commission, and time to complete DDTP variables and the NIH inhibitory control task and the Inhibit domain of the BRIEF-P, and between DDTP motor speed and time to complete and the NIH processing speed task. Significant associations were observed between NIH processing speed and motor speed phase ($r= -0.746$, $p=0.013$, $N=10$) and between NIH inhibitory control and rate of omissions ($r= -0.514$, $p=0.042$), and time taken to complete ($r= -0.494$, $p=0.044$, $N=17$). NIH inhibitory control was not associated with rate of commissions and NIH processing speed was not associated with time to complete. There were no associations between the parent report of inhibition on the BRIEF and DDTP performance.

Figure 3.6 Associations between age and (A) time to completion (B) motor speed (C) commissions and (D) omissions on the DDTP
3.5.4.3 Relation to previous research

Table 3.12 shows a review of the previous studies that have administered versions of the Picture Deletion Task with typically preschool-age children and compares their findings with the current study. Differences in the parameters reported for each study make it difficult to draw any direct comparisons.
Table 3.12. Comparison of mean variables (SD) in current study to previous studies with similar task design (8 pages, 120 targets, 360 distractors) in typically developing children

<table>
<thead>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N Tested</td>
<td>8</td>
<td>25</td>
<td>35</td>
<td>103</td>
<td>26</td>
</tr>
<tr>
<td>N Passed</td>
<td>8</td>
<td>-</td>
<td>33</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>Age</td>
<td>4-5 years</td>
<td>4.86 years</td>
<td>58.85 months (3.77)</td>
<td>61.24 months</td>
<td>56.4 months /4.7 years</td>
</tr>
<tr>
<td>FSIQ</td>
<td>-</td>
<td>-</td>
<td>112.45 (11.47)</td>
<td>-</td>
<td>110.88 (13.04)</td>
</tr>
<tr>
<td>Commissions</td>
<td>1.88 (2.3)</td>
<td>1.31 (1.64)</td>
<td>2.48 (2.09)</td>
<td>-</td>
<td>10.3 (18.4)</td>
</tr>
<tr>
<td>Omissions</td>
<td>13.63 (9.58)</td>
<td>13.07 (11.62)</td>
<td>4.00 (3.61)</td>
<td>-</td>
<td>27.3 (26.2)</td>
</tr>
<tr>
<td>Time to Complete</td>
<td>-</td>
<td>667.00 (354)</td>
<td>626.75 (169.17)</td>
<td>-</td>
<td>654 (234)</td>
</tr>
<tr>
<td>Motor Speed</td>
<td>-</td>
<td>59.00 (16.45)</td>
<td>55.33 (12.47)</td>
<td>-</td>
<td>46.6 (8.3)</td>
</tr>
</tbody>
</table>
3.5.5 Discussion

The current study found that the number of omissions and motor speed increased with age but that the number of commissions and time to complete did not. Performance on the NIH processing speed task was related to motor speed on the DDTP, but not to completion time. This suggests that the motor speed score on the DDTP may be a better measure of processing speed than the time taken to complete the task.

The NIH task of inhibitory control and attention was related to omissions and time to complete, but not with rate of commissions. This suggests that the task successfully taps attention control (i.e. faster time and less omissions) and may be a less effective measure of inhibition, since commissions are thought to reflect impulsivity yet shows no developmental effects or no associations with the standardized task, despite no floor or ceiling effects. None of the DDTP variables were associated with parent reported inhibitory control.

The current study shows the utility of the DDTP as an age-appropriate cancellation task for preschoolers, although the scoring system may need to be further altered to accommodate three year olds. The children who did not successfully pass the training phase or complete at least two pages of the test phase were all less than 3.5 years, which may indicate a need for a tiered scoring system that incorporates the training phase score with an even more simplistic task. The strong association between the DDTP motor phase and the NIH toolbox processing speed score is encouraging, despite the small population size. However, the less significant correlations between inhibitory control on the DDTP and task performance on the NIH toolbox may indicate that these tasks measure different aspects of attentional control. The NIH toolbox is an interactive computerized task and the child hears the word “middle” between each trial to orient their attention to the middle stimulus, coupled with shorter task completion times (approximately four minutes in
comparison to over 10 minutes on average for the DDTP), this task may be less reliant on sustained attention. The NIH task also gives more objective feedback to the child based on button presses during the training phase, allowing them to alter their behaviour before the task begins. The lack of any association with the parent reports of inhibitory control and the DDTP suggests that the task is capturing a specific type of inhibitory control that a parent may not ordinarily observe, a teacher report of EF may be more appropriate in this instance as the task is more related to school-based everyday tasks. Although this task shows higher levels of commission and omission errors than previous studies that employed similar task designs (see Table 3.12), the completion time and motor speed scores were comparable. The higher rates of commissions/omissions may be due to the younger mean age of the cohort in the current study and the known increase in inhibitory control between three and four years (Jones et al., 2003).

This study was the first attempt to validate the different task variables in a picture deletion task for preschool children. It is concluded that the task is a valid measure of attentional control within this age range, though further adjustments to the scoring protocol may be required to capture the range of performance at the lower end of functioning.

3.6 Scrambled Memory Task: Working memory

In this section I introduce the Scrambled Memory Task, which has been developed and refined to measure visual working memory from three to five years. Healthy three to five year old children (N=27) were recruited and assessed in the UCL London Babylab. Intellectual ability and parent reports of working memory were also collected. The amount of consecutively correct trials on the task was associated with parent reports of working memory on the BRIEF-P. In conclusion, it is reported that the Scrambled Memory task can successfully be administered to measure working memory in preschool children.
3.6.1 Introduction

Working memory describes the skill of holding and manipulating information in our minds over a short period of time. Working memory becomes more important for children as they start to follow directions and solve problems for themselves, with functional working memory capacity becoming greater during the transition from early childhood to adolescence (Gathercole et al., 2004). Working memory is particularly important in the classroom, where it is an important aid for children as they learn (Alloway, 2006). The frontal areas have been implicated in playing an important role in working memory as part of a wider brain network, and it has been found that children with SCA who have stroke in these regions perform more poorly on tasks that tap this skill (White et al., 2000). Most measures of working memory, such as the Working Memory Test Battery for Children (Pickering & Gathercole, 2001) and the Automated Working Memory Assessment (Tracy P Alloway, Gathercole, Kirkwood, & Elliott, 2008), can only be used with children older than four years and so it is currently difficult to ascertain whether working memory deficits are present in three year olds when they enter the school system. Previous studies have used scrambled boxes or pots tasks to investigate working memory in preschool children (Wiebe et al., 2011). However, task administration is not well described and task parameters change between studies, which makes it difficult to make comparisons or make informed interpretations of findings. Studies often use different numbers of boxes for the same age range, typically six, eight or nine (Skogan et al., 2014), or use varying inter-trial intervals, for example ten, fifteen, or twenty seconds (Diamond, Prevor, Callender, & Druin, 1997). The main modifications of task design in the current study includes a scripted introduction and training phase, as well as a fixed template so that the task is administered in the same way each time, reducing the potential for examiner error and bias.

AIMS
To look at the utility of the scrambled boxes task developed during the pilot phase.
To investigate convergence validity by looking at associations between task performance and parent reports of working memory.
To investigate discriminant validity by looking at associations between task performance and parent reports on other domains of EF.

3.6.2 Method

3.6.2.1 Measures

3.6.2.1.1 Scrambled Boxes Task

This task was developed based on similar scrambled boxes tasks used to measure working memory (Wiebe et al., 2011). This task was always administered at the start of a battery of tasks. The children were required to search for small toys hidden in different coloured boxes with different stickers on their lids (figure 3.7). The objective is to uncover each box and avoid going back to those already uncovered. The examiner instructs the child to find all the toys “in the least amount of go’s.” The examiner has a ‘turn’ at the game with a different set of boxes so that the child understands that the toys remain in the same boxes despite the different spatial locations. Children are permitted to open only one box per trial. Boxes are scrambled according to a predetermined protocol (figure 3.8) during a 10-second delay. The task continues until a maximum of 20 trials are administered or the child finds all of the toys. The highest number of consecutive trials, total trials (maximum of 20), and number of toys retrieved are coded by the researcher. The consecutively correct trials score was used as the dependent variable (Wiebe et al., 2011). The task was initially administered as a six-box version, similar to Diamond et al., (1997), with 13 children, but ceiling effects were observed. Further details on task development and piloting can be seen in Methodology.
Section 3.4.4.5.

Figure 3.7 Participant (a) distracted for 10 second delay and (b) finding target during task. Ethical consent for photo-use in thesis obtained.

Figure 3.8 Scrambled Memory Colour-sorting order

3.6.2.1.2 BRIEF-Preschool (Gioia et al., 2003)
The current study uses the working memory scale of the BRIEF-P to compare parent’s ratings of working memory with the child’s performance on the scrambled boxes task developed by the researcher. Seventeen items on the BRIEF-P contribute to the working memory scale. Higher scores on the BRIEF-P indicate poorer working memory (Mean=50; SD=10).

3.6.2.2 Participants
Twenty-seven typically developing children (Mean age=4.65; range=3.20-6.00; 13 males, Mean IQ=107.86(13.81)) completed the working memory
task. An additional 13 children were tested with the six-box version of the task before it was amended. Fourteen of the children were Black British, 10 were White/White British and three children were Asian British. Two children were left-handed. Two of the parent questionnaires were excluded due to non-completion and invalid completion.

3.6.3 Results

3.6.3.1 Task Completion

All children successfully completed the task. The minimum amount of total boxes retrieved was eight (N=4). All other children found all of the toys by the twentieth go.

Table 3.13 Task performance in the current study

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Memory BRIEF</td>
<td>38</td>
<td>76</td>
<td>52.2 (11)</td>
</tr>
<tr>
<td>Total Number of Trials Required</td>
<td>10</td>
<td>20</td>
<td>14.9 (3.6)</td>
</tr>
<tr>
<td>Consecutively Correct Trials</td>
<td>3</td>
<td>8</td>
<td>5.2 (1.4)</td>
</tr>
</tbody>
</table>

3.6.3.2 Associations with Standardized Measures

Convergent validity was investigated by comparing the number of consecutively correct trials with parent reported working memory on the BRIEF-P. As predicted, the number of consecutively correct trials correlated with parent ratings on the Working Memory Scale of the BRIEF-P (r=.456, p=.022). Interestingly, performance was not associated with IQ or age.
Divergent validity and specificity was investigated by comparing with the other four BRIEF-P domains. There were no associations with the Emotional Control, Plan/organize, Shift, or Inhibit Domains.

**Figure 3.9** Association between behavioural performance on scrambled memory task and parent report of working memory on the BRIEF-P
3.6.3.3 Relation to previous research

Table 3.14 Comparison of variables in current study to previous studies with similar task design (9 scrambled boxes) in typically developing children

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>228</td>
<td>56</td>
<td>27</td>
</tr>
<tr>
<td>Inter-trial-interval</td>
<td>15 seconds</td>
<td>10 seconds</td>
<td>10 seconds</td>
</tr>
<tr>
<td>Age</td>
<td>3.01 years (12.8 days)</td>
<td>55.66 months (7.18)</td>
<td>4.65 (0.84)</td>
</tr>
<tr>
<td>Greatest No. of Gos</td>
<td>4.57 (1.58)</td>
<td>Not reported</td>
<td>5.2 (1.37)</td>
</tr>
</tbody>
</table>

3.6.4 Discussion

The findings of this study show that the nine box scrambled memory task design developed for the current study is valid as a performance based task of working memory in preschool-age children. The protocol and examiner instructions can be utilised in future studies to ensure objective measurement and comparability between studies. All children completed the task and no child reached ceiling, showing that the task appropriately captures ability across this age range. The strong correlation between the behavioural task and the parent reports of working memory that is not observed for the other executive domains is encouraging, particularly as low correlations are often found between performance-based tasks and parent reports of EF (Dias & Seabra, 2012; Mahone et al., 2002). However, the lack of another standardized performance-based task of working memory is a limitation in the current study. The working memory task on the NIH toolbox was piloted as part of the battery at the start of the study but was discontinued for two reasons. Many of the younger children lost interest in the computerized tasks.
by the third task and so the task was not always completed, and the battery as a whole is long, even with breaks, so the NIH toolbox working memory task was discontinued alongside some other tasks. The findings of the current study were compared with previous studies employing similar designs (see Table 3.14). Only two studies previously used a nine-box version with a cohort of typically developing children. One study did not report group means and the second study looked only at three year olds with a different inter-trial-interval. In conclusion, the current version of the task shows a relation between task performance and parent reports of working memory, and can be confidently used to measure working memory in this age range.

3.7 Inhibition of a pre-potent and an on-going response

Impulse control develops rapidly in the preschool years. There are different types of inhibitory control and in this section I introduce two tasks that tap two aspects of inhibitory control; the Bear & Dragon task, that measures inhibition of a pre-potent response, and the Circle Tracing Task, that measures inhibition of an on-going response. Intellectual ability and behavioural task performance on executive tasks from the NIH toolbox as well as parent reports of EF were also collected. Task performance improved with age for both measures but was not related to behavioural performance on the NIH toolbox or parent-reports of inhibition and of inhibitory control. I conclude that these measures, in their current format, are not sensitive to assess subtle changes in of inhibitory control across the age range of interest and discuss the reasons for exclusion from the testing protocol in phase three.

3.7.1 Introduction

Impulsivity or poor inhibitory control could potentially play a role in the development of poor social skills in children with SCD (Hensler et al., 2014). Similar to many behavioural tasks of EF for preschool children, the Bear & Dragon task has been frequently administered but task design and scoring varies between studies, which makes it difficult to draw any firm conclusions
Different versions of the Circle-Tracing task have been applied in children with a recent group applying the task in preschool children for the first time (Traverso, Viterbori, & Usai, 2015). This study aims to validate these measures in a population of typically developing preschool children.

3.7.1.1 Circle Tracing Task

This task allows direct measurement of inhibition of an ongoing, or continuous, response (Scheres et al., 2003). It has been found that more impulsive participants find it difficult to slow down when tracing the circle for the second time (Bachorowski & Newman, 1990). It has been used with children and adults to investigate inhibition of a continuous response (Avila et al., 2004; Gandolfi, Viterbori, Traverso, & Usai, 2014; Puustinen, Kokkonen, Tolvanen, & Pulkkinen, 2004). The current task was adapted from previous studies to be more appropriate for younger participants (Scheres et al., 2003). A larger inhibition score indicates a greater ability to inhibit or slow down the tracing trial.

3.7.1.2 Bear & Dragon Task

This task involves suppressing or initiating an activity in response to a verbal stimulus direction produced by two puppets with different character voices, a “good” bear and a “naughty” dragon (Reed et al., 1984). The number of motor actions correctly performed or inhibited is coded. It has been reported to be highly correlated with parent reports and other inhibition tasks (Kochanska et al., 1996).

3.7.2 Aims

To look at the utility of the Bear & Dragon and Circle tracing tasks developed with three to five year olds during the pilot phase.

To investigate task validity by looking at associations between both tasks and by investigating associations with performance on the NIH toolbox and parent reports of impulsivity/inhibition.
3.7.3 Method

3.7.3.1 Measures

3.7.3.1.1 Circle Tracing Task
The dependent variable is ‘inhibition time’ or the time taken to trace the circle in the slow condition (Time 2) minus time taken to trace circle in neutral condition (Time 1). A greater inhibition time indicates a greater ability to inhibit the continuous response.

3.7.3.1.2 Bear & Dragon Task
In this task, the children are directed to respond to directions from “bear” but to ignore directions from “dragon” (Reed et al., 1984). The dependent variable in this task is the number of correct trials, ranging from zero to 12. Validation Measures

Further task descriptions for the below tasks can be observed in section 3.2.2.

-BRIEF-Preschool (Gioia et al., 2003)
-Children’s Behaviour Questionnaire-short (Putnam & Rothbart, 2006)
-NIH Toolbox task of Inhibitory Control and Attention (Gershon et al., 2010)

3.7.3.2 Participants

3.7.3.2.1 Circle Tracing Task
Thirty-nine typically developing children were administered the circle-tracing task (Mean age 4.4; 3.00-6.00 years). Twenty-two children were male and the mean IQ was 109 (13.48). Fifteen of the children were Black British, 19 were White/White British and five children were identified as Asian British or mixed ethnicities. All children spoke English as a first language and were attending nursery at least part-time. Two BRIEF-P questionnaires were excluded due to non-completion and 13 children did not complete the NIH toolbox tasks due to equipment and timing issues.
3.7.3.2.2 Bear & Dragon Task

Twenty-one typically developing children completed the task (Mean age 4.1; 3.00-5.75). Thirteen children were male and the mean IQ was 114 (13.5). Four children did not complete the task due to timing constraints. Two of the children were Black British, 16 were White/White British and three children were identified as Asian British or mixed ethnicities. All children spoke English as a first language and were attending nursery at least part-time. Nine children did not complete the NIH toolbox tasks due to equipment and timing issues.

3.7.4 Results

3.7.4.1 Circle Tracing Task

3.7.4.1.1 Task Completion

All children successfully completed the task. A significant correlation was found between age and inhibition time in the pilot participants during phase one (r=.517, p=.001; see figure 3.10a).

Table 3.15 Mean inhibition time for each age range

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Circle Inhibition Time (M, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years (N=15)</td>
<td>11.07 (9.2)</td>
</tr>
<tr>
<td>4 years (N=12)</td>
<td>18.15 (14.9)</td>
</tr>
<tr>
<td>5 years (N=12)</td>
<td>54.00 (66.9)</td>
</tr>
</tbody>
</table>

3.7.4.1.2 Associations with Standardized Measures

There were no significant associations between the inhibition score on the circle tracing task and parent report on the CBQ-S, BRIEF-P, or performance on the NIH behavioural task.

3.7.4.1.3 Relation to previous research

The administration and scoring of the current task was adapted from a study of older school children with ADHD (Scheres et al., 2003). This study found no
effects of intervention on the circle-tracing task, which could be due to poor task sensitivity and may contribute to an explanation for the lack of correlations with other measures of inhibitory control in the current study. However, another research group recently adapted this task for younger children in a different way and showed more encouraging associations with other inhibition measures in their study of typically developing two and three year olds (Gandolfi et al., 2014). They also administered this task to five year olds pre- and post-intervention and found improvements in performance after executive intervention, showing further evidence for task validity and sensitivity (Traverso et al., 2015). Task differences include a larger circle diameter in the current study (50.8 cm versus 17cm) and a different scoring procedure (Time 2 – Time 1 versus Time 2 – Time 1/T2 + T1).

3.7.4.2 Bear & Dragon Task

3.7.4.2.1 Task Completion
A significant relationship was found between age and inhibition score in the pilot participants during phase one ($r=.464, \ p=.034$; see figure 3.10b). Only one child reached floor levels on the task (score of zero) whilst 14 children (66.6%) reached ceiling levels. The child who failed the task was one of the youngest participants whereas all of the five year olds reached ceiling levels, suggesting that this task is not developmentally appropriate across this whole age range.

3.7.4.2.2 Associations with Standardized Measures
An association was observed with parent reports of inhibition on the CBQ-S ($r=.478, \ p=.028$) but this did not remain significant after correction for multiple comparisons. There was no association with parent report of impulsivity on the CBQ-S or inhibition on the BRIEF-P. There was also no association with performance on the NIH task of attention and inhibitory control.
3.7.4.2.3 Relation to previous research

Previous studies have found associations between the Bear & Dragon task and other measures of inhibitory control (Carlson, Moses, & Claxton, 2004; Reck & Hund, 2011). However, this study found no evidence for these associations. This could be due to differences in task design. The current study had a two level scoring system for each trial (correct [1] or incorrect [0]), similar to the original design, while the aforementioned studies had four level scoring systems (e.g. fully correct [3], completed wrong command [2], partial completion of correct command [1], did not complete [0]). The two-level scoring system may have contributed to the ceiling effects found in the current study. Reck and Hund (2011) included the same age range, however in addition to the four level scoring system, they only summed the inhibition trials (where the child had to ignore the command) but not the activation trials (where the child had to follow direction).
Figure 3.10 Association between age and (a) circle tracing task performance and (b) Bear & Dragon score

3.7.4.2.4 Associations between Bear & Dragon and Circle Tracing Task
There were no associations between performance on the Bear & Dragon and the Circle Tracing Task.
3.7.5 Discussion
Age-related improvements in performance on the Bear & Dragon and circle-tracing tasks were observed, however these tasks were not included in phase three, as there was insufficient evidence to suggest that they were sensitive to individual differences in inhibitory control across this age range. This could be due to how the tasks were designed in the current study. Task design for the developmental measures of EF often vary between studies due to a lack of standardised measures and there is a lack of evidence for task reliability and validity (Montgomery & Koeltzow, 2010). This study contributes to the investigation of the psychometric properties for these widely used tasks. Administration of the task battery spanned a long period of time in the piloting period (phase one) and it was speculated that the patients may require even more time (due to the hypothesised difficulties in EF) so it was important that only the valid tasks were prioritised for inclusion in the final battery in phase three. Further reasons for the exclusion of both tasks are outlined below.

3.7.5.1 Circle Tracing Task
As expected, the inhibition time for the current cohort of children was faster than that reported for older children (Scheres et al., 2003) and a relationship between greater inhibitory control and older age was observed. Previous studies report that more impulsive participants find it difficult to slow down when tracing the circle for the second time (Bachorowski & Newman, 1990). However, this association was not observed in the current study, as there was a lack of association between task performance and the standardised measures. The lack of association with standardized tasks could be due to the wide range of inhibition scores, and this task could potentially be more informative with age-normed categories rather than a continuous score, due to the huge impact of age on inhibition time. However, a larger study with typically developing children would be required to create these norms. The larger circle in the current study in comparison to previous studies with this age range could also have been less developmentally appropriate, as children have to inhibit their response for a longer time.
3.7.5.2 Bear & Dragon Task

This task did not produce a range of values, as it was too easy for the older children, which may explain the lack of association with parent reports of behaviour control that has been previously reported (Kochanska et al., 1996). Specifically, it was noted that this task was not an appropriate measure of inhibition in five year olds. This was unexpected, as different versions of this task have been widely used with children from three to six years in the developmental literature (Carlson, White, & Davis-Unger, 2014). This task was discontinued for phase three as fourteen children reached ceiling level in phase one. Future applications of this task across this age range could benefit from a more tiered scoring system (e.g. scoring for initiation of movement that was stopped in time) or from the addition of a more complex inhibition level after a child passes the first 12 trials (Reck & Hund, 2011).

3.8 General Discussion

There is a lack of research that addresses the validity of executive tasks for preschool children (Anderson, 2002). The current study investigated the validity of five executive tasks that were developed as part of this thesis. The attention, working memory, and ecological EF tasks were interpreted as valid and age-appropriate measures from three to five years. However, despite developmental effects on performance in the two inhibitory control tasks, these tasks were considered to require further development before application with patient groups.

Many studies administer behavioural tasks of EF to preschool children that are not validated or standardized and so the current literature is unreliable and inconsistent in both the findings that are reported and in terms of the construct validity of tasks and the extent to which they can be reliably replicated (Beck, Schaefer, Pang, & Carlson, 2011; Carlson, 2005). The psychometric properties of executive tasks in the developmental literature are often not extensively assessed (Montgomery & Koeltzow, 2010). Additionally, there is a great amount of variability in how tasks are scored and administered.
in the literature. The current chapter highlighted some key methodological concerns for further development of more sensitive and informative executive tasks across this age range. It also provided information for easy task replication and introduces the PETA for the first time as an adjunct means to assess EF using a top-down method of testing. Researchers should focus on developing more robust methods of executive assessment that can be easily replicated and interpreted. Future studies should directly compare different scoring and administration techniques in order to develop a ‘gold standard’ way of applying these tasks in research with preschool children.
Chapter 4: General functioning

An investigation of the children with sickle cell anaemia in the current study with a particular focus on factors known to have a potential impact on executive development
4 General Functioning

4.1 Introduction
This chapter aims to characterise the population of preschool children with SCA in this study in terms of selected aspects of non-executive functioning. These domains, namely intellectual ability, family functioning, temperament and sleep behaviours, are areas that have been more widely investigated in the context of school-age children, adolescents and adults with SCA, with less focus on preschool-age children. Poorer functioning in all of these domains has been reported in the literature for children above preschool age with SCA, with some noted exceptions as described in this chapter. Functioning in these domains has been related to disease status and quality of life in SCA and may also play an important role when trying to understand the development of EF in SCA. Indeed, they are known to play a role in the development of EF in the general population and so must be considered when trying to characterise the development of executive ability in any special population, particularly in the case of SCA where poorer EFs have been specifically identified in the literature. It is important to adopt a ‘totality’ approach to the development of cognitive skills in clinical neuropsychology that takes into consideration the physical, cognitive, and psychosocial aspects of a patient (Anderson, Northam, & Wrennel, 2015). The following aims address domains of functioning that have been previously described as important in the context of EF development in typically developing preschool children and in the context of cognitive development in older children with SCA. This chapter aims to elucidate a holistic picture of the children with SCA discussed in this thesis so that the trajectory of EF development in the patient group can be better understood.

4.2 Aims
1. To describe intellectual ability, temperament, sleep problems, and family functioning in preschool children with SCA.
2. To compare general domains of child functioning (intellectual ability, temperament and sleep) of children with SCA with children matched for ethnicity, age, and SES. Poorer functioning in these domains is expected based on previous studies with older children with SCA.

3. To compare family functioning in families with young children with SCA and families without SCA. It is expected that families with young children who have SCA will report poorer family functioning.

This chapter looks at the general functioning of 22 children with SCA in comparison to typically developing ethnicity, age and SES matched children. As some of the matched control children were siblings of children with SCA, the group comparison for parent-reports of family functioning focuses on families with and without SCA².

4.3 Intellectual Ability of Preschool Children with SCA

Low intellectual quotient (IQ) in SCA shows a gradient effect dependent on brain pathology. Children with overt stroke have the lowest scores, followed by those with evidence of silent infarct and infarct-free MRI scans, respectively (Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, & Armstrong, 2001). It is now widely accepted that children with SCA are at risk for neurocognitive impairment from very early on in life (Jeffrey Schatz, Finke, et al., 2002; Thompson et al., 2002). IQ decreases in children with SCA with age, even when there is no evidence of silent infarction (Wang et al., 2001). Alongside infarction, compromised cognitive ability in SCA has been attributed to both disease factors such as chronic anaemia, low haemoglobin oxygen saturation, sleep problems, and socioenvironmental factors such as parental stress, low SES, and poor family functioning (Aygun et al., 2011; Bernaudin et al., 2000 Hogan, Pitten Cate, et al., 2006; Thompson et al., 2002). There have been mixed findings in previous reports

² The family functioning study includes some families who are not ethnicity-matched to increase power, however all families are matched for SES and age.
looking at differences in FSIQ in older children and adults with SCA compared to controls, with one review reporting that only 50% of studies reviewed found a significant difference (Schatz, Finke, et al., 2002). Only one other published study has looked at the intellectual functioning of children with SCA who were less than six years old and who did not have evidence of clinical stroke using standardized IQ scales, reporting a mean IQ of 89 (8.2) (Tarazi et al., 2007). However, this study combined 15 cases of HbSS with other sickle cell genotypes and did not use a matched comparison group without SCA. Additionally, only 26.9% of their whole sample had either TCD or MRI scans to provide information on brain pathology (all were described as unremarkable). Other studies in children with SCA younger than six years have relied on general developmental scales rather than IQ measures to look at cognitive functioning. Glass et al., (2012) reported cognitive and motor delays in toddlers with SCD (HbSS=43) in 80 toddlers using the Bayley Development Scales however developmental scales measure different domains of functioning so cannot be used to predict IQ (Glass et al., 2012).

This is the first study to look at intellectual functioning in preschool children with SCA (HbSS genotype) only, who all have recent TCD scans, using an age, ethnicity and SES matched comparison group.

4.3.1 Method

4.3.1.1 Measures

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-UK; Wechsler, 2002) is a standardized IQ assessment and can be used to obtain full scale IQ as well as verbal and performance IQ. Three year olds completed four core subtests (Block Design, Information, Receptive Vocabulary, Object Assembly) and four and five year olds completed seven core subtests (Block Design, Information, Vocabulary, Matrix Reasoning, Word Reasoning, Picture Concepts, and Coding). As the version of the WPPSI that the three year olds complete differs to that completed by four and five year olds, comparisons on a subtest level will only be made for Block Design and Information which are
available on both versions as part of the core subtests. One-way ANOVAs were used to investigate IQ differences between the patient and control groups. Independent t-tests were used to investigate potential gender differences in the patient group.

4.3.1.2 Participants
SCA children (N=22) were compared with age, SES, and ethnicity-matched Black British comparison children (N=26).

4.3.2 Results

One-way ANOVAs showed no significant differences between the patients and the matched control children for any of the IQ domains although there was a trend for better performance in the Information subdomain for the typically developing children (see Table 4.1). The FSIQ for all SCA children fell within the normal distribution with children spread across the high average (n=5), average (n=10), and low average (n=7) ranges. The average difference in FSIQ between the children with SCA and the matched comparison group was 2.9 points. A clinically significant difference (defined as 15 points or greater) between VIQ and PIQ was found for 31.8% of the patient group. A mixed discrepancy profile was observed for the patients; three children showed greater PIQ whilst four children showed greater VIQ. There was no effect of gender on FSIQ (t(20)=-.27; p=.79), PIQ (t(20)=.42; p=.68) or VIQ (t(20)=-1.35, p=.19).
Table 4.1. A comparison of Full Scale IQ (FSIQ), Performance IQ (PIQ), Verbal IQ (VIQ), Block Design and Information subdomains between the patients and ethnicity-matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=22)</th>
<th>Ethnicity Matched Controls (N=26)</th>
<th>p-value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>98.6 (11.4)</td>
<td>101.5 (11.9)</td>
<td>.396</td>
<td>.02</td>
</tr>
<tr>
<td>VIQ</td>
<td>99.9 (12.6)</td>
<td>103.8 (14.9)</td>
<td>.340</td>
<td>.02</td>
</tr>
<tr>
<td>PIQ</td>
<td>97.8 (13.1)</td>
<td>100.9 (14.9)</td>
<td>.445</td>
<td>.01</td>
</tr>
<tr>
<td>Block Design</td>
<td>9.9 (2.9)</td>
<td>10.3 (3.3)</td>
<td>.693</td>
<td>.004</td>
</tr>
<tr>
<td>Information</td>
<td>9.5 (2.6)</td>
<td>11.3 (3.6)</td>
<td>.056</td>
<td>.08</td>
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Table 4.2. FSIQ for all SCA studies with children who have no known stroke using Wechsler Scales

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>HbSS only (N)</th>
<th>Age range (years) or mean ±SD</th>
<th>Mean FSIQ</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chodorkoff</td>
<td>1963</td>
<td>19</td>
<td>4-14</td>
<td>6 average (90-109) 8 low average (80-89) 3 borderline (70-79) 2 &lt;70</td>
<td></td>
</tr>
<tr>
<td>Fowler et al.</td>
<td>1988</td>
<td>28</td>
<td>6-17</td>
<td>NR but no difference between groups</td>
<td></td>
</tr>
<tr>
<td>Swift et al.</td>
<td>1989</td>
<td>21</td>
<td>7-16</td>
<td>77.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Wasserman et al.</td>
<td>1991</td>
<td>NR/43</td>
<td>8-16</td>
<td>82.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Knight et al.</td>
<td>1995</td>
<td>60</td>
<td>15-18</td>
<td>WISC-R (N=28) 72.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Armstrong et al.</td>
<td>1996</td>
<td>135/194</td>
<td>6-12</td>
<td>WAIS-R (N=32) 80.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Watkins et al.</td>
<td>1998</td>
<td>32</td>
<td>5.9-16.7</td>
<td>86.03</td>
<td>12.0</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Duration (min)</td>
<td>LS (μs)</td>
<td>HB (μs)</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>-------------</td>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Steen et al.</td>
<td>1999</td>
<td>27</td>
<td>4.3-17.9</td>
<td>79</td>
<td>14.9</td>
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<tr>
<td>Bernaudin et al.</td>
<td>2000</td>
<td>155</td>
<td>5-15</td>
<td>86.6</td>
<td>17.1</td>
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<td>Brown et al.</td>
<td>2000</td>
<td>48</td>
<td>6.33-17</td>
<td>81.67</td>
<td>16.68</td>
</tr>
<tr>
<td>Noll et al.</td>
<td>2001</td>
<td>15/31</td>
<td>9-16</td>
<td>85.65*</td>
<td>12.76</td>
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<tr>
<td>Wang et al.</td>
<td>2001</td>
<td>186</td>
<td>6-18</td>
<td>84.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Schatz et al.</td>
<td>2002</td>
<td>18</td>
<td>12.4 ± 1.9</td>
<td>89.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Kral et al.</td>
<td>2003</td>
<td>60</td>
<td>6 -16.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>2003</td>
<td>93</td>
<td>5-15</td>
<td>90.2</td>
<td>13.1</td>
</tr>
<tr>
<td>Kral et al.</td>
<td>2004</td>
<td>62</td>
<td>6-16.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steen et al.</td>
<td>2005</td>
<td>54</td>
<td>10.9 ± 2.9</td>
<td>79.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Baldeweg et al.</td>
<td>2006</td>
<td>20/36</td>
<td>17.1 (4.1)</td>
<td>92*</td>
<td>14.0</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Mean ± SD</td>
<td>Normal TCD (n=25)</td>
<td>Conditional TCD (n=15)</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Hogan et al.</td>
<td>2006</td>
<td>13/30</td>
<td>17.4± 4.2</td>
<td>87.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Kral et al.</td>
<td>2006</td>
<td>60</td>
<td>6 -16.11</td>
<td>Normal TCD (n=25) 91.2</td>
<td>Conditional TCD (n=15) 90.3</td>
</tr>
<tr>
<td>Schatz et al.</td>
<td>2006</td>
<td>12/28</td>
<td>12.3±2.7</td>
<td>87.59</td>
<td>11.42</td>
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<tr>
<td>Strouse et al.</td>
<td>2006</td>
<td>NR/24</td>
<td>6-12/8.5 ± 2.0</td>
<td>No Hx of attention problems (N=14) 101</td>
<td></td>
</tr>
<tr>
<td>Tarazi et al.</td>
<td>2007</td>
<td>15/26</td>
<td>3-5</td>
<td>89*</td>
<td>NR</td>
</tr>
<tr>
<td>Gold et al.</td>
<td>2008</td>
<td>NR/52</td>
<td>7-17</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>Hijmans et al.</td>
<td>2011</td>
<td>NR/38</td>
<td>6-18</td>
<td>80*</td>
<td>12.5</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>N/Range</td>
<td>Mean FSIQ</td>
<td>FSIQ 95% CI</td>
<td>Notes</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>---------</td>
<td>------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Scantlebury et al.</td>
<td>2011</td>
<td>10/15</td>
<td>11.67±3.15</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>Berg et al.</td>
<td>2012</td>
<td>21/22</td>
<td>8-12</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>Holloks et al.</td>
<td>2012</td>
<td>9/10</td>
<td>8-16</td>
<td>87</td>
<td>16.12</td>
</tr>
<tr>
<td>King et al.</td>
<td>2013</td>
<td>51</td>
<td>5-15</td>
<td>99.53</td>
<td>13.08</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>2013</td>
<td>50/82</td>
<td>6-12</td>
<td>93.62*</td>
<td>12.14</td>
</tr>
<tr>
<td>Kawadler et al.</td>
<td>2015</td>
<td>25</td>
<td>13.07±2.82</td>
<td>103.12</td>
<td>11.95</td>
</tr>
<tr>
<td><strong>Current Study</strong></td>
<td>2015</td>
<td>22</td>
<td>3-5</td>
<td>98.6</td>
<td>11.42</td>
</tr>
</tbody>
</table>

*Mean FSIQ for HbSS only presented combined with other genotypes. NR=Not Reported
4.3.3 Discussion

All of the children with SCA showed intellectual functioning within the average range, as defined by the Wechsler Scales (Wechsler, 2002). There was no difference between the children with SCA and the matched comparison group in line with previous reports of greater IQ decrements with age in children with SCA (Schatz et al., 2002). Table 4.2 shows a review of other studies that have used the Wechsler scales to look at FSIQ in children with SCA with no history of neurological damage. The mean FSIQ of the current patient population (98.6) is greater than the average of the listed studies that report FSIQ for children with SCA (HbSS genotype) only (87.7). The average difference in FSIQ between the children with SCA and the matched comparison group was less than the average 4.3 difference reported for school-age children (Schatz, Finke, et al., 2002). Tarazi et al. (2007) reported a significant difference between VIQ and PIQ for 54% of their patients, however the rate of significant differences between VIQ and PIQ was at a typical rate in the current group. A clinically significant difference (defined as 15 points or greater) between VIQ and PIQ was found for 31.8% of the current patient group while a rate of approximately 21% has been reported for this discrepancy in either direction in the general population (Grossman, Herman, & Matarazzo, 1985). Glass et al., (2012) reported that male toddlers with SCA had a greater rate of developmental delay than female toddlers on the Bayley Mental Index but no effect of gender was observed for IQ in the current study.

It has been reported that IQ in SCA is affected by a combination of biologic and SES factors (King et al., 2014). The mean IQ of the current SCA population is greater than the average of the reviewed HbSS studies. This may be a result of a younger age group in the current sample in line with previous reports of a decline in some domains with age and disease progression (Schatz et al., 2002; Wang et al., 2001). It could also be
attributed to better care in recent years, noting that the findings of the most recent studies reviewed are more comparable to the current study. Schatz et al., (2002) point out that the commonly used Wechsler scales used to measure IQ do not tap into important areas like EF, and as most studies in the literature typically report general IQ scores, potential deficits in specific areas, such as the Information subdomain, may be underestimated. This underscores the importance of administering tasks that tap specific skills as well as looking at general domains of functioning in children with SCA, in order to better understand the trajectory of this neurodevelopmental disorder (Schatz & McClellan, 2006), particularly at a stage where an IQ disparity from normal range cannot yet be observed for children with SCA. Through early assessment, a baseline can be formed for children with SCA, allowing for a more detailed overview of how a developmental delay or disparity in IQ may develop over time, and offering the opportunity to tackle early cognitive issues before they become more ingrained. The findings of the current study, showing the lack of difference between the two groups, also allow us to control for IQ in our investigations of executive development in subsequent chapters.

4.4 Family functioning of families with young children with SCA
There is an abundance of evidence for the effects of positive home environment and family functioning on academic and cognitive outcomes in young children (Burchinal, Campbell, Brayant, Wasik, & Ramey, 1997; Luster & Dubow, 1992; Molfese & Molfese, 2002; Payne, Whitehurst, & Angell, 1994). Family functioning concerns multiple family dimensions that look at aspects of healthy relationships within the family context, family emphasis on goals and activities, and the degree of organisation or system-maintenance in the home (Kronenberger & Thompson, 1990). Preschool-age children spend more of their time in the family context in relation to older children and adolescence and so the impact of this environment on executive development is particularly pertinent during this period (Schroeder & Kelley, 2010). Indeed, children with SCA may be specifically vulnerable to stressful home
environments due to the effects of their chronic disease (Thompson et al., 2002). Some studies have shown no association with disease severity but significant effects of environmental factors on neurocognitive functioning in children with SCA (Brown, Buchanan, et al., 1993; Tarazi et al., 2007). Greater control in families with SCA, which may foster a lack of independence in children (Kronenberger & Thompson, 1990), is hypothesized to be due to the increased stressors associated with having a child with a chronic illness (Burlew et al., 1989; Kronenberg & Thompson Jr, 1990). One study found that behavioural problems were related to parent-reported levels of family conflict (R. Thompson et al., 2003). Children with SCD are reported to display more behavioural and social problems than their non-affected siblings that increase with age and are associated with family cohesion (Brown, Buchanan, et al., 1993).

Certain aspects of family environment, such as greater expression, cohesion, organization and lower family conflict, have already been highlighted in terms of their impact on executive and behavioural development in both typically developing children and patient populations (Lucia & Breslau, 2006; Moos, 2002; Nadebaum, Anderson, & Catroppa, 2007; Schroeder & Kelley, 2010). Lucia and Breslau (2006) found that family cohesion on the Family Environment Scale (FES) at six years was predictive of internalizing and attention problems at six and eleven years in typically developing children (n=823). Another study found that family cohesion and expression served as a protective factor for problem behaviours in typically developing preschool children (Halpern, 2004). A study that looked at family environment in African-American preschool children (n=184) found that children from families with lower reported conflict had less externalizing behavioural problems (Koblinsky, Kuvalanka, & Randolph, 2006). It has been reported that poor family environment may be conducive to stress, which can impact the development of the prefrontal cortex (Fishbein, Hyde, Coe, & Paschall, 2004; Skosnik, Chatterton, Swisher, & Park, 2000).
4.4.1 Method

4.4.1.1 Procedure
Parents completed the FES, a 90-item true-false measure of family functioning that produces 10 subscales, three factor domains that describe family dynamics (conflicted, controlling, supportive) and a composite score. The Supportive factor (cohesion + expression + independence + active-recreational orientation + intellectual - cultural orientation) measures family mutual interest, concern, and support across a wide domain. The Conflicted factor (conflict- (cohesion + organization)), on the other hand, reflects a dimension of conflict that lacks organization or support. Finally, the Controlling factor ((control + achievement orientation)+moral-religious emphasis)-independence) represents the use of competition and rules to control the family (Kronenberger & Thompson, 1990). The FES composite score involves adding the subscales of cohesion, expression, organization, and active-recreational and then subtracting the conflict and control subscales. A higher FES composite indicates a more positive family environment (please refer to Chapter 2 for further task description). A one-way MANOVA was performed to examine whether family environment differed across all subscales as a function of SCA categorisation.

4.4.1.2 Participants
Thirty-three families with preschool-age children with SCA participated in the study (two questionnaires were not completed). Thirty-two comparison families without children with SCA (or any other chronic illness) were recruited (four questionnaires were not completed). The two family groups were matched for socioeconomic status based on postcode, mother’s education, age, and gender. The two groups were not matched for ethnicity. All of the families with SCA identified as Black British whilst the comparison group was comprised of 22% Black British, 18% Mixed or Asian British, and 60% White/White British.
4.4.2 Results

4.4.2.1 Comparison with current sample of typical families
There was a statistically significant difference in overall parent reports between those who had a child with SCA and those who did not, F (10,44)=7.03, p<.001, Wilk’s ^ = .385. Further analysis showed that parent reports on six of the 10 scales were statistically different (see figure 4.1 for individual subscales). Families without SCA showed higher cohesion and higher expression, but less of an emphasis on achievement/orientation and moral/religious values, organization, and control. To increase power and reduce the likelihood of a Type 1 error, a FES composite score was also calculated by combining the six most internally reliable scores as described by Perrin, Ayoub, and Willett (1993). As expected, significantly poorer FES composite scores in families with children with SCA were found (Mean=115.7, SD=28.1) as compared to families without young children with SCA (Mean=134.5, SD=27.3; p=.008). When looking at group differences for higher order FES factors in families with SCA (Kronenberger & Thompson, 1990), significant differences were seen for supportiveness and controlling (p<.05), but not for conflicted. The SCA group was compared with the ethnicity-matched families only from the comparison group (n=7) on the individual subscales and the total composite score. A significant difference remained for cohesion (p=.017) and control (p=.015), with trends for differences in expression (p=.08) and the total composite score (p=.09).
**Figure 4.1.** Group profiles on the Family Environment Scale Report Form for the families with SCA and the control group
Table 4.3. Previous studies with SCD and other reported chronic childhood illnesses that have administered the FES.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetes (Kronnenberg &amp; Thompson, 1990; n=31)</th>
<th>Cancer (Kronnenberg &amp; Thompson, 1990; n=29)</th>
<th>Spina Bifida (Kronnenberg &amp; Thompson, 1990; n=49)</th>
<th>SCA w/ bp (Thompson et al., 1999; n=86)</th>
<th>SCD w/o bp (Thompson et al., 1999; n=203)</th>
<th>SCD preschool (Barakat et al., 07/Tarazi et al., 07; n=27)</th>
<th>SCD adolescent (Barakat et al., 07; n=41)</th>
<th>Current SCA (n=33)</th>
<th>Current typical ethnicity (n=32)</th>
<th>Current typical ethnicity match subgroup only (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohesion</td>
<td>50.4</td>
<td>54.8</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td>53.5</td>
<td>60.7</td>
<td>62.8</td>
<td></td>
</tr>
<tr>
<td>Expression</td>
<td>54.9</td>
<td>52.4</td>
<td>52.2</td>
<td></td>
<td></td>
<td></td>
<td>48.8</td>
<td>57.8</td>
<td>57.0</td>
<td></td>
</tr>
<tr>
<td>Conflict</td>
<td>50.9</td>
<td>51.8</td>
<td>47.9</td>
<td></td>
<td></td>
<td></td>
<td>43.2</td>
<td>43.1</td>
<td>43.8</td>
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</tr>
<tr>
<td>Independence</td>
<td>46.2</td>
<td>51.8</td>
<td>48.9</td>
<td></td>
<td></td>
<td></td>
<td>48.5</td>
<td>48.5</td>
<td>55.0</td>
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<tr>
<td>Achievement</td>
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<td>54.0</td>
<td>49.4</td>
<td></td>
<td></td>
<td></td>
<td>54.1</td>
<td>44.1</td>
<td>49.5</td>
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<tr>
<td>Intellectual-culture</td>
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<td>46.3</td>
<td>45.7</td>
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<tr>
<td>Active-rec</td>
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<td>44.4</td>
<td>46.9</td>
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<td></td>
<td></td>
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<tr>
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<td>61.9</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Moral-religious</td>
<td>51.9</td>
<td>51.9</td>
<td>52.9</td>
<td>49.8</td>
<td>49.2</td>
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<tr>
<td>Organization Control</td>
<td>52.7</td>
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<td>*Supportive</td>
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<td>249.7</td>
<td>246.7</td>
<td>260.5</td>
<td>270.1</td>
<td>282.2</td>
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<td>*Conflicted</td>
<td>-51.3</td>
<td>-54.9</td>
<td>-58.0</td>
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<td>-70.2</td>
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<tr>
<td>*Controlling</td>
<td>118.1</td>
<td>116.8</td>
<td>115.3</td>
<td>115.2</td>
<td>86.7</td>
<td>92.2</td>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>120.28</td>
<td>96.03</td>
<td>115.7</td>
<td>134.5</td>
<td>138.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4.3 Discussion

In this study, families with SCA showed poorer family functioning, particularly in the domains of supportiveness and control. Mean FES composite score for the families with young children with SCA were comparable to that reported by Tarazi et al., (2007) in a group of African American preschool children with SCD. A summary of the findings from previous studies that investigated family functioning using the FES in families with children with SCD and other chronic conditions is shown in Table 4.3. Only two previous studies reported the family composite scores for children with SCD. The composite score for patients in the current study is similar to the previous study in families with SCD with preschool children (Barakat et al., 2007; Tarazi et al., 2007) but are more positive than the findings of families who have adolescent children with SCD (Barakat et al., 2007). Although individual subscales were not reported in previous SCA studies, other studies that have looked at chronic childhood illnesses show some similarities to the current group (Table 5.3). In contrast to the findings of the current study and previous sickle cell studies, the only other study to administer the FES in the UK found that families with SCD reported more cohesion than comparison families (Midence, McManus, Fuggle, & Davies, 1996). The reasons for this contrast in findings are unclear. The previous study was conducted in the UK over two decades ago and they also used a combination of HbSS and HbSC families, rather than HbSS only, making it difficult to tease out the influence of a typically more severe disease presentation in patients with HbSS. Greater control in families with SCA in comparison to control families has been hypothesized to be due to the increased stressors associated with having a child with a chronic illness (Burlew et al., 1989). Studies have found that parents of children with SCD report that they find their caring responsibilities to be stressful and demanding (Atkin & Ahmad, 2000). Disease-related parenting stress was shown to be a mediator between pain frequency and health related quality of life in adolescents with SCD.
Thompson and colleagues (2003) found that family functioning did not change over time in a longitudinal study that spanned nine years. However, Barakat and colleagues (2007) report poorer family functioning in families with adolescent children with SCA than the figures reported for families with young children with SCA, suggesting a potential decline over time. Children with SCD have been reported to display more internalizing and externalizing behavioural, as well as social problems than their non-affected siblings (Brown et al., 1993). These problems were reported to increase with age and were associated with family cohesiveness. More adaptive family functioning can allow for better adjustment to dealing with SCA diagnosis (Anie, 2005).

Thompson and colleagues found that low levels of support and high control were associated with poor maternal adjustment (Thompson et al., 1993). Family functioning has been previously been flagged as a salient target for intervention for families with SCA (Thompson et al., 1999). Several studies have found that family environment has an impact on both internalizing and externalizing behaviours in children with SCA (Brown, Buchanan, et al., 1993; Burlew, Telfair, Colangelo, & Wright, 2000; Lewis & Kliewer, 1996). There have been very few studies but mixed findings have been found for family functioning interventions for families with SCA largely due to high rates of study attrition (Daniel et al., 2015; Davis-Kean, 2005). The relationship between family environment and the development of executive skills is likely to be a multifaceted one. Figure 4.2 shows a proposed model that delineates the impact of family functioning, alongside other socio-demographic and psychosocial factors, on the cognitive development of children with SCD. The key components for intervention are likely to be complex. However it is a worthwhile avenue for future research given the growing body of research that conveys the impact of poor home environments on behavioural and cognitive development. Chapter 8 further investigates the potential influence of family functioning on executive development.
Figure 4.2. Proposed pathway reproduced from Thompson et al., (2002), showing the proposed impact of combined parenting coping mechanisms, and biomedical risks factors, on neurocognitive development in children with SCA.

Hence, understanding family functioning in the context of executive development is particularly important for children with SCA for two reasons; they are at a heightened risk of developing executive deficits and the impact of poor SES on development has been specifically highlighted for this patient population in the literature who often are facing challenges associated with immigration and ethnic minority factors. Poor SES is known to particularly affect the executive system in comparison to other cognitive domains (Noble et al., 2005). As family functioning is reported as a mediator for SES (Sarsour et al., 2011), there is a potential for the development of psychosocial interventions with the goal of promoting cognitive and behavioural development(Thompson et al., 1999).

4.5 Temperament of preschool children with SCA

Children with SCD have more internalizing and externalizing behavioural problems than their siblings (Brown et al., 1993). Thompson et al., (2003)
found that 9% of their sickle cell cohort had problem behaviours. Sickle cell disorders have been associated with increased anxiety, depression, aggression, and social withdrawal, which emphasizes the importance of a focus on adaptive responses in children with SCA (Anie, 2005). Temperament can be described as individual differences in emotional, motor, and attentional response to events and the way we can modulate or self-regulate our reactions (Rothbart, 2007). It is typically characterised as a biological predisposition to respond to the environment in certain ways and it is hypothesised to surface very early and to be relatively stable throughout life (Caspi & Shiner, 2006; McCrae et al., 2000). It has been postulated that increase autonomic nervous system reactivity to stress in children with SCA may have an influence on temperament (Schatz & Roberts, 2007).

Few studies have investigated the potential impact of SCA on temperament with mixed results in the available literature (Noll et al., 2001). Schatz and Roberts (2007) used the Emotionality-Activity-Sociability (EAS) Temperament Survey to look at emotionality, activity, shyness, and sociability in 61 toddlers between 12-18 and 32-40 months, 24 with “low” (HbSC/HbSB+) and 37 with “high” risk (HbSS/HbSB0) SCD. They found that the high-risk group, mostly HbSS children, showed less activity than the less severe group, which they hypothesized may be a result of behavioural adaption to the disease. Brown et al., (1993) used the Teacher Temperament Questionnaire to look at the domains of task orientation, adaptability, and cohesion in 6-17 year olds (n=61), finding no differences with ethnicity-matched sibling controls (n=15). Noll and colleagues found no differences in temperament between 34 8-14 year olds with SCD (HbSS/HbSB0=18) and their classroom peers using the Revised Dimensions of Temperament Survey (Noll et al., 1996). Aspects of temperament may be associated with EF (Rothbart, Posner, & Kieras, 2006). Previous studies have described the potential importance of exploring temperament constructs, such as effortful control and their relation to EF (Schatz & Roberts, 2007). A strong relationship between the development of executive functions and maladaptive temperament on the
CBQ and problem behaviour on the Children’s Behaviour Checklist has been reported in preschool children (Espy, Sheffield, Wiebe, Clark, & Moehr, 2011). This study is the first time that temperament has been investigated in preschool-age children with SCA. The current study investigates potential parent reported differences in temperament for children with SCA and ethnicity, age, IQ, and SES matched controls. As this is the first time that the CBQ has been used to look at temperament in children with SCA, I will also investigate the internal consistency of the scale. It cannot be assumed that the reliability of a measure established for typically developing children will generalize to a specific patient group (Hepburn & Stone, 2006).

4.5.1 Method

4.5.1.1 Procedure
The short version of the Children’s Behaviour Questionnaire (CBQ-S; Putnam & Rothbart, 2006) was administered to parents to assess temperament. The questionnaire consists of 94 items that form 13 dimensions including impulsivity, inhibitory control, focusing attention, shyness, sadness, anger/frustration, and activity levels. Parents are asked to answer, on a scale of 1 (extremely untrue) to 7 (extremely true), how true each statement is for their child (see Chapter 2 for further task description). Cronbach’s alpha was used as the reliability analysis to investigate the internal consistency of the CBQ subdomains in children with SCA. A one-way MANOVA was performed to examine whether overall temperament differed between groups.

4.5.1.2 Participants
The parents of 21 patients with SCA aged 3 to 5 years (one parent did not complete the questionnaire) successfully completed the questionnaire. Twenty-six ethnicity-matched children, that were also age, IQ, and SES-matched, were drawn from the larger cohort of typically developing preschool-age children with completed CBQ-S (N=159) that were collected as part of this thesis.
4.5.2 Results

4.5.2.1 Scale Reliability in SCA

Alpha scores are generally lower in the current patient group than the values reported for typically developing children with many not meeting the generally accepted value of .65 (Putnam & Rothbart, 2006; Table 4.5).

4.5.2.2 Group Differences

There was no statistically significant difference in overall temperament between children with SCA and those without SCA; F (13,33)=1.51, p=.166, Wilk’s ^^ = .627. Further analysis of the 13 subdomains showed that there was a significant difference between the two groups for discomfort only (Table 4.4). This discrepancy was further investigated for the patient group to explore whether parent-reported discomfort was related to disease severity (defined as number of hospital admissions in the previous year for the current study). Figure 4.3 shows that higher negative affect related to sensory stimulation on the CBQ was associated with the number of hospital admissions in the previous year for the patients (r=.567, p=.007).
Table 4.4. Group differences on individual subscales of the CBQ-S using one-way ANOVA.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Patients (N=21) Mean (SD)</th>
<th>Ethnicity Matched Controls (N=26) Mean (SD)</th>
<th>Group Effect F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity Level</td>
<td>4.6 (0.93)</td>
<td>4.9 (.75)</td>
<td>1.225</td>
<td>0.274</td>
</tr>
<tr>
<td>Anger/Frustration</td>
<td>4.4(1.02)</td>
<td>3.9 (1.2)</td>
<td>2.42</td>
<td>0.127</td>
</tr>
<tr>
<td>Attentional Focusing</td>
<td>4.9 (1.04)</td>
<td>4.9 (0.89)</td>
<td>.003</td>
<td>0.953</td>
</tr>
<tr>
<td>Discomfort</td>
<td>5.14 (0.99)</td>
<td>4.25 (1.02)</td>
<td>10.294</td>
<td>.002**</td>
</tr>
<tr>
<td>Falling Reactivity/Soothability</td>
<td>5.1 (0.99)</td>
<td>5.5 (0.65)</td>
<td>2.931</td>
<td>.094</td>
</tr>
<tr>
<td>Fear</td>
<td>4.4 (0.96)</td>
<td>3.9 (1.11)</td>
<td>3.708</td>
<td>.060</td>
</tr>
<tr>
<td>High Intensity Pleasure</td>
<td>4.42(1.06)</td>
<td>4.62 (0.84)</td>
<td>.411</td>
<td>0.525</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>4.3 (0.67)</td>
<td>4.4 (1.01)</td>
<td>.183</td>
<td>.671</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>5.0 (0.99)</td>
<td>4.7 (0.61)</td>
<td>.785</td>
<td>.380</td>
</tr>
<tr>
<td>Perceptual Sensitivity</td>
<td>5.8 (0.66)</td>
<td>5.33 (0.92)</td>
<td>3.013</td>
<td>0.089</td>
</tr>
<tr>
<td>Sadness</td>
<td>4.4 (1.17)</td>
<td>3.9 (0.87)</td>
<td>2.243</td>
<td>0.141</td>
</tr>
<tr>
<td>Shyness</td>
<td>3.9 (1.2)</td>
<td>3.2 (1.3)</td>
<td>2.884</td>
<td>.096</td>
</tr>
<tr>
<td>Smiling/Laughter</td>
<td>5.6 (0.77)</td>
<td>5.8 (0.85)</td>
<td>.375</td>
<td>0.543</td>
</tr>
</tbody>
</table>

***p<.001 ** p<.01 *p<.05
Figure 4.3. **CBQ Discomfort**: A higher negative affect is related to sensory stimulation on the CBQ was associated with the number of hospital admissions in the previous year ($r=.567$, $p=.007$).
Table 4.5. Comparison of Cronbach’s Alpha for the CBQ in children with SCA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity Level</td>
<td>.75</td>
<td>.46</td>
<td>.39</td>
</tr>
<tr>
<td>Anger/Frustration</td>
<td>.76</td>
<td>.33</td>
<td>.71</td>
</tr>
<tr>
<td>Approach/Positive</td>
<td>65</td>
<td>.12</td>
<td>.64</td>
</tr>
<tr>
<td>Attentional Focusing</td>
<td>.75</td>
<td>.40</td>
<td>.20</td>
</tr>
<tr>
<td>Discomfort</td>
<td>.79</td>
<td>.57</td>
<td>.59</td>
</tr>
<tr>
<td>Soothability</td>
<td>.73</td>
<td>.58</td>
<td>.11</td>
</tr>
<tr>
<td>Fear</td>
<td>.68</td>
<td>.36</td>
<td>.41</td>
</tr>
<tr>
<td>High Intensity Pleasure</td>
<td>.72</td>
<td>.68</td>
<td>.38</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>.72</td>
<td>.77</td>
<td>.79</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>.72</td>
<td>.11</td>
<td>.12</td>
</tr>
<tr>
<td>Low Intensity Pleasure</td>
<td>.69</td>
<td>.77</td>
<td>.61</td>
</tr>
<tr>
<td>Perceptual Sensitivity</td>
<td>.73</td>
<td>.25</td>
<td>.65</td>
</tr>
<tr>
<td>Sadness</td>
<td>.61</td>
<td>.37</td>
<td>.45</td>
</tr>
<tr>
<td>Shyness</td>
<td>.85</td>
<td>.64</td>
<td>.84</td>
</tr>
<tr>
<td>Smiling/Laughter</td>
<td>.71</td>
<td>.35</td>
<td>.60</td>
</tr>
</tbody>
</table>
4.5.3 Discussion

The patients with SCA scored significantly poorer on the discomfort domain than the matched comparison group. The higher scores in discomfort and perceptual sensitivity for the patient group could be due to a higher reactivity to pain as a result of the SCD process (Dampier, Ely, Brodecki, & O'Neal, 2002). This is in line with the reasoning that the finding for lower activity could be directly attributed to the disease process in young children with SCA (Schatz & Roberts, 2007).

Noll et al. (1996) purposefully chose a measure that excluded behavioural items relating to the potential medical effects of SCA, such as overtiredness and underactivity, which may be a more informative route when making future comparisons. The lack of significant differences in other domains resembles the lack of temperament differences reported in the only other study that looked at temperament in young children with SCA (Schatz & Roberts, 2007). Although the CBQ is widely used in the preschool literature, to the author’s knowledge it has not been previously administered to families with SCA so specific comparisons within that population cannot be made. A limitation of this study is that due to the number of questionnaires the parents were asked to complete, the short version of this questionnaire was chosen so each subscale is based on six to eight items. This may have reduced the breadth of information captured for temperament; however the short version of the form has been found to show good reliability in typically developing children. Although poorer internal consistency has been found in African American and lower SES families for the short form, the alpha coefficients for internal consistency are generally stronger for the subdomain of discomfort in the short scale than the standard scale (Putnam & Rothbart, 2006), the only domain that was significantly different between the two groups. Nevertheless, the current study generally found lower alpha scores for the CBQ domains in children with SCA, so interpretation of this measure must be made with caution. Lower alpha scores for this measure have also been observed in other patient groups such as children born pre-term, children who have Down’s syndrome or children with ASD (De Pauw, Mervielde, Van Leeuwen, &
De Clercq, 2011; Nygaard, Smith, & Torgersen, 2002). Notably, low alpha value were also observed for the matched comparison group in the current study which is in line with reports of poorer scale reliability in lower SES and ethnic minority families (Putnam & Rothbart, 2006).

In conclusion, the children with SCA are similar in temperament to ethnicity and age-matched control children, apart from their levels of discomfort which may directly be influenced by aspects of the physical sickle disease process, specifically the experience of pain, as supported by the association with number of hospital admissions. Interestingly, there were no differences on the temperament variables of effortful control that have been previously related to EF. The lack of difference may be due to the reliability of the measure or it may be that if there are differences between the groups on these domains, they may not have yet emerged or may not be observable on an everyday level. This measure was not as reliable as in prior reports of typical children, for children in this study with SCA or the ethnicity and SES matched controls, so future research should consider measuring reliability within the SCA group when applying future temperament measures.

### 4.6 Sleep Problems in children with SCA

Sleep problems are reported more frequently in preschool children than school-age children and are associated with poorer quality of life, behavioural problems, and higher rates of attention disorders (Goodlin-Jones et al., 2008; Hiscock, Canterford, Ukoumunne, & Wake, 2007). Higher rates of sleep problems have been reported in children with SCA when compared to typically developing children (Daniel et al., 2010). There are reports of an increased occurrence of sleep disorders such as sleep disordered breathing (SDB) and enuresis as well as more disrupted sleep in general in children with SCA (Daniel et al., 2010).

The potential neurocognitive sequelae of the nocturnal physiologic disturbances of SDB, such as higher rates of nocturnal hypoxemia (Hill et al., 2006), on regions of the brain including the prefrontal cortex and the
hippocampus, can affect EF during the day, as well as the impact of disrupted sleep and daytime tiredness on a child’s ability to concentrate (Simola et al., 2010). Clinical SDB prevalence rates as high as 41% have been reported in children with SCA (Samuels et al., 1992; Telfer et al., 2012; Rosen et al., 2014). Research suggests that the impact of sleep problems on EF can be detected in the preschool years (Jackman et al., 2012; Karpinski et al., 2008; Scullin et al., 2011). One study found that preschool children with SDB were significantly impaired on tasks of EF (Landau et al., 2011). However, there has been little focus on the impact of sleep on EF in paediatric patient populations who have known EF deficits and a higher prevalence of sleep problems, despite the impact of poor sleep quality, such as frequent snoring, on EF (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2015). Thus, sleep behaviours should be monitored in a study of children with SCA that investigates EF for two reasons; 1) the higher rate of reported sleep problems found for this population in previous studies and 2) the hypothesised impact of the combined burden of SCA and SDB on executive development.

4.6.1 Method

4.6.1.1 Procedure
All parents filled out an adapted version of Children Sleep Habits Questionnaire (see Chapter 2 for task description). The rater created weighted sleep composite scores based on the amount of poor sleep symptoms and their rate of occurrence. Scores could range from 0 (no reported problems ever observed) to the possible highest rating of 80 (all of the 20 potential symptoms occurring ‘6-7 nights’ a week). An independent t test was used to compare the sleep composite score between patients and the matched controls.

4.6.1.2 Participants
Parents of 22 patients completed the questionnaire as well as the parents of 26 ethnicity, age, SES, and IQ-matched controls (two parents did not complete the whole questionnaire and were excluded from analysis). Data collected from parents of a larger sample of typically developing preschool
children in Greater London (n=166) were also included to establish the prevalence of sleep issues in unselected preschool children in Greater London. Eleven of the questionnaires from the larger cohort were not completed so data is presented for 155 typically developing children.

4.6.2 Results
The patients had a significantly higher rate of sleep problems (M=21.47, SD=11.67) as reflected by a higher sleep composite score when compared to the matched controls (M=11.21, SD=9.83; p=.002). Over 27% of children with SCA in the current population had sleep composite scores greater than 1.5 standard deviations over the London normative mean obtained in this study (M=14.41, SD=9.64, N=155), mirroring a recent preliminary report on 1 to 4 year-olds with SCA where 27% were found to have sleep-disordered breathing via oximetry (Dundas et al., 2012). This is in comparison to two (8.3%) of the matched comparison children and twelve (8%) of the total London cohort of typically developing children. Table 4.6 shows the parent-reported rates of each of the 20 night-time sleep problems in the patient group, showing snoring, resisting bed-time, restless sleep and bed-wetting to be the most frequently reported issues.
Table 4.6. Rate of parent-reported night-time symptoms

<table>
<thead>
<tr>
<th>Night time weekly symptom occurrence N (%)</th>
<th>Never (Does not occur)</th>
<th>Not often (&lt;1 night)</th>
<th>Sometimes (1 to 2 nights)</th>
<th>Often (3 to 5 nights)</th>
<th>Always (6 to 7 nights)</th>
<th>Don’t Know/Missing</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snores</td>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (9.1)</td>
<td>3(13.8)</td>
<td>9(40.9)</td>
<td>2(9.1)</td>
<td>6(27.3)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Matched Controls</td>
<td>14(58.3)</td>
<td>4(16.7)</td>
<td>4(16.7)</td>
<td>1(4.2)</td>
<td>1(4.2)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>London Cohort</td>
<td>66(39.8)</td>
<td>30(18.1)</td>
<td>40(24.1)</td>
<td>9(5.4)</td>
<td>4(2.4)</td>
<td>17(10.2)</td>
</tr>
<tr>
<td>Difficulty breathing while asleep Patients</td>
<td>14(63.6)</td>
<td>2(9.1)</td>
<td>2(9.1)</td>
<td>1(4.5)</td>
<td>2(9)</td>
<td>-</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Matched Controls</td>
<td>20(83.3)</td>
<td>3(12.5)</td>
<td>1(4.2)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>London Cohort</td>
<td>132(79.5)</td>
<td>15(9.0)</td>
<td>5(3.0)</td>
<td>2(1.2)</td>
<td>-</td>
<td>12(7.2)</td>
</tr>
<tr>
<td>Stops breathing during sleep Patients</td>
<td>19 (86.4)</td>
<td>1(4.5)</td>
<td>2(9.1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Matched Controls</td>
<td>23(95.8)</td>
<td>-</td>
<td>1(4.2)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>------------------</td>
<td>---------------</td>
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</tr>
<tr>
<td>Noisy breathing Patients</td>
<td>143(91.1)</td>
<td>2(1.2)</td>
<td>2(1.2)</td>
<td>1(0.6)</td>
<td>-</td>
<td>18(10.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Matched Controls</td>
<td>10 (45.5)</td>
<td>1(4.5)</td>
<td>6(27.3)</td>
<td>2(9.1)</td>
<td>3(13.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>London Cohort</td>
<td>17(70.8)</td>
<td>2(8.3)</td>
<td>1(4.2)</td>
<td>-</td>
<td>2(8.3)</td>
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<td></td>
</tr>
<tr>
<td>Restless sleep Patients</td>
<td>85(51.2)</td>
<td>28(16.9)</td>
<td>26(15.7)</td>
<td>9(5.4)</td>
<td>5(3.0)</td>
<td>13(7.8)</td>
<td></td>
</tr>
<tr>
<td>Matched Controls</td>
<td>6(27.3)</td>
<td>4(18.2)</td>
<td>6(27.3)</td>
<td>4(18.2)</td>
<td>2(4.5)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>London Cohort</td>
<td>17(70.8)</td>
<td>5(20.8)</td>
<td>1(4.2)</td>
<td>-</td>
<td>1(4.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>London Cohort</td>
<td>62(37.3)</td>
<td>51(30.7)</td>
<td>27(16.3)</td>
<td>9(5.4)</td>
<td>2(1.2)</td>
<td>15(9.0)</td>
<td></td>
</tr>
<tr>
<td>Sweating when sleeping Patients</td>
<td>209(51.2)</td>
<td>138(37.3)</td>
<td>138(37.3)</td>
<td>85(51.2)</td>
<td>2(1.2)</td>
<td>15(9.0)</td>
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</tr>
<tr>
<td>Matched Controls</td>
<td>70(75.0)</td>
<td>60(65.0)</td>
<td>60(65.0)</td>
<td>51(51.0)</td>
<td>3(16.7)</td>
<td>14(8.4)</td>
<td></td>
</tr>
<tr>
<td>London Cohort</td>
<td>143(91.1)</td>
<td>143(91.1)</td>
<td>143(91.1)</td>
<td>143(91.1)</td>
<td>2(1.2)</td>
<td>18(10.8)</td>
<td></td>
</tr>
<tr>
<td>Nightmares Patients</td>
<td>6(27.3)</td>
<td>5(22.7)</td>
<td>5(22.7)</td>
<td>3(13.6)</td>
<td>-</td>
<td>3(13.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Matched Controls</td>
<td>18(75.0)</td>
<td>18(75.0)</td>
<td>18(75.0)</td>
<td>18(75.0)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>before falling asleep</td>
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<td>-</td>
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<td>8(33.3)</td>
<td>2(8.3)</td>
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<td>43(25.9)</td>
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<td>12(7.2)</td>
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<td>Trouble staying in bed at</td>
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<td>2(8.3)</td>
<td>1(4.2)</td>
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<tr>
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<td>Matched Controls</td>
<td>London Cohort</td>
<td>London Cohort</td>
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<tr>
<td><strong>Night</strong></td>
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<td><strong>Patients</strong></td>
<td>18(75.0)</td>
<td>4(16.7)</td>
<td>1(4.2)</td>
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<td>4(2.4)</td>
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<td><strong>Grind his/her teeth</strong></td>
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<td>1(4.5)</td>
<td>3(13.6)</td>
<td>1(4.5)</td>
<td>-</td>
<td>.58</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Matched Controls</strong></td>
<td>18(75.0)</td>
<td>2(8.3)</td>
<td>-</td>
<td>3(12.5)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>London Cohort</strong></td>
<td>98(59.0)</td>
<td>19(11.4)</td>
<td>10(6.0)</td>
<td>13(7.8)</td>
<td>2(1.2)</td>
<td>24(14.5)</td>
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<td><strong>Wets the bed</strong></td>
<td>6(27.3)</td>
<td>2(9.1)</td>
<td>9(40.9)</td>
<td>1(4.5)</td>
<td>3(13.6)</td>
<td>-</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Matched Controls</strong></td>
<td>13(54.2)</td>
<td>6(25.0)</td>
<td>4(16.7)</td>
<td>1(4.2)</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td><strong>London Cohort</strong></td>
<td>90(54.2)</td>
<td>28(16.9)</td>
<td>20(12.0)</td>
<td>10(6.0)</td>
<td>3(1.8)</td>
<td>15(9.0)</td>
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*P-Values indicate differences between the patients and the matched controls*
### Table 4.7. Sleep Behaviour Habits of patients with SCA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>School Bed Time (pm)</td>
<td>7.5 (2.5)</td>
</tr>
<tr>
<td>School Actual Sleep Time (hours)</td>
<td>8.8 (1.02)</td>
</tr>
<tr>
<td>School Wake Time (am)</td>
<td>7.3 (.62)</td>
</tr>
<tr>
<td>Hours asleep per night during week</td>
<td>10.38 (1.4)</td>
</tr>
<tr>
<td>Non-school Bed Time</td>
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</tr>
<tr>
<td>Non-school Actual Sleep Time</td>
<td>9.8 (1.1)</td>
</tr>
<tr>
<td>Non-school Wake Time</td>
<td>9.0 (1.3)</td>
</tr>
<tr>
<td>Number of Naps during Day</td>
<td>1.2 (1.18)</td>
</tr>
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<td>Regular Bed Routine</td>
<td>77%</td>
</tr>
<tr>
<td>Own Bedroom</td>
<td>62%</td>
</tr>
<tr>
<td>Own Bed</td>
<td>77%</td>
</tr>
<tr>
<td>TV in Bedroom</td>
<td>32%</td>
</tr>
<tr>
<td>Typically has one or more caffeinated drinks during the day</td>
<td>33%</td>
</tr>
</tbody>
</table>
Child falls asleep in..

- own room in own bed (alone) 42.9%
- parents’ room in own bed 0%
- parents’ room in parents’ bed 38.1%
- sibling’s room in own bed 4.8%
- sibling’s room in sibling’s bed 14.2%

Child spends most of night in..

- own room in own bed (alone) 42.9%
- parents’ room in own bed 9.5%
- parents’ room in parents’ bed 33.3%
- sibling’s room in own bed 4.8%
- sibling’s room in sibling’s bed 9.5%

Child wakes up in..

- own room in own bed (alone) 42.9%
- parents’ room in own bed 9.5%
- parents’ room in parents’ bed 33.3%
- sibling’s room in own bed 4.8%
- sibling’s room in sibling’s bed 9.5%
4.6.3 Discussion

This study found that preschool children with SCA have a significantly greater burden of sleep problems than typically developing children. Over 27% of children with SCA in the current population had sleep composite scores greater than 1.5 standard deviations over the London normative mean, mirroring a recent report on 1 to 4 year-olds with SCA where 27% were found to have sleep-disordered breathing (Telfer et al., 2012). In contrast, the matched control group had a similar rate of sleep problems to the London norm, which illustrates a three-fold increase of reported sleep problems in preschool children with SCA. All patients, except for two cases (one who recently had their adenoids and tonsils removed in order to alleviate obstructive sleep apnoea), were reported to snore at least sometimes. Snoring, resisting bed-time, restless sleep/waking up at night, and bed-wetting, were the most frequently reported issues in the patient group, reported to occur at least sometimes for over two thirds of the current patient cohort, similar to previous findings in older children with SCA (Samuels et al., 1992). This is in contrast to the rate of occurrence of these issues in approximately one quarter of matched controls in the current study, 30% of 54 month olds that were reported to experience bed-wetting in a recent British cohort (n=13, 973) study (Butler & Heron, 2008) and 26% of the matched controls in the current study and 13% of four year olds in another British cohort study (n=1,100) that were reported to snore (Kuehni, Strippoli, Chauliac, & Silverman, 2008). There is a lack of data on sleep behaviour and sleep hygiene for typically developing preschool children in the UK, but a recent study looked at typically developing 3 year-olds (n=84) and found a regular bedtime routine for 79% of their cohort (Jones & Ball, 2014), similar to the rate in the current patient group (77%).

Sleep problems must therefore be taken into consideration when looking at executive development in children with SCA, and may even be a potential avenue for intervention. The average sleep duration on a school night for the
patient group was 10.5 hours (wake time minus actual sleep time). However, the sleep duration recommended by the UK National Health Service and the Royal College of Psychiatrists for three to five year olds is 11-12 hours. Table 5.6 shows that 33% of the group typically has at least one caffeinated drink during the day and 32% have televisions in their bedrooms. Mindell et al. (2009) found that preschool children (n=385) who consumed one or more caffeinated beverages slept over 40 minutes less than those who did not, and children with a TV in their own bedroom slept 30% less on average (Mindell, Meltzer, Carskadon, & Chervin, 2009). A recent UK study in adolescents (n=47) showed that, along with shorter sleep duration and later bed times, caffeine intake and the use of electronics such as televisions and mobile phones before bedtime was associated with poorer academic performance through the mediating effects of poor sleep (Dimitriou, Knight, & Milton, 2015). Behavioural interventions that focus on positive sleep hygiene, e.g. removing caffeine and TV from environment and encouraging nighttime reading (Mindell et al., 2009), may have a positive impact on sleep behaviours in children with SCA. As symptoms of sleep disordered breathing, particularly snoring, were reported, medical interventions to improve sleep disordered breathing may also have a positive impact on executive outcomes. Encouragingly, a recent study found that older children with SCA who received a sleep intervention for sleep disordered breathing improved on a task of attentional control (Marshall et al., 2009). However, there have been no investigations for the impact of sleep interventions in young children with SCA, despite compelling findings for the impact of sleep interventions such as Montelukast and adenotonsillectomy in otherwise typically developing preschool children with OSA (Goldbart, Greenberg-Dotan, & Tal, 2012; Marcus et al., 2013; Walter et al., 2015).

In conclusion, preschool children with SCA have a greater burden of sleep problems than matched controls. Hence, a future focus on sleep and EF in the preschool years, a developmental stage when sleep problems typically emerge, could lead to earlier targeted interventions with an emphasis on improving EF, school readiness, and socio-emotional development.
4.7 General Discussion

The current chapter explored factors commonly related to executive dysfunction in preschool children. The main function of this chapter was to provide information to aid the investigation of the development of EF in SCA in a multi-faceted way, incorporating potential influences on EF beyond SES and disease-related factors. The findings support a holistic or ‘totality’ approach (Anderson, Northam, & Wrennall, 2014) in the subsequent investigation of executive development in children with SCA, but also independently stand-alone as novel and informative contributions to the sickle cell literature.

No significant differences in IQ were observed between the children with SCA and the ethnicity-matched comparison group suggesting that the IQ gap frequently reported for older children may not yet be observed at this early stage. This is an important result as it allows us to control for IQ in the investigation of executive differences between these groups in the subsequent chapters. The only difference observed on the CBQ was in the domain of discomfort, which could be attributed to the direct effects of living with a chronic illness. However, the CBQ was found to be less reliable in the current cohort than previous studies of typically developing children, which calls for caution in the interpretation of results. As expected, children with SCA showed a much higher rate of sleep problems. Snoring, sleep disruption, and bed-wetting were the most frequently reported issues, similar to previous findings in older children (Daniel et al., 2010). This finding must be considered in the context of executive development in preschool children, as there is accumulating evidence for an association between sleep problems and executive dysfunction (Bernier, Beauchamp, Bouvette-Turcot, Carlson, & Carrier, 2013; Karpinski et al., 2008).

Families with young children with SCA reported poorer family functioning than young families with the same socio-economic background. These differences were particularly apparent in the domains of supportiveness and control. Future studies should aim to include more information on the family profile, including number of children, parental vocation, and maternal mental health,
as these factors have been reported to influence family functioning and may have differed between the two groups. Nevertheless, family functioning may be an important avenue for further investigation in families with SCA. Chronic childhood conditions have been associated with lower family functioning (Knafl et al., 2013) and evidence is accumulating for a relationship between SCA and poorer family functioning (Barakat et al., 2007). The burden of managing a chronic condition may affect the family dynamic and indirectly have an impact on the development of EF in young family members. Perhaps, children with SCA are more likely to be impacted by poorer family functioning as they are already, as Hijmans and colleagues (2011) describe, at a ‘double disadvantage.’ Table 4.8 shows the co-occurrence of low scores across domains in individual children.

The findings of the current chapter help will help us to better interpret executive performance of children with SCA in subsequent chapters by considering a child’s ecology rather than the consideration of SCA as a disease in isolation. They support, in particular, the consideration of family functioning and sleep problems when investigating influences on EF development and dysfunction in SCA. The influence of these factors on executive development in preschool children with SCA is explored further alongside medical factors in Chapter 6.
Table 4.8 Co-occurrence of lower scores across domains of interest for patients and matched controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients</th>
<th>Matched Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26</td>
</tr>
<tr>
<td>VIQ*</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>PIQ*</td>
<td>x  x</td>
<td>x</td>
</tr>
<tr>
<td>FES**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBQ</td>
<td>x  x  x  x</td>
<td></td>
</tr>
<tr>
<td>Discomfort**</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Sleep Score***</td>
<td>x  x  x  x  x</td>
<td>x  x  x</td>
</tr>
</tbody>
</table>

*Note: x indicates a lower score in the respective domain.*

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“Lower scores” defined as: *VIQ/PIQ < 85; **Defined as greater than 1.5 SD above control mean in current study for CBQ and 1.5 SD below mean for FES (note that some FES controls have siblings with SCA); **Defined as greater than 1.5 SD above London cohort mean in current study. Shaded areas illustrate missing data. CBQ= Children’s Behaviour Questionnaire. FES= Family Environment Scale. PIQ= Performance IQ. Sleep Score = Composite sleep score on the adapted sleep questionnaire. VIQ= Verbal IQ.
Chapter 5: Executive functioning

Investigating the early development of executive functioning in children with sickle cell anaemia using measures that tap specific components as well as measures that look at executive functioning in a more ecologically-valid way.
5 Executive Functioning

5.1 Introduction
This chapter aims to investigate the executive profile of preschool children with SCA. This will fill a gap in the literature, as previous studies in preschool children with SCA have relied on global measures of cognitive ability or parent reports of executive functioning (EF), or did not have age appropriate measures of EF for pre-school age children (Drazen, Abel, Gabir, Farmer, & King, 2015; Glass et al., 2012; Schatz & Roberts, 2005; Steen et al., 2002; Tarazi et al., 2007; R. J. Thompson et al., 2002; Wang et al., 1998). Sickle cell researchers have called for more appropriate measures of EF in preschool children, as it has been difficult up to this point to ascertain the extent of the potential decline in executive skills that has been widely reported for older children (Schatz et al., 2007). The following sections describe the sickle cell literature to date for different domains or aspects of EF and lay the framework for why each of these domains are of interest for the current study. The testing protocol for EF employed in this chapter was based upon Anderson’s (2002) conceptual model of EF development and consists of recently developed assessments that are used to assess the EFs of children with SCA in greater detail than was previously possible. Parents’ reports of EF, as well as the behavioural findings for preschool children with SCA on specific tasks of attention, inhibitory control, processing speed, working memory, and cognitive flexibility and a general ecologically valid measure of EF, are investigated. The findings for each EF domain of interest are discussed in turn, followed by a discussion on the overall EF findings of this chapter.

5.1.1 Proxy-reports of Executive Functioning
Poor executive skills and adaptive behaviour have been reported for children with SCA, even when there is no evidence for neurological morbidity (Berkelhammer et al., 2007; Hijnans, Grootenhuis, et al., 2011; Nabors & Freymuth, 2002; Noll et al., 2001). Previous studies in school age children have found higher ratings of proxy-reported executive dysfunction in children
with SCA. Although the BRIEF measure has been used to measure EF in older children in the sickle cell literature and has shown associations between EF and disease factors such as cerebral blood flow velocity and overnight oximetry (Berg et al., 2012; Hensler et al., 2014; Hollocks et al., 2011; Mary C Kral & Brown, 2004), there is no existing research that targets the parents of preschool children in this patient population. The current study aims to administer the BRIEF-P to parents of preschoolers with SCA in order to establish whether parents of younger children with SCA are also reporting everyday executive deficits at this early stage.

5.1.2 Inhibitory Control

Inhibitory control, also described as attentional/cognitive control or the management of conflict, is hypothesized to rely on the anterior cingulate cortex and the prefrontal cortex as well as additional regions in adults depending on specific task characteristics whereas a more immature and variable pattern of activation is seen for children (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). There has been limited focus on this aspect of EF in children with SCA. Lesions in the prefrontal or ‘performance-monitoring’ network have been found to disrupt neural processing during attentional control tasks such as the classical Eriksen Flanker task or the choice response task (Hogan, Vargha-Khadem, et al., 2006; Wessel et al., 2015). One study found that children with SCA who have frontal lobe infarction made more accuracy errors than children with SCA with no history of infarction on a stimulus response reversal task (Christ, Moinuddin, McKinstry, DeBaun, & White, 2007). The only study that looked at children with SCD (n=24; 4 years, 10 months-15 years, 4 months) who had no history of stroke found no difference when compared with a sibling comparison group (n=11; 7 years, 5 months-15 years, 11 months) on a performance-based cognitive control task (Goonan et al., 1994), however they combined genotypes and had a restricted group size for a sample where the age range spans 10 years. Given the lack of focus on this specific area of EF, it is appropriate and novel to look at inhibitory control in
preschool children with SCA and to implement an age-appropriate version of the Eriksen Flanker task (Eriksen, 1995) with this patient population, particularly as inhibitory control is thought to be an earlier emerging EF skill that can influence the development of later emerging EF domains (Anderson, 2002).

5.1.3 Processing Speed

Processing speed can be described as reaction time or speed of information processing, and its efficiency has been related to white matter integrity in the frontal lobes (Kochunov et al., 2010). Most studies in the sickle cell literature have used subtests from the Wechsler Scales to measure processing speed. Armstrong and colleagues found that children with SCD with silent stroke had slower processing speed than children who had no MRI abnormalities (Armstrong et al., 1996). However, adults and children with SCA who have no evidence of stroke still show reduced speed of processing on the Wechsler scales (Steen, Fineberg-Buchner, et al., 2005; Vichinsky et al., 2010). Scantlebury and colleagues also found poorer processing speed in children with SCA (n=15) when compared to 10 typically developing children (Scantlebury et al., 2011). They showed evidence for associations between increased diffusion coefficients in the white matter of the right frontal lobe and the cerebellum (despite no lesions) and poorer processing speed in the patients. Another study found that a greater volume of white matter hypertensities in children with SCD with otherwise normal MRI was a predictor of poorer processing speed on the Wechsler Scales (Van Der Land et al., 2014). This current investigation examines processing speed in preschool-age children with SCA without evidence of MRI pathology using a matched comparison group. Thus far, there are mixed findings in the limited literature with regards to the development of processing speed in children with SCA who have no evidence of neurological morbidity, and there have been no attempts to measure these skills in children younger than school-age.

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3 Increased diffusion coefficients suggest a potentially compromised white matter microstructure. This would not be measured in a clinical MRI scan.
5.1.4 Attention

Sustained attention is the ability to focus attention on the task at hand in order to see it to completion. Several studies have used cancellation tasks to identify deficits in sustained attention in school-age children with SCA who show evidence of stroke (Brown et al., 2000; Elsayed, Lshorbagy, Sehlo, & Ashour, 2012; Jeffrey Schatz et al., 2001). These studies have compared SCA patients with no evidence of neurological pathology with patients who have infarcts, finding poorer performance in those who have experienced stroke. One study looked at attention in school-age children with SCA with and without stroke (n=26; MRI information was only available for the children with stroke) and 13 sibling controls using a visual scanning task and coding scores from the Wechsler Scales. They attributed much of the differences in task performance to stroke, although noting that all of the children with SCA showed slower processing speed (Nabors & Freymuth, 2002). However, most of the studies in this area have not employed matched control groups of typically developing children (Elsayad et al., 2012) or have combined results from various tasks or do not sufficiently describe how they determined successful or poor performance on an EF task (Schatz et al., 2001). One study reported improved performance on a cancellation task in children with SCA who underwent intervention for sleep disordered breathing but how they derived their scores is not reported (Marshall et al., 2009) and another study reported that 20% of SCA patients (n=96, aged 6 to 24 years) failed the Bell Cancellation Task⁴ but the criteria for failure, based on omissions only, were unclear, and as their Cameroonian cohort have restricted access to MRI scanners, the proportion of children with silent or overt stroke was unknown (Ruffieux et al., 2013).

⁴ Used in this instance to measure attention but typically administered to measure spatial neglect.
5.1.5 Cognitive Flexibility

Cognitive flexibility, or the ability to appropriately adapt behaviour in response to the environment, is most commonly measured using ‘switching’ or ‘set-shifting’ tasks that require the participant to change their behaviour in response to rule-changes (Dajani & Uddin, 2015). Several studies have used card-sorting tasks such as the Wisconsin Card Sort Task (WCST) and the Animal Sorting Task (AST) to show evidence for more perseverative behaviours or cognitive inflexibility in children with SCD (Hensler et al., 2014; Hogan et al., 2006; Schatz et al., 2001; Watkins et al., 1998). These tasks involve shifting between rules in order to sort cards into different categories and are hypothesized to be largely reliant on the frontal lobe, particularly the dorsolateral prefrontal cortex and the right inferior frontal lobe, as well as the basal ganglia (Cools, Clark, & Robbins, 2004). However, it is difficult to draw any conclusions from the literature thus far on task switching in SCD as most studies have combined genotypes and neurological histories, and have reported findings differently (Watkins et al., 1998). For example, Schatz et al., (2001) retrospectively looked at the proportion of children who performed in the clinical range on a series of executive tasks and did not specify how many children completed the WCST as opposed to other attention or executive tasks and so their findings cannot be used for comparison to the current data.

A potential executive deficit in switching was highlighted in a recent study that administered a series of executive tasks to school age children with SCD (n=20, n=14 with HbSS) and found that mean performance tended to fall within the average range on parent reports of EF, as well as specific tasks of attention and processing speed, but that performance on the AST, the switching task, fell below average (Hensler et al., 2014). This study aims to administer a version of a card-sorting task that has been developed for preschool-age children, called the EF Scale for Early Childhood (Carlson, 2013). This task has previously been used to characterise executive deficits in preschool children with fetal alcohol syndrome and children with early life adversity (Fuglestad et al., 2014; Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012). Previous to this, this aspect of EF has not been investigated in
children with SCA younger than school-age except in an isolated study that found some evidence for more perseverative behaviours in nine month old infants with SCA using the A not B task (A.M. Hogan et al., 2012).

### 5.1.6 Working Memory

Working memory, the ability to hold and manipulate information in mind, has been closely associated with the dorsolateral prefrontal cortex (Levy & Goldman-Rakic, 2000). Impairments in working memory have been described to be prevalent in school age children with SCD who have frontal infarcts when compared to children with SCD who have posterior infarcts or no MRI pathology (Brandling-Bennett et al., 2003; White et al., 2000). Brandling-Bennett et al., (2003) found poorer performance in patients with frontal pathology (n=10) than patients without frontal pathology (n=21) on the digit span backwards but no differences on the digit span forwards task of the Childrens’ Memory Scale. Adults with SCA (n=149) with no brain pathology have been reported to have poorer working memory than controls (Vichinsky et al., 2010). However, results are mixed when looking at working memory in children with SCA who have no evidence of neurological morbidity (Bernaudin et al., 2001; Brown et al., 1993; Noll et al., 2001; Schatz & Roberts, 2005). One study found a difference between children with SCD (5-15 years, n=173, HbSS=155) and 76 sibling controls on digit span that did not remain when patients with MRI pathology were removed from analysis (Bernaudin et al., 2000). Noll et al. (2001) used the Wide Range Assessment of Memory and Learning (WRAML) to look at 31 children with SCD (15=HbSS) aged between nine and 16 years and case-matched controls, reporting generally poorer performance in an attention/memory factor domain, but not providing specific information on working memory performance. In a recent doctoral dissertation, Tagliareni (2009) reported significantly poorer performance in working memory on the WRAML in school-age children with SCD (mean age=15.4 (SD=3.7); HbSS=12) but their 19 control children were neither ethnicity nor SES matched to the patient group, so there may have been an influence of environmental factors. Another study found that school-age
children with SCD with normal MRI (n=25; 20=HbSS) had difficulties in verbal working memory but not visual working memory when compared with a group of ethnicity and age-matched (6.9-16 years) controls suggesting a potential modality-specific deficit in working memory (Schatz & Roberts, 2005). Some studies have found relations between age and markers of disease severity, such as haematocrit and cerebral blood flow velocity, and working memory in children who do not have stroke (Kral et al., 2006; Kral et al., 2003). Previous research in this area has used patient populations with mixed genotypes and neurological histories, as well as combining memory scores on digit span forwards and backwards tasks despite digit span backwards requiring more executive control (Baddeley, 2003). Most studies have only investigated verbal working memory with little focus on visual working memory (Schatz & Roberts, 2005) and there is no performance-based evidence from preschool age children. The current study aims to investigate visuo-spatial working memory in preschool children with SCA.

5.1.7 Executive Functioning on an Ecologically Valid Level

It is important to understand the impact of an executive deficit on a child in an ecological context (Burgess et al., 2006). EF is a term that subsumes a range of integrated skills, including initiation, planning, sequencing, and impulse control. In an everyday context, these skills are used cooperatively, unlike the artificial separation that most neuropsychological assessments require. To understand the functional impact of executive problems in a patient group, we must go beyond the application of tests that solely discriminate specific deficits by applying tasks with greater verisimilitude in tandem. Although the BRIEF questionnaire is considered an ecologically-valid measure and was developed in response to traditional performance based assessments that were viewed as ‘limited’ or ‘incomplete’ reflections of true EF (Isquith, Roth, & Gioia, 2013), it was developed to be used in conjunction with behavioural assessment, not to act as a replacement. The BRIEF relies on accurate responses from the parent who may not be a reliable source and responses may not reflect how a child performs in the classroom context as different components of EF in a young child may be tapped in the home and classroom.
environments (Kral et al., 2004). In addition to this, results from the BRIEF do not directly inform the clinician in terms of specific supports that a child may benefit from in terms of the level or timing of support that they may require to succeed in the classroom context. Thus, examiners should not rely solely on a proxy-report of EF but should consider these reports alongside performance-based assessments (Toplak, West, & Stanovich, 2013). A performance based assessment that assess EF in a micro-analytic way and feeds back quantitative and qualitative information that helps inform targeted interventions is an invaluable resource in the neuropsychological assessment of patients with potential EF deficits (Burgess et al., 2006).

Only one previous study has administered a performance-based ecological task of EF in adults or children with SCD. Berg et al., (2012) looked at EF in a group of eight to 12 year old children with SCD (n=22; 21=HbSS) in comparison to matched controls using the Children's Kitchen Task Assessment (CKTA; Rocke et al., 2008). This task was developed based on Vygotsky’s premise that understanding a child’s level of ability and the level of support they require to complete tasks is integral to the promotion of development in children who have cognitive deficits (Vygotsky, 1978). Berg et al. observed several differences between children with SCD and a matched comparison group in their task performance which led them to emphasise the importance of triangulation, combining specific neuropsychological tasks with performance-based tasks and parent or teacher reports, in order to obtain a holistic picture of the child’s ability at home and at school.

5.2 Aims

The aim of this chapter is to describe the neuropsychological profile of EF in preschool-age children with SCA who have no clinical evidence of neurological pathology and to compare the EF performance of children with SCA on executive tasks with ethnicity, age, IQ, and SES matched typically developing children. It is hypothesized that children with SCA will show a poorer EF profile on executive measures that tap specific EF skills as well as measures that look at general EF. It is expected that children
with SCA will show more observable deficits on specific EF tasks, while
more subtle differences will be observed on macro-level ecologically valid
measures of EF reflecting the application of multiple EF skills in tandem in
naturalistic contexts. Conceptually, EF as an integrated entity, is related to,
but also distinct from, its individual domains (McClelland & Cameron,
2012). If emerging deficits in specific domains of EF are observable on
specific lab-based tasks at this early stage of development in patients with
SCA, they may not yet have fully translated to group differences in
everyday EF tasks.

5.3 General Methodology

5.3.1 Participants
Twenty-two patients with SCA between three and five years old whose
parents identified themselves as Black British and had no history of
neurological morbidity (Mean age 4.8, SD=.94; Mean IQ=98.6, SD=11.4; 13
males) were compared with 24 ethnicity, age, SES, and IQ-matched
comparison children\(^5\) (Mean age 4.8, SD=.88; Mean IQ=101.5, SD=11.8; 10
males) that were recruited through the same clinics as the patients as well as
schools in the same boroughs of East London where the patients reside.
Thirteen of the comparison children attended the London Babylab and 11
were assessed at school. The children assessed at school were only
administered the Preschool Executive Task Assessment (PETA) and the
Behaviour Rating Inventory of Executive Functioning-Preschool Version
(BRIEF-P) due to time restrictions whereas the whole battery of executive
tasks were administered to all of the children who attended the London
Babylab. The group comparisons for the National Institute of Health Toolbox
(NIHTB) tasks, EF Scale for Early Childhood, Doggie Deletion Task for
Preschoolers (DDTP), and Scrambled Memory Task have less statistical
power due to the smaller comparison group sizes (n=13) so to overcome this
potential issue, additional group comparisons with a larger control group from

\(^5\) Further information for IQ can be found in Chapter 5.
a sample of 12 children that were tested with the same battery at the London Babylab are included in the appendices. These children were not matched for ethnicity but remained matched for age, IQ, and SES.⁶

5.3.2 Procedure
All of the patients and 13 of the matched comparison children were tested in the London Babylab whilst the remaining control children were tested in a separate space in their school. Both the testing space in the lab and the school testing spaces were closed off spaces with no overt distractions and only minor background noise. The PETA always followed the Wechsler Primary and Preschool Scales of Intelligence (WPPSI-III-UK) in the school-testing environment and the London Babylab. At the lab, the Scrambled Memory Task was always administered first, followed by the DDTP. The PETA and the WPPSI-III-UK were administered next before the EF Scale for Early Childhood and the NIHTB tasks; Pattern Comparison Processing Speed (Carlozzi et al., 2013) followed by the NIHTB Flanker Inhibitory Control and Attention test (Zelazo et al., 2013) in that order. All tasks were completed in one day with one large break in the middle and multiple small breaks as necessary.

5.3.3 Measures
Each measure is briefly described below but further descriptions of each measure can be found in Chapter 2 (Methodology) with the newly developed measures further described in Chapter 3 (Validation).

5.3.3.1 Proxy-reports of Executive Functioning
The BRIEF-P (Gioia et al., 2003) questionnaire (further described in section 2.4) was administered to parents. The researcher scored the BRIEF-P using a computerized scoring program that also checked for rater negativity and inconsistency. Raw scores were converted to standardized T-scores (Mean=50; SD=10). T-scores over 65 (greater than 1.5 SD above the mean) are considered potentially clinically significant. One patient and two controls

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⁶ The additional tables for the larger control groups matched for age, IQ, and SES, but not for ethnicity, on these measures can be found in Appendix 6.
had an incomplete BRIEF-P so were not included in this study. Classroom teachers completed nine of the control BRIEF-P forms instead of parents.

5.3.3.2 Inhibitory Control and Processing Speed

The NIHTB computerized measures of inhibitory control and processing speed were administered. This new toolbox, which has been normed from 3 to 85 years, offers the opportunity to tap these domains for the first time using validated computerized tasks in children with SCA, free from experimenter bias. The additional benefit of the battery’s wide age range is it allows the opportunity to directly compare findings in the present cohort with older children with SCA in future studies (further described in section 2.4). Technical issues prevented two patients from completing the measure whilst one participant did not complete these tasks due to time restrictions. The child always completed the NIHTB Pattern Comparison Processing Speed first, followed by the NIHTB Flanker Inhibitory Control and Attention task. Additionally, the Coding subtest from the WPPSI-III-UK, another measure of processing speed that was available for the four and five year olds only as part of their IQ assessment battery, is also investigated.

5.3.3.3 Attention

The DDTP was administered (see further task description in sections 2.4 and 3.3). The dependent variables of omissions, commissions, time to completion, and motor speed were analysed. Number of omissions and commissions were combined to obtain the mean rate of errors in the typically developing children (as presented in Chapter 4; the Validation chapter) so that the number of patients performing greater than 1.5 standard deviations below the average score of typically developing children could be computed. The current version of the task was not administered to two control children that were recruited at the start of the study, before additional modifications were made to the measure, and so they were not included in the analysis.

5.3.3.4 Cognitive Flexibility

The EF Scale for Early Childhood assesses cognitive flexibility in children aged 2.5 to seven years across seven levels with increasing difficulty (Beck et
al., 2011). It is a newly developed graded measure of EF that incorporates three tasks; categorization (Carlson, Mandell, et al., 2004), dimensional change card sort (Diamond, Carlson, & Beck, 2005) and integrated/advanced dimensional change card sort (Zelazo et al., 2003). It requires the participant to sort cards according to one rule for the first half of each level and then switch to a new rule for the second half of the level (see further description in section 2.4). Working memory demands are minimized by reminding the child of the rule before each trial. The dependent variables are the number of correct trials or the highest level at which the child passes both pre and post switch trials. The task was not administered to two patients and one comparison child due to time restrictions.

5.3.3.5 Working Memory
All children attending the London Babylab completed the Scrambled Memory Task (see further task description in sections 2.4 and 3.4) as the first task at the start of the battery. Total retrieved stimuli within 20 trials were coded along with the number of consecutively correct trials and the total number of trials required to complete the task.

5.3.3.6 Executive Functioning on an Ecologically Valid Level
The current study involves the administration of the Preschool Executive Task Assessment (PETA) that has been developed based on the CKTA and the KTA (Rocke et al., 2008). This task was piloted, validated, and normed as part of the current thesis (see Chapter 3) and incorporates similar scoring and cueing guidelines to the CKTA. The PETA assess EF in a an ecologically valid micro-analytic way and aims to capture a true reflection of integrated executive skills in everyday tasks. It provides qualitative and quantitative scores for specific domains of EF as well as a general composite EF score. Children receive a total weighted composite score as well as completion time, highest level required during task, total number of cues required, and cues required to initiate, sequence, and complete task. Qualitative scores for working memory, distractibility, organization, and emotional control are also noted by the examiner.
5.4 Results

5.4.1 Proxy-reports of Executive Functioning

Clinically elevated scores for the General Executive Composite (GEC) score were observed for three (14.3%) of the patients and two (9.1%) of the comparison children on the BRIEF-P (figure 5.1). For the clinical indices, scores for four (19%) of the patients were in the clinical range or elevated on the Inhibitory Self Control Index (ISCI) in comparison to three (13.6%) of the control children, three (14.3%) of the patients were elevated on the Emergent Metacognitive Index (EMI) in comparison to two (9.1%) comparison children, and three (14.3%) of the patients were elevated on the Flexibility Index (FI) in comparison to two (9.1%) of the control children. Multivariate analysis of variance on the five subdomains showed no overall group differences on the BRIEF-P (F1,43=1.63, p=.17). Table 5.1 shows group means for the individual subdomains.

Table 5.1. Group comparisons of the BRIEF-P domains

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=21)</th>
<th>Typical (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>BRIEF-GEC</td>
<td>53.95(13.9)</td>
<td>49.72(11.7)</td>
<td>.286</td>
</tr>
<tr>
<td>ISCI</td>
<td>54.19(13.2)</td>
<td>49.09(11.4)</td>
<td>.183</td>
</tr>
<tr>
<td>EMI</td>
<td>54.05(13.3)</td>
<td>50.50(12.4)</td>
<td>.372</td>
</tr>
<tr>
<td>FI</td>
<td>52.67(14.16)</td>
<td>47.5(10.5)</td>
<td>.180</td>
</tr>
<tr>
<td>Inhibit</td>
<td>52.19(11.8)</td>
<td>51.36(12.8)</td>
<td>.828</td>
</tr>
<tr>
<td>Shift</td>
<td>50.66(11.4)</td>
<td>45.91(7.8)</td>
<td>.116</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>54.38(14.17)</td>
<td>46.73(8.7)</td>
<td>.038*</td>
</tr>
<tr>
<td>Working Memory</td>
<td>54.43(12.3)</td>
<td>51.27(11.51)</td>
<td>.390</td>
</tr>
<tr>
<td>Plan/organise</td>
<td>52.86(13.9)</td>
<td>52.86(13.85)</td>
<td>.374</td>
</tr>
</tbody>
</table>

*Does not remain significant after Bonferroni correction.

GEC= General Executive Composite. ISCI= Inhibitory Self Control Index. EMI= Emergent Metacognition Index. FI= Flexibility Index.
There was a trend for higher scores in some of the subdomains for the patient group; particularly emotional control; however this did not reach significance. The emotional control domain is not included in the school-age version of the BRIEF questionnaire and so it is not reported for previous studies that have used the BRIEF with children with SCA. However, previous studies that investigated emotional functioning in children with SCA reported no issues with emotional control for school-age children with SCA (Noll, Reiter-Purtill, Vannatta, Gerhardt, & Short, 2007; Noll et al., 1996). The GEC was more typical for the current patient population in comparison to older children with SCA on the school-age version of the BRIEF in previous reports; however
different subdomain composite categories on the older questionnaire measure precludes direct comparison of the subdomain scores with the older patient groups. Hollocks et al. (2012) found a higher mean GEC (M=62.2; SD=13.51) for a group of children with SCA between eight and 16 years (N=10; 9 neurologically normal) and Berg et al., (2012) found a significantly higher mean GEC (teacher-report: M=59.1; SD=13.54; parent report: M=52.5, SD=8.7) in a group of children with SCA between eight and 12 years (N=22; 13 neurologically normal; one child with Sβ0 thalassaemia) in comparison to a matched control group on both teacher and parent reports of the BRIEF, with a higher mean GEC reported by teachers than parents. However, in a more recent study, Hensler et al., (2014) found a more comparable GEC to the current study in their cohort of children from 8 to 16 years with SCD (M=54.3 SD= 14.4). Hensler et al. also observed that the GEC was predictive of behavioural control and social skills in their patient group. Similar to Kral et al., (2004), the parent-reported group mean for the current patient group was not in the clinical range; however the teacher ratings for the patients in the study by Kral and colleagues were in the clinical range leading the authors to suggest that future studies may benefit from incorporating teacher ratings of EF rather than relying on parent-reports. The authors postulate that this may be due to structured classroom settings being more conducive to observing metacognitive skills whereas the unstructured home environment may be more suited to observing behavioural and emotional control.

Limitations of the current findings include a lack of teacher-reports for the patient group and a mixture of parent- and teacher-rated questionnaires for the control group. However, this is the first attempt to look at parent-reports of EF in preschool children with SCA and it shows that parents are likely to report more positively at this early stage of development. The more typical GEC in a preschool population may indicate that executive deficits become more observable on an ecological level with age or that executive skills decline with age.
5.4.2 Inhibitory Control and Processing Speed

Patients had lower mean scores for inhibitory control (t(30)=.76, p=.38) and processing speed (t(30)=.24, p=.27), but these did not reach significance (see Table 5.2). However, when looking at individual scores, seven (35%) patients were more than 1.5 standard deviations (SD) below the age-adjusted mean scores for processing speed in comparison to three (23%) of the matched comparison children while three (15%) of the patients were more than 1.5 SD below the age-adjusted mean for inhibitory control in comparison to none of the control children. These differences in frequency did not reach significance on further exploration with Chi-square analysis; however there was a trend for a difference in inhibitory control (p=.07). The lack of significant difference for processing speed was explored further by looking at findings on the Coding subtest from the WPPSI-III-UK. Again, no significant differences were observed between the patients (n=16, mean=9.8, SD=2.5) and the comparison group (n=14, mean=10.0, 2.7), for processing speed on this Scaled Score (t(28)=.19, p=.84). Two patients and two control children obtained weak Scaled Scores (defined as seven or less). The same children also obtained low scores on the NIH Toolbox Processing speed task, ranging from 59.9 to 78.

Table 5.2. Group means for the NIHTB tasks

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=20) M(SD)</th>
<th>Matched Controls (n=13) M(SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Inhibitory Control Age adjusted SS</td>
<td>92.38(22.6)</td>
<td>98.45(21.8)</td>
<td>.38</td>
</tr>
<tr>
<td>NIH Processing</td>
<td>80.28(12.71)</td>
<td>85.9(14.9)</td>
<td>.27</td>
</tr>
</tbody>
</table>
Figure 5.2. Graphical illustration of age-adjusted standard scores for the patient group and the matched control children on the NIHTB tasks of processing speed and inhibitory control. The horizontal bars reflect the normative group mean (100) and standard deviation (85) showing low scores in both groups for the processing speed task relative to normative means.
There was a trend for poorer inhibitory control and processing speed in the patient group but no significant differences were observed, despite the greater rate of patients who obtained scores over 1.5 standard deviations less than the standard norm. These findings inform future investigations as they show evidence for relatively intact processing speed in children with SCA less than six years in comparison to previous reports in older children with SCA, particularly those with MRI pathology. There has been a lack of research looking at inhibitory control and processing speed in older children with SCA who have no neurological pathology for inhibitory control and processing speed. However, Steen and colleagues found significantly poorer processing speed on the Wechsler Intelligence Scale for Children in school-age children with SCA (n=30, mean age =10.9, SD=2.9) who had normal MRI scans (Steen, Fineberg-Buchner, et al., 2005). As part of a doctoral dissertation, Tagliareni (2009) also found significantly poorer performance in school-age children with SCD (mean age=15.4 (SD=3.7); HbSS=12) on the Processing Speed Index of the Wechsler Scales but their 19 control children were neither ethnicity nor SES matched to the patient group (Tagliareni, 2009). In contrast, Goonan et al., (1994) reported no difference for inhibitory control in school age children with SCA in their study, however they combined children with SCA with less severe sickle genotypes and did not indicate the number of children with each genotype. They also used a small sample considering the wide age range they included.

Previous reports suggest that processing speed and IQ are strongly related (Fry & Hale, 2000; Sheppard & Vernon, 2008) and so matching the current groups for IQ may have impacted the current findings for processing speed. It is noteworthy that both groups have relatively low scores for NIH processing speed with the mean group score for the comparison group (85.9) just within the one standard deviation range of normal performance (85-115). However, a recent validation study for the processing speed task reports that it may not be as reliable for three and four year old children in its current format with scores becoming more representative of true performance in five year-
olds (Carlozzi, Beaumont, Tulsky, & Gershon, 2015). A limitation of this study is the small sample in the matched comparison group, nevertheless when additional children (n=12, matched for age, IQ, and SES but not for ethnicity) are included in the group comparison (Table S1, Appendix 6), there remains no significant effect for group, though the difference for inhibitory control becomes near significant.

In conclusion, this study shows a trend for poorer inhibitory control in the patient group but the lack of significant difference between groups for processing speed suggests that the children with SCA are still relatively on track with the development of their peers at this developmental stage. The findings of the current study encourage future investigations of these two domains in a longitudinal study in order to better understand when the achievement gap between these groups becomes significant and where interventions may be most efficacious. Although the processing speed task may not be fully reliable for some of the younger children in this study, the availability of cheap, easily accessible and normed computerized measures such as the NIHTB allows the opportunity to track the progression of EF deficits over time in this patient population. The NIHTB is now also available in iPad format meaning testing can be more mobile allowing researchers to more easily capture a representative population in the future, and not rely just on those who can attend the researcher’s lab for assessment.

5.4.3 Attention

Four patients and one comparison child did not pass the practice phase. Three patients did not complete the task so scores for total time, omissions, and commissions were pro-rated based on the proportion of task completed. Greater than 1.5 standard deviations above the combined mean score for omissions/commissions (M=33.1) in the Validation sample (Chapter 4) was considered poorer than average performance. Seven patients performed lower than the average range in comparison to three comparison children. In total, 50% of the patients did not pass the training phase or obtained poor
combined scores in comparison to 33.3% of the matched group. For those who passed the practice phase, an ANOVA including the individual test phase factors (omissions, commissions, time to completion) found no overall group differences (F1,29= .338, p=.34) with significant group differences observed for commission rate only (see Table 5.3). There were no group differences for motor speed in the motor phase.

**Table 5.3. Group differences for DDTP variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCA Group M (SD)</th>
<th>Matched Group M (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Tested</td>
<td>22</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>N Passed</td>
<td>18</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Commissions</td>
<td>77.9 (111.2)</td>
<td>13.6 (22.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Omissions</td>
<td>22.9 (22.9)</td>
<td>26.7 (30.4)</td>
<td>.73</td>
</tr>
<tr>
<td>Time to Complete</td>
<td>12.1 (4.9)</td>
<td>11.06 (4.2)</td>
<td>.52</td>
</tr>
<tr>
<td>Motor Speed</td>
<td>51.9 (13.7)</td>
<td>46.6 (8.3)</td>
<td>.54</td>
</tr>
</tbody>
</table>

The rate of commissions, which has been specifically associated with the inhibitory control aspect of sustained attention, was higher in the patients than in comparison children. Inhibitory control is typically associated with the ventromedial or orbitofrontal areas of the prefrontal cortex as well as additional areas such as the basal ganglia (Casey et al., 1997; Konishi et al., 1999). Altered patterns of activity in these frontal brain regions has been noted in a previous sickle cell ERP study of EF, with the authors suggesting a disruption to the underlying function of the tracts despite the lack of lesions (Alexandra M Hogan, Vargha-Khadem, et al., 2006). The lack of normed scores in this task is a limitation but despite the difficulty in task performance interpretation, there is some evidence for early indications of a growing gap between the children with SCA and the matched comparison group. Schatz et al., (2001) report that children with SCA with silent infarcts
(n=19; mean age =10.8 years) performed poorer than patients without silent infarcts (n= 45) but that matched siblings (n=18) obtained better scores in attention; however the cancellation task scores were combined with other executive tasks to create composite score so they provided no information on specific error rates.

Previous studies, including those of Brown et al. (n=63, aged 6-17 years) and Elsayed et al. (n=60, 6-12 years) report a gradient effect in sustained attention when comparing children with normal MRI, silent stroke, and overt stroke with children who had overt stroke producing the most omissions and commissions (Brown et al., 2000; Elsayed et al., 2012). Ruffieux et al., (2013) looked at sustained attention in children with SCA aged six to 24 years (n=92) using a Continuous Performance Task and though they reported poorer EF in the patient group across the EF/attention domain in general, the differences between groups for omissions and commissions were non-significant when compared with an age matched comparison group. They reported poorer performance with age in their cohort; however, they did not have information on general intellectual functioning or MRI and 8% were reported to have clinical signs of cerebrovascular accidents.

In conclusion, the current patient group showed a specific deficit in the inhibitory control component only of the sustained attention task. The small group sizes successfully completing the task means that these findings must be interpreted with caution as they may not be representative of a wider population. However, the current findings do mirror the findings for a poorer mean score reported in the NIH inhibitory control task for the current patient group in Section 5.4.2. Despite the lack of clear and consistent data on the development of this domain in children with SCA, some evidence for improvement in sustained attention with intervention (e.g. Marshall et al., 2009) is encouraging for this patient group. As this task has been shown to be particularly sensitive to MRI pathology in children with SCA, it is
recommended that future research further validates tasks of sustained attention for preschool children (Brown et al., 2000; Elsayed et al., 2012).

5.4.4 Cognitive Flexibility

An independent t-test found a main effect for group on both the switching score and the highest level reached, showing poorer cognitive flexibility in children with SCA ($t(30)=2.5$, $p=.02$). Children with SCA had a poorer switching score ($M=46.6; SD=14.4; N=20$) than the comparison group ($M=56.9; SD=9.7; N=12$) with the patient group typically reaching ceiling on level four of the task in comparison to the comparison group who typically reached level five. Individual analysis of scores found that six patients (30%) did not reach the normed average highest level for their age range in comparison to one child in the comparison group (8.3%). Children with SCA performed poorer than their matched counterparts in the cognitive flexibility task of set-shifting. Hensler et al. reported that 45% of patients were impaired on the sorting task. In the current study, 30% of patients did not reach the average level for their age range as indicated in normative data (Fuglestad et al., 2014). The mean switching score for the patients in the current study was poorer than the mean score that Hassinger-Das and colleagues reported for a group of preschool children with poor number sense (at risk for mathematical difficulties) on the same measure ($M=49.05, SD=9.68, N=107$)(Hassinger-Das, Jordan, Glutting, Irwin, & Dyson, 2014). They found that poor performance on the EFS in otherwise typically developing preschool children predicted later emerging mathematical problems which may indicate that children with SCA may also be at-risk for difficulties with specific issues in school and that interventions targeted at EF, particularly cognitive flexibility, may improve school readiness and prevent children with SCA falling further behind as they progress through the school system. Indeed, reports of poor mathematics and academic achievement have been reported in older children with SCA (Schatz et al., 2001; W. Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, & Armstrong, 2001). Wang et al., (2001) reported a decline in mathematical
ability, amongst other areas of functioning, with increasing age in children with SCA with normal MRI scans. These findings indicate that cognitive flexibility or switching, an aspect of EF not previously targeted in previous SCA studies, may be a potential focus for assessment and intervention in young children with SCA.

### 5.4.5 Working Memory

One patient only found seven stimuli by the final trial (4.5%), while five patients (22.7%) found eight stimuli, and the rest found all nine stimuli (72.8%). There was no significant difference to the comparison group where two comparison children (15.4%) found eight stimuli whilst the rest found all nine stimuli ($X^2= .64, p=.72$). A multivariate ANOVA found no statistically significant differences between groups for the amount of total trials required or the number of consecutively correct trials ($F_{2,32}=.181, p=.84$, Table 5.4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCA Group (n=22)</th>
<th>Matched Group (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number of Trials</td>
<td>14.68(3.92)</td>
<td>14.64(3.99)</td>
<td>.98</td>
</tr>
<tr>
<td>Consecutively Correct</td>
<td>5.63(2.21)</td>
<td>5.28(1.49)</td>
<td>.67</td>
</tr>
</tbody>
</table>

Similar to the parent reports on the working memory subscale of the BRIEF-P (section 5.4.1), no significant differences for working memory were observed between groups on the visuo-spatial working memory task. Notably, nearly twice the rate of patients did not successfully complete the task, i.e. they did not retrieve all of the stimuli within the twenty trials, however this did not reach statistical significance. Schatz and Roberts (2005) found deficits in auditory working memory for digit span backwards but not for digit span forwards,
spatial span forwards and backwards, or the self-ordered pointing test in a
group of school age children with SCD; however eight of the patients in their
population had a history of severe headaches while eight had a history of
transient ischemic attacks. Schatz and Roberts hypothesized that working
memory deficits in SCA may be modality specific as no differences were seen
in the spatial span and self-ordered pointing tasks that rely on visual systems.
Auditory processing has previously been highlighted as a potential deficit in
preschool children with SCA (Steen et al., 2002). However, in contrast to the
findings reported by Shatz and Roberts (2005) and the current study, Hijmans
and colleagues found visuo-spatial working memory deficits using the N-back
task in 41 children with SCA and 38 controls but not for verbal working
memory (Hijmans, Fijnvandraat, et al., 2011). Hogan et al., (2012) also show
some evidence for delays in visuo-spatial working memory development on
the A not B task in infants with SCA at 9 months with SCA. A limitation of this
study is the small sample in the matched comparison group, nevertheless
when additional children (n=10, matched for age, IQ, and SES but not for
ethnicity) are included in the group comparison (Table S4, Appendix 6), there
remains no effect of group. The results of the current study suggest that visual
working memory is relatively preserved in preschool-age children with SCA in
comparison to their peers. However, considering the accumulating evidence
for a decline in working memory ability in SCD with age in older children and
adults (Hijmans et al., 2011; Kral et al., 2006; Vichinsky et al., 2010) and the
trend for poorer working memory with lower haemoglobin levels in the current
cohort, it is recommended that children with SCA undergo baseline
neuropsychological assessment before they enter the school system so that
the developmental trajectory of working memory in the context of SCA is
better understood. The current study did not include a verbal working memory
task so it cannot be concluded whether working memory is also preserved in
this modality at this early stage of development. It is recommended that future
studies with preschool children with SCD include both measures of verbal and
visual working memory for comparison. It is also recommended that future
researchers gain a better insight into what component of this task is the most
sensitive measure of working memory as studies using similar methods to date have interchangeably reported for amount of boxes retrieved, total number of trials required and maximum consecutively correct trials (Skogan et al., 2014; Wiebe et al., 2011).

5.4.6 Executive Functioning on an Ecologically Valid Level

A MANOVA on the quantitative PETA scores (Initiation, Sequencing, Meta-Cognition, Judgment/Safety, Completion) found no overall significant difference between groups, although a trend for poorer performance in patients was observed \((F_{1,45}=2.1, p=.10)\). Inspection of individual quantitative subdomains revealed that the patients performed poorer on the domains of Completion and Sequencing (see Table 5.5). Independent T Tests revealed a trend for poorer performance on the Total Summary Score \((t_{(44)}=-1.3, p=.19)\) and Total Cues \((t_{(44)}=-1.6, p=.11)\), but not for Completion Time \((t_{(44)}=-.51, p=.62)\). Although non-significant, the patients also required more cues for the Meta-Cognition and Judgment/Safety domains. Chi-square analyses on the qualitative examiner-rated domains (Working Memory, Organisation, Emotional Lability, Distractibility) and Highest Level domain revealed significant group differences for Distractibility only \((X^2=10.18, p=.002)\).

Raw scores were converted to z scores in order to compare patient performance with the London cohort mean (this cohort includes the children in the matched control group). A MANOVA on the quantitative PETA scores (Initiation, Sequencing, Meta-Cognition, Judgment/Safety, Completion) revealed that the patients were significantly different from the mean norms \((F_{5,178}=10.42; p<.001)\). for Total Cues, and Completion Time, with significantly different means observed for Sequencing, Judgment/Safety and Completion. Chi-square analyses showed group differences for Distractibility only in the qualitative domains \((X^2=5.7, p=.02)\). Independent T Tests showed a trend for a poorer Total Summary Score in patients \((t_{(184)}=-1.8, p=.07)\) and significantly poorer performance for Total Cues \((t_{(184)}=-22.2, p=.03)\) and Completion Time \((t_{(184)}=-2.6, p=.01)\) in the patient group. Figure 5.3 shows a
graphical representation of the patient and matched control performance in comparison to the quantitative population norms for the PETA.

**Figure 5.3** Profile of the quantitative PETA scores for the patients (green), matched controls (beige), and London cohort (blue)
Table 5.5. Group comparisons on the domains of the PETA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient (n=22)</th>
<th>Matched Controls (n=24)</th>
<th>P* (d)</th>
<th>London Mean Norms</th>
<th>P (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD) /[range]</td>
<td>63.18 (48.2)</td>
<td>47.54 (31.2)</td>
<td>.195 (0.4)</td>
<td>46.6 (38.3)</td>
<td>.067 (.04)</td>
</tr>
<tr>
<td>Total Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cues</td>
<td>34.32 (18.2)</td>
<td>26.71 (13.3)</td>
<td>.111 (0.5)</td>
<td>26.3 15.8</td>
<td>.028 (0.5)</td>
</tr>
<tr>
<td>Completion Time</td>
<td>16.2 (3.3)</td>
<td>15.5 (4.7)</td>
<td>.618 (0.2)</td>
<td>13.96 3.9</td>
<td>.011 (0.6)</td>
</tr>
<tr>
<td>Initiation</td>
<td>2.32 (2.7) [0-8]</td>
<td>2.33(2.4) [0-7]</td>
<td>.984</td>
<td>2.6 0-9</td>
<td>.623</td>
</tr>
<tr>
<td>Sequencing</td>
<td>.82 [0-3]</td>
<td>1.5 [0-5]</td>
<td>.034</td>
<td>1.87 0-7</td>
<td>.004</td>
</tr>
<tr>
<td>Variable</td>
<td>Patient</td>
<td>Matched</td>
<td>P</td>
<td>London Mean</td>
<td>Norms</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------</td>
<td>---------</td>
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<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>Judgment/Safety</td>
<td>1.18 [0-6]</td>
<td>.54 [0-5]</td>
<td>.122</td>
<td>.43</td>
<td>0-5</td>
</tr>
<tr>
<td>Completion</td>
<td>2.77 [0-7]</td>
<td>1.21 [0-6]</td>
<td>.003</td>
<td>1.1</td>
<td>0-6</td>
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<tr>
<td>Working Memory</td>
<td>.123</td>
<td>11</td>
<td>.196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>13.6</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>68.2</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Very Good</td>
<td>18.2</td>
<td>45.5</td>
<td></td>
<td></td>
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<tr>
<td>Organization</td>
<td>27.3</td>
<td>.924</td>
<td>17</td>
<td>.538</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>22.7</td>
<td>31.8</td>
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<td></td>
<td>36.4</td>
<td>40.9</td>
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<td>40.9</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Typical</td>
<td>Very Good</td>
<td></td>
<td></td>
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<td>--------------------------</td>
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<td>---------</td>
<td>-----------</td>
<td></td>
<td></td>
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<tr>
<td>Emotional Lability</td>
<td>68.2</td>
<td>18.2</td>
<td>54.5</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>13.6</td>
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<td></td>
<td></td>
<td>6</td>
<td>.223</td>
<td></td>
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<tr>
<td>Distractability</td>
<td>27.3</td>
<td>18.2</td>
<td>54.5</td>
<td></td>
<td></td>
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<td></td>
<td>54.5</td>
<td>.002</td>
<td>13</td>
<td></td>
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<td></td>
<td></td>
<td>13</td>
<td>.017</td>
<td></td>
<td></td>
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<tr>
<td>Highest Level of Support</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>--------------------------</td>
<td>--</td>
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<tr>
<td><em>Verbal Guidance</em></td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td><em>Gestural Guidance</em></td>
<td>13.6</td>
<td>4.9</td>
<td></td>
<td></td>
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<tr>
<td><em>Direct Verbal</em></td>
<td>36.4</td>
<td>19.5</td>
<td></td>
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<tr>
<td><em>Physical Assistance</em></td>
<td>36.4</td>
<td>41.5</td>
<td></td>
<td></td>
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<tr>
<td><em>Examiner Completes</em></td>
<td>13.6</td>
<td>23.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Self-talk</em></td>
<td>47.4%</td>
<td>.485</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Yes</em></td>
<td>41.2%</td>
<td>48.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>.825</td>
<td>.551</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Downes  277
It was expected that executive deficits would be observable on an ecological level in children with SCA, similar to the findings on the CKTA in Berg et al., (2012), when compared with a matched comparison group. The patient group showed a trend for poorer performance in the Total Summary Score and Total Cues but there was no difference for Completion Time. There was a non-significant trend for poorer performance across the quantitative subdomains that is driven by the poorer patient scores in the Completion Domain, Sequencing, and Judgment/Safety domains. In the examiner-reported qualitative subdomains, there were differences observed for Distractibility only. The patient group means were also compared with the normative scores for the PETA. Significant differences were observed for Total Cues and Completion Time, and a near significant difference for the Total Summary Score. Performance across the quantitative subdomains was significantly poorer in the patient group and similar to the findings for the qualitative domains when compared with the matched controls, the patients only had significantly poorer examiner ratings for distractibility.

The lack of significant differences in Total Summary Score and Total Cues between the patients and the matched controls indicate that differences in EF in specific domains may not translate to differences in every day EF. The medium effect size for Total Cues indicates that there was a tendency for patients to obtain more cues throughout the task. This meant that patients required more cues to stay on task and to provide scaffolding through the sequence of steps. Despite the lack of significant group differences on the macro level of the task, there were notable differences in specific quantitative and qualitative domains that were also observed when performance was compared with the normative scores.

Completion involves the number of cues required for the child to finish the task once they reach the final page where they see the ‘Stop’ sign. The patients required more support from the examiner to finish the task. Distractibility was scored as one of three qualitative categories: poor, typical,
and very good. This domain incorporated both internal and external distractibility and the results indicate that patients were more susceptible to distraction. The sequencing score pertains to the amount of steps the child could complete independently, with no assistance from the examiner, capturing the child’s ability to move from one step to the next. The trend for a lower score in the patient group means that the patients tended to require more support to move from one step to the next. The Judgment/Safety domain refers to the child’s ability to refrain from engaging in impulsive or risky behaviours such as standing on the chair or putting scissors in their mouth and is measured by the judgment/safety related cues that the examiner delivered throughout task. The trend for poorer Judgment/Safety in the patient group meant that they had more Judgment/Safety cues administered during the task.

Significant group differences were observed for Organisation, Initiation, and Completion in Berg and colleagues’ (2012) cohort of eight to 12 year olds on the CKTA that uses similar scoring and cueing guidelines but only significant group differences for the Completion domain were found in the current cohort. Differences in study findings could be due to the differences in task design or could be a result of a younger and more homogenous population in the current study. Berg et al. included children who had a history of neurological morbidity and also included a patient with a different genotype (sickle cell thalassemia) whereas the current study excluded children with other sickle genotypes and children with a known history of neurological morbidity. However the shared group difference between studies for difficulties in task completion is particularly interesting as it is an aspect of EF research that has not previously been investigated in the sickle cell literature. Similar to the older children in the study by Berg et al., the patients in the current study also required more cues to complete the task. Maintaining intentions, or goal-directed behaviour, is the management of behaviour, including the activation and inhibition of actions, in order to reach goal completion, and is often impaired in disorders that affect the frontal lobes (Levine et al., 2000).
To conclude, the current study shows that children with SCA are already showing a trend for differences in executive performance on an ecological every day task of EF. The results of this study shed light on the potential domains, such as task completion, that patients may struggle with in everyday life and paves the way for future developments in informing parents and educators, as well as highlighting areas of strength. A potential limitation of this study is examiner bias as the experimenter was aware of the child’s diagnosis, however some sessions were filmed and double scored by another examiner who was blinded to diagnosis and good inter-rater reliability was found. Strengths of this study are the ethnicity matched comparison group who were also matched for age, IQ, gender, and SES. This is important as the validation study for this task (Chapter 3) found evidence for a potential influence of these factors on EF performance. A second strength of this study was the availability of the London population norms so that a profile of strengths and weaknesses in performance could be better established in the children with SCA. Future translational research is required to build upon the current study so that meaningful assessments and interventions are developed and instigated so that children with SCA can receive support that is easily translated and meaningful in everyday contexts.

5.5 General Discussion
The aim of this chapter was to describe the neuropsychological profile of EF in preschool-age children with SCA who have no clinical evidence of neurological pathology and to compare their performance with ethnicity-matched controls. It was predicted that children with SCA would show poorer EF performance across executive measures. The overall findings of this investigation are discussed below, along with a summary of patient performance across different measures.
5.5.1 A summary of EF performance

Until recently, the lack of appropriate measures has been a barrier in the characterization of executive development in preschool children with SCA despite widely reported executive deficits in older children (Berkelhammer et al., 2007). This chapter is the first robust assessment of EF in preschool children with SCA. Through the administration of seven executive measures some particular strengths and difficulties emerged for the preschool children with SCA. There were no overall differences between groups on the parent-reported BRIEF-P, though some trends for poorer shifting and emotional control were observed. There were no significant differences on the age-adjusted standard scores obtained on the computerized NIHTB tasks of inhibitory control and processing speed, though the patients tended to obtain poorer scores (it is also noted that the matched control group also obtained relatively low scores for processing speed). When compared with a larger control group not matched for ethnicity the group difference for inhibitory control became near significant. Although no differences were observed for rate of omissions, there was a significant difference between groups on the rate of commissions made on the DDTP sustained attention task and more patients failed the practice phase so did not complete task. A significant difference was also observed for groups on the switching task. No group differences were observed for working memory, although again, fewer children in the patient group successfully completed the task (retrieve all stimuli within the 20 trials). The PETA, the ecologically valid task of EF, produced summary scores for overall or integrated “EF” as well as scores for specific EF subdomains. There was a trend for poorer performance in the patients for the composite EF score but this did not reach significance. On further analysis of the individual PETA subdomains; completion, distractibility, and sequencing were poorer in the patient group than the matched controls. The PETA Completion Time did not differ to the matched controls though both groups tended to have longer completion times than the population mean.
5.5.2 Cognitive Flexibility and Inhibitory Control

Although there was a trend for poorer performance in the patient group across most tasks with a greater proportion of patients struggling on all of the individual tasks (Table 5.6), a specific pattern for difficulties with task switching and attention/inhibitory control was observed. A significant group difference was observed on the EF Scale for Early Childhood task of cognitive flexibility where the child had to sort by one rule, and then switch to another. The only significantly different subdomains on the PETA were completion and sequencing; both these domains require completing a step and then switching to the next task at hand. Notably, there was a trend for poorer performance in the Shift subdomain and the Flexibility Index for the patients on the parent-reported BRIEF-P but these differences did not reach significance. Potential issues with attention/inhibitory control were noted due to the high error rate for commissions (stamping incorrect stimuli) and the trend for poorer performance on the NIHTB Flanker task (pressing button that matches the direction of the peripheral fish rather than the central target fish). Poorer inhibitory/attention control for the patients was also observed on the PETA through a higher rate of distractibility reported for the patients, a trend for patients requiring more cues to stay on task in general and more cues for the category of judgment/safety (i.e., putting fingers in ink or scissors in mouth). Although there was no difference on the Inhibit domain of the parent-reported BRIEF-P, patients obtained poorer reports on the Emotional Control domain that involves the inhibitory control of emotional responses. The evidence for a specific deficit in switching builds upon two previous studies that found poorer switching in infants and older children with SCA who have normal MRI (Hensler et al., 2014; Hogan et al., 2012). There are no other studies that look at switching in SCD patients with no brain pathology and a HbSS genotype only using a matched control group and no studies that exclusively focused on inhibitory control in otherwise healthy HbSS patients using a comparison group. This study emphasizes the importance of focusing on switching and inhibitory control in future assessment and intervention studies with children with SCA.
5.5.3 Working Memory and Processing Speed

Despite a greater proportion of patients falling into the ‘impaired’ range on the working memory and processing speed tasks when compared with matched controls, performance in working memory and processing speed were particular strengths in the current cohort, with patients showing comparable performance to the matched controls across multiple measures. There were no differences between groups for parent-reported working memory on the BRIEF-P of for the examiner rating on this domain in the PETA. Although more patients failed to retrieve all of the stimuli, the number of consecutively correct trials was comparable to the matched controls. Mixed findings have been found for working memory performance in older children and adults with SCA with normal MRI, however the current study shows evidence for intact working memory in patients with SCA in the preschool years (Bernaudin et al., 2001; Brown et al., 1993; Noll et al., 2001; Schatz & Roberts, 2005; Vichinsky et al., 2010). Slightly slower speed of processing was seen for the patients across all timed measures, but this did not reach significance for the NIH processing speed task, the motor phase of the DDTP, or the completion times for the DDTP and PETA. However, in comparison to normative scores available for the NIHTB and the PETA, both the patients and the matched controls had slower processing speed and completion times which may be a reflection of the factors that they were matched on such as IQ or SES (Sheppard & Vernon, 2008). Poorer processing speed has been widely reported in older children and adolescents with SCA and normal MRI (Steen et al., 2005; Scantlebury et al., 2011; Vichinsky et al., 2010). This study is the first study to provide evidence for relatively intact working memory and processing speed at this early developmental stage in SCA when compared with matched controls.

5.5.4 Patient performance across Executive Tasks

Measures that investigate EF from both top-down and bottom-up perspectives were included in the battery of assessments. The inclusion of the BRIEF-P
and the PETA provides us with an insight to the general EF of preschool children with SCA in everyday settings and how behaviour in school or at home might generally differ to their peers. Additionally, the inclusion of tasks that separately focus on working memory, attention control, cognitive flexibility, and processing speed allows us to build a profile of EF and inform us of specific areas that may be at risk in children with SCA. Table 5.7 and Table 5.8 show the proportion of patients who were categorised as ‘impaired’ on particular tasks and the tasks that were most frequently failed. Interestingly, the composite scores on the two general EF measures, namely the BRIEF and the PETA, captured patients who performed poorly on at least two other tasks that tapped specific aspects of EF. Two of three patients who scored in the clinical range on the BRIEF were also two of four children that had poor executive composite scores on the PETA. This shows evidence for the utility of multi-method assessment of EF in this patient group rather than a complete reliance on tasks that tap specific and separated aspects of EF. Findings on the BRIEF-P reflected a lower level of EF impairment in the patient group than the proportion of impairment observed on any of the behavioural tasks. This could be attributed to multiple factors, including less readily observable every day executive skills at this young age which could lead parents to under-report problems, or potentially more subtle ecological differences at this young age that become more apparent in every day settings from middle childhood. This is potentially reflected in patient performance on the PETA where significant differences were observed on some of the subdomains but this did not translate to statistically significant group differences on the composite score level. However, the utility of using the BRIEF-P measure in tandem with performance-based measures is through its ability to provide the clinician or researcher with a holistic picture of an individual child’s ability and as a useful reference for comparison with performance on behavioural tasks.
5.5.5 The Value of Early Executive Assessment in SCA

The integrated information from this battery of tasks will help inform researchers and clinicians of the impact of SCA on early brain development and guide future interventions. Recent reports have called for early neuropsychological assessment in young children with SCA in the absence of brain pathology, particularly EF, however this is currently not a standard practice (Daly et al., 2011; Glass et al., 2012). There have been few attempts to develop neuropsychological interventions for young children with SCA (Drazen, Abel, Lindsey, & King, 2014). This is despite the known issue of EF deficits in older children and the potential widespread influences that EF deficits have for children in all aspects of their lives, including social and emotional functioning, disease management, and academic achievement (Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008; Blair & Razza, 2007; Daly et al., 2011), areas also known to be implicated in children with SCA (Brown et al., 1993; Schatz et al., 2001). For example, Hensler et al., (2014) showed a specific association between executive dysfunction, particularly deficits in switching, and poorer social skills in school age children with SCD while the association between switching and mathematical ability reported for typically developing preschool children may contribute to an explanation for reports of poorer mathematical ability in children with SCA (Hassinger-Das et al., 2014; Wang et al., 2001). Several studies have shown a relation between poorer EF and increasing age and disease progression in SCA (Hijmans et al., 2011; Kral et al., 2006; Vichincky et al., 2010). Ruffieux et al., (2013) showed a significant effect of increasing age on attention and EF development but not for memory or sensory-motor deficits in 96 children with SCA aged six to 20 years. They reported a significant effect for age and disease on EF performance with the youngest children performing similar to the controls but a widening gap in EF ability with age in comparison to other cognitive factors that remained stable over time (figure 5.4). Despite the findings in the literature for poorer EF with increasing age, there have been
limited intervention studies in the SCA literature that have focused on executive skills as an end point (Marshall et al., 2009) and no interventions specifically aimed at improving EF in preschool-age children with SCA.

**Figure 5.4.** Reproduced from Ruffieux et al., (2012). This figure shows the increase in executive dysfunction (factor score created from nine EF measures) with age in SCD.
Table 5.6. Descriptive data summarizing performance on the EF tasks in the children with SCA in comparison to the matched controls (reference point for impairment changes between tasks and so results must be interpreted with caution)

<table>
<thead>
<tr>
<th>Measure</th>
<th>No. of impaired Patients (%)</th>
<th>No. of impaired Matched Controls (%)</th>
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<tbody>
<tr>
<td>BRIEF GEC*</td>
<td>3 (13.6)</td>
<td>3 (12.5)</td>
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<tr>
<td>NIH Inhibitory Control*</td>
<td>3 (15.8)</td>
<td>0</td>
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<tr>
<td>NIH Processing Speed*</td>
<td>7 (35)</td>
<td>3 (23)</td>
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<tr>
<td>DCCS**</td>
<td>6 (30)</td>
<td>1 (8.3)</td>
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<tr>
<td>Scrambled Memory^</td>
<td>6 (27.2)</td>
<td>2 (15.4)</td>
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<tr>
<td>DDTP&gt;</td>
<td>11 (50)</td>
<td>4 (33.3)</td>
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<tr>
<td>PETA Total Score*</td>
<td>4 (18.2)</td>
<td>0</td>
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</table>

*Impairment defined as >1.5 SD below the standard mean. ^Impairment defined as not retrieving all 9 boxes. **Impairment defined as not reaching highest level as typical for age range. > Impairment defined as failing practice phase or obtaining a score greater than 1.5 calculated SD above average on combined rate omissions and commissions.
Table 5.7 Pattern of individual ‘impaired’ scores across the seven executive measures

<table>
<thead>
<tr>
<th>Patient</th>
<th>BRIEF</th>
<th>NIHCC</th>
<th>NIHPS</th>
<th>DDTP</th>
<th>WM</th>
<th>DCCS</th>
<th>PETA TS</th>
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X = impairment on measure
Table 5.8 Summary of performance of children with SCA across all seven executive measures

<table>
<thead>
<tr>
<th>Individuals ‘impaired’* on</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tr>
<td>Individuals ‘impaired’ on 0</td>
<td>6</td>
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<td>Individuals ‘impaired’ on 1</td>
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<td>Individuals ‘impaired’ on 2</td>
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<td>Individuals ‘Impaired’ on 3</td>
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<td>Individuals ‘impaired’ on 4</td>
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<td>Individuals ‘impaired’ on 5</td>
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<td>Individuals ‘impaired’ on 6</td>
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<td>Individuals ‘impaired’ on 7</td>
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*‘Impaired’ defined in Table 5.6

5.5.6 Theoretical Interpretation

In Anderson’s developmental model of EF, basic EF skills emerge first that both lay down the foundation for and are then used in combination with later emerging EF skills (Anderson, 2002). Specific EF abilities ‘come on-line’ at different points of development. Improvements in attention control, switching, and fluency, are reported up to six years, significant gains in information processing speed are reported to typically occur between nine and 12 years olds with efficiency and fluency increasing in adolescence, and the higher order skills of goal setting, such as conceptual reasoning, planning and organisation are reported to develop rapidly between seven and 10 years old (Anderson, 2002). It has been purported that the development of EF skills can be divided into three phases; emerging, developing, and established, and that EF skills are only assessable in the established phase so the full impact of neurological damage acquired early in life may not be fully realised until a later stage of development (Dennis, 1988).

The results of this study can be mapped onto Anderson’s model. Anderson proposes that children with impairments in the early emerging foundational
domain of attentional control can be impulsive, have poor self control, find it difficult to complete tasks, and make procedural errors that are not corrected.

The findings for specific deficits in the domains of inhibitory control and switching in the current patient cohort, however, did not translate to the composite scores on the PETA and the BRIEF-P, perhaps reflecting the combination of EF skills that these measures report and the developmental stage of the children (Garon et al., 2008; Garon et al., 2014). In clinical neuropsychology, children with early brain insult are sometimes described to ‘grow into’ later emerging deficits where impairments are reported to emerge with brain development and as developmental expectations grow to incorporate higher-order or more complex skills such as planning, organising, and problem-solving, that build upon simple EF skills such as attention control. For example, a child with early brain insult with expected frontal issues may, on a whole, show no EF deficits in comparison with their peers on a composite score level at five years old on a developmentally appropriate task such as the PETA but may show more of a discrepancy at 12 years old on a similar every day task after ‘critical periods’ for other EF domains such as goal setting occur in the intervening years (V. Anderson et al., 2014). This is why it is important that neuropsychological assessment protocols adopt micro-analytic quantitative and qualitative scoring approaches so that as much information as possible can be gathered for the different EF subdomains of a task (Anderson, 2002).

Despite the evidence for group differences in aspects of attention control, patients were not performing significantly poorer in the domains of working memory and processing speed. These findings was unexpected due to the relatively larger SCD literature reporting EF deficits in these domains in comparison to other EF areas, however are in line with developmental cognitive theories that suggest that developmental increases in information processing, such as the critical periods reported later in childhood and adolescence for speed and efficiency may enhance EF (Anderson, Anderson,
Anderson, Northam, and Wrennall (2014) describe the example of working memory where it has been historically theorized that the storing and retention of information in memory is a basic capacity that enhances with development. However, the improved ‘memory capacity’ could be attributed to more efficient information processing or the employment of recall strategies, which means that an integrated relationship between memory, processing speed and EF is responsible for this developmental progression.

5.5.7 Limitations
The small control group sizes limit the statistical power for some of the studies in the current chapter. To circumnavigate this potential issue, additional appropriately matched children who are matched on all factors except for ethnicity are included in additional comparisons in appendix 6 for further information. However, the larger group sizes do not impact any of the findings except for the case of inhibitory control (section 5.4.2), which becomes near significant. Nevertheless, the strength of this chapter lies in the homogeneity of the patient population in terms of overcoming the shortcomings of previous studies that mixed genotypes and patients with and without stroke, as well as the narrow age range of focus and the well-matched controls. The findings for differences between groups in certain EF domains carry more weight as the groups are matched for age, IQ, ethnicity, gender, and SES; reducing the likelihood of spurious differences being uncovered. More compelling differences may have been uncovered in this group had they not been matched for IQ and these other factors (Hill, 2004; Schatz, Finke, et al., 2002; Steen, Fineberg-Buchner, et al., 2005; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990). The stringent approach adapted in the current chapter allows us to elucidate differences due to illness without the influence of previously reported confounding factors. Ethnicity matched controls have been cited as being particularly relevant to the study of children with SCA (Barbarin & Christian, 1999). Richard and Burlew emphasized minimum standards for sickle cell control groups in comparison studies for cognitive and behavioural
functioning nearly two decades ago yet many studies continue to include comparison groups that are not matched for ethnicity and SES (Richard & Burlew, 1997). This is a particularly important caution for research concerning EF development as children with SCA are often from a minority group and face socioeconomic disadvantages that have been shown to influence EF development (Noble et al., 2005; Sarsour et al., 2011). Indeed all of the patients and matched controls in this study were second-generation immigrants and a recent UCL report on minority children in the UK from the Millenium Cohort Study reports that they experience disadvantages in achievement before entering the school system (Dustmann, Frattini, & Theodoropoulos, 2010).

Task difficulty and order of administration must also be considered in the interpretation of the pattern of executive difficulties observed as the tasks were not equated on difficulty level, so it could be that poorer performance could instead reflect general task difficulty, rather than executive dysfunction and that children performed poorer on certain tasks due to fatigue. However, the matched control group can control for this limitation to an extent. For example, the low group mean for processing speed in the matched control group on the NIHTB allowed us to better interpret the performance of the patient group on this task. Without a matched control group, it could have been interpreted that the patients were performing poorer than their peers if the scores were just compared with the normative values for this task. However, it can instead be observed that the control group also obtained low scores on average which could be attributed to one of the factors that the groups were matched on, such as SES, or the administration and/or the reliability of the task.

5.5.8 Conclusion

The findings for group deficits in different EF domains in the current chapter support baseline neuropsychological assessment for EF in preschool children with SCA before they enter the school system. This is necessary to further
delineate the profile and developmental trajectory of EF in the context of SCA and to gain an insight into an individual child’s ability before other environmental and disease-related factors in school-age children, such as school absenteeism and disease progression, further complicate the picture of EF in SCA. For example, in the current cohort inhibitory control and switching were observed as particular impairments while working memory and processing speed remain relatively preserved at this early stage as compared to later reports for older children. Historically, there has been more research in working memory and processing speed in children with SCA than switching and inhibitory control; however no study has previously looked at executive functions at the preschool stage. Additionally, few studies have focused on children without known brain pathology and have combined genotypes, which makes findings difficult to interpret, as children with stroke tend to perform poorer while children with other sickle cell genotypes typically have less severe phenotypes. Few studies have employed matched control groups when looking at cognitive development in children with SCA. The comparison group in the current study was matched for age, IQ, SES, and ethnicity making the findings for EF more compelling despite the small sample size. By matching for SES and ethnicity, the impact of potential environmental factors such as immigration status, second language at home, social, cultural, and economical issues on EF is greatly reduced. However, by also matching for IQ the influence of general cognitive ability on task success was removed.

The majority of lesions in SCA are in the frontal cortex (Armstrong et al., 1996; Moser et al., 1996), an area strongly implicated in EF, yet it remains unclear as to why this brain region that subsumes the development of EF seems the most vulnerable to insult and why EF seems to be implicated in SCA even when no evidence of cerebral vasculopathy is observed (Mary C Kral & Brown, 2004). Future research should build upon the findings presented in the current chapter in order to investigate the development of EF and the impact of neurocognitive, psychosocial, and medical interventions on this development. EF has not been a primary end point for any intervention studies in sickle cell
research despite its integral role in academic achievement and adaptive and social functioning, and despite the accumulating evidence for its malleability with appropriate intervention.

5.5.9 Case Study Description

The following case study example illustrates the case of Patient G who obtained the most ‘impaired’ scores across tasks on the EF battery. Patient G is 5.1 years with an FSIQ of 85 (average VIQ=100 and below average PIQ=79) was impaired on 5/7 executive measures as illustrated in Table 6.7. He also had the slowest completion times for the PETA and the second slowest completion time for the DDTP. This patient had four A&E admissions in the previous year and was reported to have the highest rate of sleep problems, classified as having moderate OSA after undergoing a sleep study in infancy. His most recent TCD reading was in the conditional range and his daytime oxygen saturation on the day of testing was 96% (the lower end of the normal range); however his haemoglobin levels were in the normal range. He was in the lowest SES category and the parent-reported family functioning was lower than the patient group mean. There are several factors at interplay in the case of patient G that may be influencing his poor EF performance across multiple EF measures. Compared to the other patients in the current study, patient G has a more severe disease history, has a history of sleep problems, faces more socio-economic disadvantage and his parent-reported family functioning is less positive. He also has the lowest performance IQ. The case of Patient G emphasizes the importance of focusing on interventions to improve EF. EF can act as a protective factor in children at risk for academic failure due to poor environmental factors and disease (Blair & Razza, 2007; Johnson, 2012b). Patient G highlights a case of a young child that could be particularly considered at-risk of academic failure due to a multitude of factors including poorer disease and SES status and poor performance IQ, and who may benefit from early EF assessment and intervention.
Chapter 6: Predictors of executive dysfunction

An investigation of factors that contribute to poorer executive functioning in preschool children with sickle cell anaemia
6 Predictors of executive dysfunction

6.1 Introduction

Despite the growing body of literature showing evidence for domain specific deficits in executive functioning in children with SCA who have not experienced stroke, there is a limited understanding of the underlying aetiology of these deficits. There has been little focus on what factors may be associated with executive deficits, with most research looking at the potential impact of disease factors on more general cognitive development. Research to date has largely focused on the neurocognitive effects of overt or covert stroke (Van Der Land et al., 2014; White et al., 2000), with some focus on CBFV (Kral & Brown, 2004; Sanchez, Scahtz, & Roberts, 2010), haemoglobin levels, or anaemia severity (Hijmans, Grootenhuis, et al., 2011; Steen, Fineberg-Buchner, et al., 2005; Steen et al., 2003). More recently, there has been a shift in attention to the effects of sleep problems, particularly sleep-disordered breathing, which has a higher incidence in children with SCD and is associated with executive dysfunction in the general population as well as in those with SCD (Beebe & Gozal, 2002; Hollocks et al., 2011). There has also been an emerging focus on socio-environmental factors, which some studies have found to be even more predictive of neurocognitive dysfunction than biomedical factors (King et al., 2013, 2014; Tarazi et al., 2007).

6.1.1 Disease factors as predictors of poor neurocognitive functioning

Physical symptoms of SCA typically emerge in the first three to six months of life. Sickled red blood cells break down much faster than typical red blood cells causing a shortage of red blood cells, or anaemia, and consequently a shortage of oxygen, or hypoxia. Anaemia severity can be measured by investigating haemoglobin levels with low levels of haemoglobin indicating a greater severity of anaemia. Due to the ‘sickling’ of their red blood cells, children with SCA are prone to infection, have a greater incidence of chronic and acute pain, and are at a greater risk for pulmonary and cardiac problems, as well as stroke. Ischaemic stroke occurs due to a restriction in blood supply,
and thus oxygen and glucose, to the surrounding brain tissue, and haemorrhagic stroke occurs when a blood vessel ruptures due to a blockage of the vessel with sickled cells. Stroke due to ischaemia is more commonly observed in children with SCA (Kirkham, 2007). The risk for stroke can be predicted through Transcranial Doppler screening with higher cerebral blood flow velocities (CBFV) indicating a greater risk for stroke.

Though there is some evidence for an association between high CBFV and poorer cognitive functioning, findings have been inconsistent. Studies have found that children with SCD who have developmental delays show higher CBFV (Kral & Brown, 2004; Sanchez, Schatz, & Roberts, 2010). High CBFV is predictive of future neurological problems in children with SCA. Two studies in infants with SCA with no MRI screening have shown some evidence for a relationship between CBFV and neurodevelopmental delay and adaptive behaviour (Armstrong et al., 2013; Hogan, Pit-ten Cate, et al., 2006). Sanchez, Schatz, & Roberts (2010) found associations between CBFV and language functioning but not between CBFV and attention/working memory or visuomotor functioning in children with SCD with no MRI screening (n=39; five to eight years old). Kral et al. (2003) found that children with SCD with no stroke who had conditional CBFV (on the boundary between normal and abnormal) performed poorer on executive tasks than those with CBFV within the normal range (Kral et al., 2003), although the lack of association with abnormal TCD may have reflected transfusion treatment for the latter group. Other studies have reported potential effects of CBFV on memory and IQ (Bernaudin et al., 2000; Ruffieux et al., 2013). However, some research has not found any association between CBFV and cognitive development (Aygun et al., 2011; Kral et al., 2006; Onofri et al., 2012; Strouse et al., 2006). The variable findings for the impact of CBFV on different domains of cognitive functioning may be due to studies that have employed mixed genotypes and combined patients with neurological pathology with patients who have no history of cerebrovascular accidents (CVA), as well as differences in treatment. Additionally, studies have used different means to measure CBFV with some studies looking at the most recent reading and other studies
looking at an average of a number or readings. Some studies have divided patients into clinical severity categories based on their reading and other studies looking at CBFV as a continuous variable which makes it difficult to draw comparisons between studies in the literature to date.

Low haemoglobin levels have also been described as a predictor of poorer cognitive functioning (Bernaudin et al., 2000; Brown, Buchanan, et al., 1993; Kral et al., 2006; Steen et al., 1999; Swift et al., 1989). Hijnmans et al. (2011) looked at the association of anaemia severity and CBFV with neurocognitive skills, including EF, in a group of 37 children with SCD aged six to 18 years. The authors found that haemoglobin was associated with verbal short-term memory, however CBFV was not associated with any neurocognitive outcomes. Vichinsky and colleagues reported an association between poor neurocognitive function and anaemia in older patients in their study of 19 to 55 year olds (N=149). The authors concluded that neuropsychological deficits might be associated with chronically reduced oxygen flow in the brain, indicated by haemoglobin levels (Vichinsky et al., 2010). However, as the authors combined genotypes and studied a wide age range for a developmental population, it is unclear whether these relationships would be consistent within genotypes or more specific age groups. In addition, as the authors recruited a relatively small sample, it is unclear whether disease-related factors that were not statistically significantly associated in this study may nevertheless be associated with performance.

Recently, studies have looked at treatments such as transfusion and hydroxyurea, suggesting potential cognitive benefits for treated children although the data for IQ in older children undergoing transfusion is not convincing (DeBaun et al., 2014; Puffer et al., 2007), while a handful of studies have looked at alternative biomedical factors such as oxygen saturation levels (SpO₂), height-for-age and body mass index (Kirkham et al., 2001; Knight, Singhal, Thomas, & Serjeant, 1995; Puffer, Schatz, & Roberts, 2014). Overall, findings between biomedical markers of disease severity and
neuropsychological outcomes are inconsistent, which has led researchers to explore the role of psychosocial factors in neurocognitive development. Higher rates of sleep problems have been reported for children with SCA when compared to typically developing children, particularly sleep disordered breathing which causes low nocturnal $\text{SpO}_2$ or hypoxia, a pathological process that co-occurs in SCA (Daniels et al., 2010). A recent study in 24 children with SCA and sleep disordered breathing found that children with SCA who received a sleep intervention for SDB improved on a processing speed task (Marshall et al., 2009).

6.1.2 Psychosocial factors as predictors of poor neurocognitive functioning

Poor family environment, characterised by conflict and unsupportive or inconsistent environments, may be conducive to stress, which can impact the development of the prefrontal cortex, and has been associated with poorer physical and mental health outcomes in typically developing children (Fishbein et al., 2004; Repetti, Taylor, & Seeman, 2002; Skosnik et al., 2000). Low SES, usually measured through family income and parental education and occupation status, has been reported to have negative implications for health, cognitive, and SES outcomes in children and is known to particularly affect the executive system in comparison to other cognitive domains (Bradley & Corwyn, 2002; Noble et al., 2005). Theories such as the Family Stress Model and the Investment Model suggest that SES may impact child development in an indirect way; through affecting parental behaviour and family processes (Conger, Conger, & Martin, 2010). An accumulating evidence base shows that more positive family functioning, such as the provision of stimulating experiences in the home environment, lower maternal stress, and more positive parenting practices mediates, or acts as a protective factor against the impact of poor SES on child development (Linver, Brooks-Gunn, & Kohen, 2002).
Children with SCA are often faced with issues associated with lower SES and ethnic minority status as well as the burden of their chronic condition (Barakat, Lash, Lutz, & Nicolaou, 2006). King et al., (2014) argue that cognitive outcomes in children with SCA are best accounted for by multivariate models that include both biomedical and socio-economic factors.

Several studies have linked the SES proxy of parental education to cognitive outcomes in children with SCA. In King et al’s study of 150 children with SCA with and without evidence for silent infarction (aged 5 to 15 years old), they found that a regression model that incorporated parental education as well as haemoglobin oxygen saturation and silent stroke predicted FSIQ, with parental education as the strongest independent predictor (absence of parental university education was associated with a decrease of 6.2 IQ points in the patients). Smith and colleagues also found that parental education was an important determinant of academic achievement in children with SCA, alongside IQ, chronic transfusion status, and quality of life (Smith et al., 2013). Parental education may be the most important aspect of SES, as a higher parental educational level could prove a protective factor for cognitive development in children (Brown, Buchanan, et al., 1993; Davis-Kean, 2005). Schatz and McClellan argue that most research in SCA so far has focused on socioeconomic factors such as income and maternal education rather than potentially modifiable psychosocial factors such as family functioning and parental stress (Schatz & McClellan, 2006). Thompson and colleagues investigated disease-related and psychosocial factors contributing to cognitive development and found that a learned-helplessness style of parenting was found to have an adverse association with neurocognitive outcomes in young children with SCD (Thompson et al., 2002). The same group also found that improvements in behavioural control over nine years were related to better family functioning (n=222) (R. Thompson et al., 2003). Conversely, another study found that socioeconomic variables were predictive of cognitive functioning in children with SCD however they found no effect for family functioning and parental adjustment (Devine, Brown, Lambert, Donegan, & Eckman, 1998). One review declared concerns for family function in families...
with SCD in the UK (Midence et al., 1996) while a more recent British review found that SCA patients in the most socio-economically deprived areas were most likely to have greater disease-related morbidity and mortality (AlJuburi & Majeed, 2013).

### 6.1.3 Predicting Executive outcomes in preschool children with SCA

There has only been one previous investigation of predictors of neuropsychological functioning that looked specifically at preschool children with SCD (n=26; n with HbSS=15). Tarazi et al. (2007) found that socioeconomic status was a more pertinent target than disease-related factors for neuropsychological deficits in preschool children with SCA. However, they did not include specific tasks to measure executive functions across this age range (3 to 5.99 years old). They initially included the Developmental Neuropsychological Assessment (NEPSY) Visual Attention task in their battery but this was found to be inappropriate for three year olds and thus was not included in their final analysis. The Visual Attention task has since been removed from the more recent version of the NEPSY due to poor sensitivity (Brooks, Sherman, & Strauss, 2009). Tarazi and colleagues still attempted to measure attention in their patients by looking at their performance on NEPSY memory tasks, which they hypothesised to reflect brief attention. They found that there was no direct association between disease factors and neuropsychological functioning in their cohort, with mean neuropsychological scores in the low average to average range.

Environmental factors, including SES and parental stress, were most strongly associated with the three domains of ‘memory/brief attention’, ‘language’, and ‘visuospatial’ skills.

The lack of executive tasks appropriate for preschool children has so far been a barrier to the investigation of the development of executive deficits in children with SCA. Previous reports in older children with SCA have suggested that behavioural measures of EF are more sensitive to potential
deficits than parent-report, underscoring the importance of not relying completely on parent report measures in executive research (Jones, 2013). A greater understanding of the complex relationship between EF in children with SCA and disease-related and socio-environmental factors could inform the development of more targeted and, importantly for executive development, earlier assessment and intervention. Improved assessment and intervention, in turn, could lead to improved school readiness and academic attainment as well as improved social functioning and overall quality of life, including greater adaption to disease management (Jones, 2013; Tarazi et al., 2007).

The current study looks at predictors of EF in preschool children with SCA. Building upon previous research, both biomedical and psychosocial factors have been included. This study is focused on children with SCA, typically considered the most severe type of SCD, who do not have clinical evidence of overt stroke. As the literature on the predictive value of biomedical factors in the context of children with SCD who have not experienced stroke is inconsistent, I hypothesis that psycho-socio-environmental factors will be more predictive of executive outcomes. More specifically, as this young age group typically spends most of their time in the family context in comparison to older children and adolescents, and patient families reported poorer family functioning (see Chapter 4), I hypothesise that more positive family dynamics will be conducive to better EF. Secondly, as there has been recent evidence for a greater incidence of sleep problems in SCA (as reflected in Chapter 4), particularly sleep-disordered breathing, which, like SCA itself, results in low oxygen haemoglobin saturation likely to be additive in terms of exposure, I hypothesised that a greater burden of reported sleep problems will be related to poorer EF.

6.2 Aims
Children with SCA have a greater prevalence of executive deficits than their typically developing peers even when there is no evidence of neurological infarct. The previous chapter (Chapter 5) presented evidence for a poorer
executive profile in preschool children with SCA when compared with typically developing preschool children. There remains no clear picture of the factors that contribute to executive deficits in older children with SCA with previous studies showing mixed results. While some studies have found that socio-environmental predictors are more predictive of neurocognitive outcomes than disease-related factors (Brown, Buchanan, et al., 1993; Tarazi et al., 2007), others have shown evidence for the impact of markers of disease severity (Kral & Brown, 2004; Sanchez et al., 2010).

This chapter aims to explore possible predictors of these executive deficits in preschool children with SCA by investigating the association of socio-environmental and disease markers of SCA with EF. None of the children have a history of clinical stroke so the well-established connection between stroke and executive deficits will not be discussed. Based on previous research that has looked at predictors of general functioning in preschool children with SCA (Tarazi et al., 2007), it is hypothesised that socio-environmental markers will have a greater influence on executive outcomes at this young age than biomedical factors. As Chapter 5 showed poorer parent-reported family functioning and more sleep problems in the SCA cohort, it is expected that these variables will have an influence on executive outcomes due to a strong case for associations between executive development and these factors in the literature on typically developing preschool children (Bernier et al., 2013; Karpinski et al., 2008) and an emerging literature in older children with sickle cell disease (Hollocks et al., 2011).

6.3 Methods

6.3.1 Participants

Children with SCA aged three to five years who did not have any evidence of neurological morbidity or additional developmental diagnoses were recruited through the Royal London Hospital and Barts NHS Trust between February 2014 and April 2015. All participants underwent fully informed consent and neurocognitive assessment at the UCL London Babylab and consented for relevant medical data to be obtained from their hospital files via their
paediatric haematology consultant, Dr Paul Telfer. All children were in a clinically stable condition at the time of testing and provided assent for participation on the day of testing.

### 6.3.2 Measures

#### 6.3.2.1 Medical

A consultant paediatric haematologist used a TCD as part of patient clinical care to measure CBFV. Measurements were routinely collected for four regions; right middle cerebral artery, left middle cerebral artery, right anterior cerebral artery, and left anterior cerebral artery. All TCD measures were obtained within nine months of neuropsychological assessment with a mean delay between TCD and neuropsychological assessment of 60 days. Maximum CBFV was calculated as the highest variable for each available TCD reading (from maximum TAMM of right and left middle carotid artery).

Haemoglobin levels were obtained on the most recent hospital visit or the day of neuropsychological assessment if not available. The number of hospital admissions for the previous year was obtained from medical records. End-tidal carbon dioxide (CO₂) and daytime oxygen saturation (SpO₂) levels were collected on the day of neuropsychological testing by the researcher using capnography and pulse oximetry measures, respectively. Disease severity was indicated by a history of complications associated with SCA including dactylitis, splenomegaly or splenic sequestration, or regular transfusion of hydroxyurea treatment, obtained through review of medical records.

#### 6.3.2.2 Socio-environmental

Environmental factors included maternal education and socio-economic status. Maternal education was a categorical variable (‘at least some college’ or ‘secondary school only’). SES was represented by average weekly net income (before housing costs) based on residential postcode, estimated through and Office for National Statistics methods (Nation, Cocksey, Taylor, & Bishop, 2010). Children were divided into five SES categories, from very low to very high: £791+ (5), £671-£790 (4), £591-670 (3), £521-£590 (2), and up to £520 (1). Levels of positive family environment were measured by
administering the Family Environment Scale (FES) questionnaire to parents. The FES Summary Score was obtained by creating a composite score that consisted of the addition of scores on the subdomains of cohesion, expressiveness, active/recreational, and organisation and the inverse of conflict and control. The composite score has been previously used in children with SCA and other chronic conditions and a higher score reflects a more positive family environment (Barakat et al., 2007; Perrin et al., 1993).

6.3.2.3 Neuropsychological

6.3.2.3.1 Executive
Parents completed the Behaviour Rating of Executive Function-Preschool (BRIEF-P) questionnaire. Participants completed the NIH Toolbox Tasks of Inhibitory Control and Processing Speed, the Executive Functioning (EF) Scale for Early Childhood, the Doggie Deletion Task for Preschoolers (DDTP), the Scrambled Memory Task, and the Preschool Executive Task Assessment (PETA). See Chapter 5 for further task description and the results of individual executive tasks.

6.3.2.3.2 Sleep Behaviour
Parents completed the Children Sleep Habits Questionnaire (CSHQ). See Chapter 4 for further details on methodology and results.

6.3.2.3.3 Intelligence
Full scale IQ was obtained by administering the core subtests of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-UK). See Chapter 4 for further details on methodology and results of WPPSI-III-UK.

6.3.3 Data Reduction and Analysis

6.3.3.1 Executive Composite Scores
Individual neurocognitive test scores were grouped based on Anderson’s four main developmental model executive domains (Cognitive Flexibility, Goal Setting, Attention Control, and Information Processing) (Figure 6.1). Similar to data reduction procedures adopted by Noble and colleagues, individual test
scores were used to create composite scores within each of the four domains (Noble et al., 2005). Test scores were converted to z-scores based on the SCA group continuous raw scores, and the composite score was defined as the average z-score across tasks within a particular domain. (z-score = (score-mean)/standard deviation). In the few cases of missing scores on individual tasks, composite scores were replaced with a mean z-score of 0 (mean for the group), to create representative composite scores. Lower composite scores on these executive domains reflect better EF. Finally, a general EF score was calculated as the average score of all individual tasks. Inter-correlations between individual task scores and the corresponding domain composite score, and between individual task scores and the general EF score are displayed in Table 6.1. The overall general EF score was compared with the BRIEF general executive composite score and the PETA total score (the two other ‘general’ indicators of EF in this thesis, one parent-report and one behavioural, that were not included in the generated composite score) in order to establish its validity and was significantly correlated with both tasks (r= .52 and r= .73, respectively).

**Figure 6.1.** Tasks organised into domains as described in Anderson’s theoretical developmental model of EF (Anderson, 2002)
Table 6.1 Inter-correlations between individual tasks and composite scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Attention Control</th>
<th>General EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Flanker</td>
<td>-.571**</td>
<td>-.286</td>
</tr>
<tr>
<td>DDTP OMM</td>
<td>.204</td>
<td>-.174</td>
</tr>
<tr>
<td>DDTP Comm</td>
<td>.507*</td>
<td>.612**</td>
</tr>
<tr>
<td>BRIEF-P Inhibit</td>
<td>.625**</td>
<td>.631**</td>
</tr>
<tr>
<td>NIH pattern comparison</td>
<td>-.654**</td>
<td>-.432*</td>
</tr>
<tr>
<td>DDTP time to complete</td>
<td>.750**</td>
<td>.474*</td>
</tr>
<tr>
<td>PETA Total Time</td>
<td>.777**</td>
<td>.621**</td>
</tr>
<tr>
<td>PETA learning score</td>
<td>-.680**</td>
<td>-.238</td>
</tr>
<tr>
<td>BRIEF Shift</td>
<td>.693**</td>
<td>.246</td>
</tr>
<tr>
<td>BRIEF Working Memory</td>
<td>.746**</td>
<td>.444*</td>
</tr>
<tr>
<td>PETA Initiation</td>
<td>.657**</td>
<td>.626**</td>
</tr>
<tr>
<td>BRIEF metacognition</td>
<td>.856**</td>
<td>.655**</td>
</tr>
<tr>
<td>PETA Completion</td>
<td>.765**</td>
<td>.651**</td>
</tr>
<tr>
<td>BRIEF-Plan/organise</td>
<td>.213</td>
<td>.320</td>
</tr>
</tbody>
</table>

**P<.005; *P<.05

6.3.3.2 Statistical Analyses
Potential differences between those who were receiving treatment in the form of blood transfusions and hydroxyurea, and those who had indicators of OSA (section 2.4.8, Table 2.7) were investigated. There was no significant group difference in executive composite scores for children who were on regular blood transfusion or receiving hydroxyurea treatment, although there was a trend for better goal setting in the children who were on transfusion (n=5).
There was also a potential trend for improved cognitive flexibility in children on hydroxyurea; however only two children were receiving hydroxyurea at the time of the study.

Bivariate correlational analysis was used to determine what variables were to be excluded in the regression analyses. As several tests were carried out, a Bonferroni correction was applied to any estimated p-values to reduce the potential for a Type I error. I tested for normality of the distribution of each of the four executive domains and the general EF score, by plotting data as histogram. I then carried out a series of hierarchical regression analyses with each of these variables as the dependent outcome. Factors were entered into the model based on the amount of focus they have received in the sickle cell literature (King et al., 2014).

Age (Step 1) was entered into the model first as EF improves dramatically in the three to five year age range. Disease variables (CBFV, max CBFV, SpO2, haemoglobin, number of hospital admissions; Step 2) were then entered, as they have been traditionally associated with executive outcomes in the wider literature, followed by environmental variables (maternal education, SES category; Step 3), followed by the FES composite score (Step 4) and sleep composite score (Step 5), as it was hypothesised that these factors would contribute to the model over and above age and disease status (figure 6.2). Haemoglobin was eventually removed as an independent variable from the model due to multicollinearity with the FES score in Step 4 and the sleep composite variable in Step 5 (figure 6.2). Multicollinearity between haemoglobin and sleep scores has previously been reported for older children with SCD (Hankins et al., 2014). The variable of number of hospital admissions in the previous year was also removed due to multicollinearity with SES level in Step 3 and the sleep composite variable in Step 5. CO₂ was removed due to multicollinearity with CBFV in Step 2. Reported pain was removed, as a lot of the three year olds did not understand the task as administered using the Pain Scale. FSIQ was not included as predictor in
regression analyses as it did not correlate with executive variables and it was not a factor of interest. Given these considerations, the final regression model had five levels. Post hoc analyses were conducted to further explore significant predictors of EF. Effect sizes were also reported. A regression coefficient greater than 0.8 was interpreted as large, <0.8 and >0.5 as moderate, and minimum value accepted to represent a possible association as .2, and a large $R^2$ was interpreted as .64, moderate as .25, and minimum acceptable value for an association as .04 (Ferguson, 2009).

![Graph A](image1.png)

![Graph B](image2.png)

$r=.532$, $p=.011$

$r=.496$, $p=.019$

**Figure 6.2.** Associations between sleep composite score and (a) haemoglobin levels (b) number of hospital admissions in previous year

### 6.3.4 Results

#### 6.3.4.1 Patient Characteristics and Missing Data

Twenty-two patients were recruited and assessed. Group means for variables of interest are displayed in Table 6.2. One parent did not complete the FES
questionnaire, and so the FES score mean is based on 21 data points. CO₂
data points were unavailable for two patients due to non-administration on day
of testing as a result of time restrictions and a blocked nasal airway. The
previous chapter (Chapter 5) shows poorer performance on individual EF
tasks and subtests in the current patient population in comparison with a
matched control group, while Chapter 4 shows that the same families with
SCA reported a less positive family environment and a higher incidence of
sleep problems than the matched comparison group.

Table 6.2. Summary of Patient Characteristics and Neuropsychological
Functioning

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4.8</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>98.6</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFV</td>
<td>157.1</td>
<td>26.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2</td>
<td>97.1</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>8.9</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-tidal pCO₂</td>
<td>37.2</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. hospital admissions in</td>
<td>1</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the previous year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SES* (based on postcode)</td>
<td>3.1</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FES score</td>
<td>114.4</td>
<td>25.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep score</td>
<td>21.4</td>
<td>11.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>54.0</td>
<td>13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETA TS</td>
<td>62.3</td>
<td>46.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SES Scale = 1 (lowest) to 5 (highest)

6.3.4.2 Relations between variables of interest and general executive
functioning
Results of bivariate correlation analyses between predictors and outcome variables are presented in Table 6.3. Chi-square analyses showed that the categorical variables, maternal education (mothers had at least some college education; n=12) and single parent status (n=14), had no significant influence on EF.

Table 6.3. Inter-correlations between disease-related and socio-environmental factors with executive composite scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>General EF</th>
<th>Attention Control</th>
<th>Information Processing</th>
<th>Cognitive Flexibility</th>
<th>Goal Setting</th>
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<tbody>
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<td>CBFV</td>
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<td>.108</td>
<td>.103</td>
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<td>SpO2</td>
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<td>.057</td>
<td>.306</td>
<td>-.110</td>
<td>-.016</td>
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<td>.187</td>
<td>-.099</td>
<td>.078</td>
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<tr>
<td>Co²</td>
<td>-.112</td>
<td>.039</td>
<td>.101</td>
<td>-.317</td>
<td>-.261</td>
</tr>
<tr>
<td>Admissions</td>
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<td>-.091</td>
<td>.281</td>
<td>.292</td>
</tr>
<tr>
<td>SES</td>
<td>-.230</td>
<td>-.169</td>
<td>-.085</td>
<td>-.149</td>
<td>-.269</td>
</tr>
<tr>
<td>FES score</td>
<td>-.460*</td>
<td>-.574**</td>
<td>-.274</td>
<td>-.504*</td>
<td>-.241</td>
</tr>
<tr>
<td>Sleep score</td>
<td>.295</td>
<td>.327</td>
<td>.012</td>
<td>.396^</td>
<td>.284</td>
</tr>
</tbody>
</table>

**p<.01  *p<.05  ^p=.06 (near significant); Admissions= number of hospital admission in the previous year; SES= indicated by postcode
6.3.4.3 Predictors of General Executive Functioning

The hierarchical regression model significantly accounted for variability in outcomes at stage one \( (F_{1,19} = 6.1, p = .024, R^2 = .252) \). Introducing the medical and environmental variables in stage two and three did not substantially alter the \( R^2 \) value; however adding the family functioning variable in stage three explained an additional 18.2% of the variation in EF, and this change in \( R^2 \) was significant \( (F_{6,19} = 3.8, p = .022, R^2 = .634) \). Finally, the addition of the sleep composite score to the regression model did not contribute a significant difference to \( R^2 \) change but the model remained significant \( (F_{7,19} = 3.5, p = .027, R^2 = .673) \). When all variables were included in the model, it was found that a more positive family environment was the strongest predictor of better general EF in this young cohort. Taken together, the variables accounted for 67.3% of the variance in EF. Regression statistics are summarised in Table 6.4.
Table 6.4 Summary of stepwise regression analysis for variables predicting general executive functioning

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*p<.05
6.3.4.4 Predictors of Cognitive Flexibility

The hierarchical multiple regression showed that age did not significantly account for variation in outcome at stage one. At Stage one and two neither the medical nor environmental variables independently accounted for variation in outcomes. The addition of the family functioning variable in stage four significantly contributed to the model, with a significant $R^2$ change of 20% ($F_{1,13} = 3.2, p=.04, R^2 = .60$). The addition of the sleep composite score in stage five did not contribute a significant difference to $R^2$ change but the model remained significant ($F_{1,12} = 3.4, p=.03, R^2 = .67$). When all variables were included in the model, it was found that a more positive family environment was a significant predictor of better cognitive flexibility with lower CBVF showing a near significant contribution (see Table 6.5).
**Table 6.5** Summary of stepwise regression analysis for variables predicting cognitive flexibility

<table>
<thead>
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<th>p-value</th>
<th>R²</th>
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</table>
6.3.4.5 Predictors of Goal Setting

The hierarchical regression model was significant at stage one \( (F_{1,18} = 10.3, \ p=.005, \ R^2 = .365) \). Introducing the medical, environmental, and family variables did not show a significant \( R^2 \) change, however adding the sleep variable in stage five explained an additional 10% of the variation in goal setting, and this change in \( R^2 \) was significant \( (F_{1,12} = 3.2, \ p=.038, \ R^2 = .649) \). In the final model, it was observed that older age and a lower indication of sleep problems were significant and near significant predictors of better goal setting, respectively (Table 6.6).
Table 6.6 Summary of stepwise regression analysis for variables predicting goal setting

<table>
<thead>
<tr>
<th>Variable</th>
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<th>p-value</th>
<th>R²</th>
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</table>
6.3.4.6 Predictors of Attentional Control

The hierarchical multiple regression showed that age did not contribute significantly to the model at stage one. Stage one and stage two showed that neither the medical nor environmental variables contributed to the model. The addition of the family functioning variable in stage four significantly contributed to the model, with significant $R^2$ change of 45.6% ($F_{1,13} = 7.9$, $p<.001$, $R^2 = .785$). The addition of the sleep composite score in stage 5 did not contribute a significant difference to $R^2$ change but the model remained significant ($F_{1,12} = 6.7$, $p=.002$, $R^2 = .796$). When all variables were included in the model, it was found that a more positive family environment and higher SES were significant predictors of better attentional control (Table 6.7).
Table 6.7 Summary of stepwise regression analysis for variables predicting attentional control

<table>
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6.3.4.7 Predictors of Information Processing

Table 7.8 shows the results of the hierarchical regression for information processing. No factors independently contributed to the outcome variable and no steps contributed to a significant change in variability. Together, all of the variables accounted for 33% of the variance of information processing.
Table 6.8 Summary of stepwise regression analysis for variables predicting information processing

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<td>SpO2</td>
<td>.378</td>
<td>.173</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Load 1</td>
<td>Load 2</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>-.157</td>
<td>.584</td>
<td></td>
</tr>
<tr>
<td>Maternal Education</td>
<td>.028</td>
<td>.922</td>
<td></td>
</tr>
<tr>
<td>FES</td>
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<td>.578</td>
<td></td>
</tr>
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<td>Step 5</td>
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<td></td>
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<td>SpO2</td>
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<td>.206</td>
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<tr>
<td>FES</td>
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</tr>
<tr>
<td>Sleep</td>
<td>-.066</td>
<td>.855</td>
<td></td>
</tr>
</tbody>
</table>
6.3.4.8 Exploring Family Functioning Further

As overall family functioning was a relatively strong predictor of EF, an exploratory stepwise linear regression was employed to look at what factors of family functioning contributed most to the outcome variable of EF. Bivariate correlations between EF and the individual subdomains of the FES are displayed in Table 6.9. The regression model revealed that achievement (β=.616) and independence (β=.418) were most predictive of general EF ($F_{2,20} = 15.5$, $p<.001$, $R^2 = .632$). None of the domains independently predicted cognitive flexibility ($F_{10,20} = 1.339$, $p=.326$, $R^2 = .573$) although there was a non-significant trend for an effect of conflict (β=.551, $p=.058$). A focus on more active-recreational activities (β=-.584) and reduced conflict (β=.359) predicted greater attention control ($F_{2,20} = 8.694$, $p=.002$, $R^2 = .491$). Although total FES score did not independently contribute to goal setting and information processing, stepwise regression analyses was also used to investigate individual family factors. Goal setting ($F_{2,20} = 17.457$, $p<.001$, $R^2 = .661$) was predicted by achievement orientation (β=.662) and independence (β=.381) whilst independence (β=.463) was the only independent predictor of information processing ($F_{1,20} = 5.187$, $p=.035$, $R^2 = .214$).
Table 6.9 Bivariate correlations between FES and executive composite scores

<table>
<thead>
<tr>
<th></th>
<th>Cohesion</th>
<th>Expression</th>
<th>Conflict</th>
<th>Independence</th>
<th>Achievement</th>
<th>Intellectual/Cultural</th>
<th>Active/Recreational</th>
<th>Moral</th>
<th>Organisation</th>
<th>Control</th>
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<tr>
<td>General EF</td>
<td>-.049</td>
<td>-.206</td>
<td>.227</td>
<td>.511*</td>
<td>.679**</td>
<td>-.243</td>
<td>-.526*</td>
<td>.410</td>
<td>.089</td>
<td>.380</td>
</tr>
<tr>
<td>Attention Control</td>
<td>-.116</td>
<td>.389</td>
<td>.243</td>
<td>.506*</td>
<td>-.080</td>
<td>-.602**</td>
<td>.280</td>
<td>.280</td>
<td>-.177</td>
<td>.137</td>
</tr>
<tr>
<td>Information Processing</td>
<td>-.229</td>
<td>-.123</td>
<td>.009</td>
<td>.463*</td>
<td>.423^</td>
<td>-.214</td>
<td>-.272</td>
<td>.239</td>
<td>.117</td>
<td>.299</td>
</tr>
<tr>
<td>Cognitive Flexibility</td>
<td>-.157</td>
<td>-.247</td>
<td>.355</td>
<td>.308</td>
<td>.245</td>
<td>-.100</td>
<td>-.368</td>
<td>.390</td>
<td>.018</td>
<td>.301</td>
</tr>
<tr>
<td>Goal Setting</td>
<td>.212</td>
<td>-.198</td>
<td>.119</td>
<td>.482*</td>
<td>.720**</td>
<td>-.272</td>
<td>-.407</td>
<td>.396</td>
<td>.214</td>
<td>.405</td>
</tr>
</tbody>
</table>
6.3.5 Discussion

This study examined the influence of disease-related and psychosocial factors on the development of executive skills in preschool children with SCA. The neurocognitive development of children with SCA is subject to several risk factors even when there is no history of stroke. Previous studies have highlighted the role of disease factors such as chronic pain and school absences as well as the impact of poor parenting and lower SES on neurocognitive development (King et al., 2013, 2014; Schatz et al., 2004; Thompson et al., 2002; Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, Armstrong, et al., 2001). Findings from the current study revealed a strong relationship between family functioning and EF, except not information processing and goal setting.

Although these analyses reveal family functioning as an important variable in the development of EF, the influences of biomedical, socio-environmental, and sleep factors on specific aspects of EF are likely to be interrelated, and must be considered in future investigations (King et al., 2014). Different executive components may be impacted in different ways by disease-related and socio-environmental factors (Bradley & Corwyn, 2002). The varying influence of the predictor variables on the different EF composite scores suggests that EF is not a unitary construct, even in these early years, as Anderson’s model suggests. Anderson (2002) also hypothesise that the domain of attentional control becomes established earlier in development, laying a foundation for the other three interrelated domains to develop. This could potentially rationalize why a positive family environment was such a strong predictor for this domain, as these skills are more malleable at a stage when the child is in the family context the majority of their time, and may have cascading effects on the other domains of EF, as seen for cognitive flexibility and the general executive composite score.
Another important predictor for attentional control was SES, which could interact with family functioning in the context of executive development. Research has shown that low SES can have an impact on health and family relations over time (Matthews & Gallo, 2011) and this could have an even greater cumulative impact on children with SCA. Family environment may have more of an impact on the cognitive outcomes of children from lower SES families. Low SES environments, high rates of single parent families (as observed in our patient population) and reduced resources may cause parents to feel socially isolated and have an impact on family management, affecting parent-child relations (Wilson, 1991). One study looked at the effects of home environment and maternal intelligence for typically developing African-American preschool-age children and school-age children, noting that the effects of home environment on cognition was stronger in the younger children, potentially having less of an impact on older children who are spending more time outside the home environment (Luster & Dubow, 1992). Devine et al., (1998) did not find a significant influence of family functioning on IQ or adaptive behaviour in their study of older children (n=74, 9.75 years) with SCD; however they used different predictor and outcome variables, as well as combining children with different genotypes and including those with a history of stroke. They used a caregiver adjustment questionnaire as their family functioning variable, which arguably only looks at one domain of family environment in comparison to the family environment scale and, crucially, their cognitive battery did not contain any executive measures.

Although they did not reach significance, small effect sizes for relationships between CBFV and cognitive flexibility, and between sleep problems and goal setting were observed. Kral and Brown (2004) presented associations between CBFV and elements of EF including working memory and flexibility as reported by parents and teachers of school-age children with SCA (n=62). A relationship between CBFV and memory was also previously reported in children with SCA (Ruffieux et al., 2013), which could bear some relevance to the working memory component of cognitive flexibility. Poor sleep, and
specifically sleep disordered breathing, has been associated with poor planning and problem solving in the general paediatric population (O’Brien et al., 2004) with some preliminary evidence for problem solving in SCA being related to the severity of sleep-disordered breathing, in terms of overnight oxygen desaturation and arousals (Hollocks et al., 2012). Surprisingly, no effects were seen for maternal education or for daytime oxygen saturation in any of the domains. Maternal education was entered as a categorical variable as some parents reported starting college in their native country or participating in tertiary level courses that were not full undergraduate or postgraduate degrees. Maternal education could have been more informative as a variable if entered as total years of education, but this information was not collected. Oxygen saturation was collected on the day by the researcher and had a narrow range of values. A mean value collected over a number of occasions during daytime or nighttime could have been more representative but this was not feasible for the current study. Another unexpected finding was the lack of predictors for information processing that could potentially be explained better by variables not included in the study. Poor processing speed, more specifically, has been associated with the degree of white matter damage visible on MRI in older children (Armstrong et al., 1996; Van Der Land et al., 2014), which might remain relatively intact in this younger age group, although covert infarction has been reported in the first few years of life and is highly prevalent by school age (DeBaun et al., 2012). Imaging was not included in the current protocol but it may be feasible to examine white matter integrity in young unsedated children in future studies of prevention of progressive overt infarction (DeBaun & Kirkham, 2016).

### 6.3.5.1 Limitations

There are some limitations in the current study that should be considered in the interpretation of results and addressed in future research. This study lacked a matched control group with information on the medical variables, which prevented further examination of the differential contributions of disease and environmental factors to executive outcomes. It would be useful in future investigations to include typically developing children in order to investigate
more appropriately whether environmental factors differentially impact children with SCA. However, the lack of full data sets for a comparable group of matched children precluded the generation of representative domain scores. Another limitation of this study is the small patient population. The sample size warrants caution for the over-interpretation of the regression analyses due to the reduced power based upon the number of predictors included in the analyses (Cohen, 1992). However, the predictors were reduced in number where possible while still attempting to maintain a ‘totality’ approach by including the physical and psychosocial experiences that may influence EF development in this exploratory investigation (Anderson, Northam, & Wrennel, 2014). Measures were taken during the statistical analysis stage to reduce the impact of using multiple predictors in a small population size. Instead of a multiple linear regression, where all variables are entered at once, a multilevel regression was chosen to reduce the noise created by multiple predictors (Gelman & Hill, 2006). A stepwise regression, where order of entry does not matter, was not used. Instead, a theory-driven hierarchical regression model was adopted so that the entry of variables was based upon what is known from the existing literature. Additionally, effect sizes, ranging from moderate to large, revealing potentially meaningful effects that may be more robust in a larger population, are displayed in the accompanying tables for the independent predictors to assist in the interpretation of findings and in the guidance of the design of future studies with larger patient populations (Ferguson, 2009). The small sample size was due to strict inclusionary (e.g. HbSS only) and exclusionary criteria and a narrow age range. The study managed to recruit a population that represented approximately a quarter of the patient population diagnosed with HbSS in this age range in East London. The recruited cohort likely represented more than the current conservative estimation of eligible patients. Information on additional diagnoses and history of stroke was not available for the children who did not participate (see section 2.3.2). Finally, the creation of executive composite scores also increased power and measurement precision in the analyses (Gibbons et al., 2012).
Another potential limitation is that the population recruited could have been biased such that families who were most likely to take part did not represent the families with the poorest SES or family functioning. However, the researcher made the study as accessible as possible to all eligible families by organising transport for families and working around schedules (i.e. most of the testing took place at the weekends) as well as recruiting through a clinician that the families trusted and who had a well-established rapport with them. Another limitation of the study was the lack of neuroimaging. However, the markers used represented the most widely used disease markers in the literature on SCD and EF. As well as the strict inclusionary criteria, a further strength of this study was the inclusion of age-appropriate executive measures with pre-schoolers with SCA for the first time.

6.3.5.2 Implications for future research and practice

Disease, family, and environmental factors cannot be easily disentangled in the determination of their impact on child development (Gustafson, Bonner, Hardy, & Thompson, 2006) as there are likely bidirectional and interactive relations between these factors. Models of mediation or moderation that could help further identify targets for future intervention could not be further explored in the current study due to the small population size. However, there is emerging evidence for the role in executive development of family functioning, which has even been reported as a mediator for SES and other external factors (Sarsour et al., 2011). Children with SCA may be specifically vulnerable to stressful home environments due to the effects of their chronic disease (Brown, Kaslow, et al., 1993; R. J. Thompson et al., 2002) and family functioning may mediate any impact of SES and disease severity on cognitive development (Sarsour et al., 2011). Poor SES has even been associated with a higher incidence of paediatric obstructive sleep apnoea (Spilsbury et al., 2006). However, as family functioning is reported as a mediator for poor SES
(Sarsour et al., 2011), there is a potential for the development of psychosocial interventions with the goal of promoting cognitive and behavioural development (Thompson, Armstrong et al., 1999).

Early screening for neuropsychological deficits, particularly EF deficits, has been championed in the sickle cell literature (Daly et al., 2011). However, it is still not an established routine for preschool children with SCA to undergo neuropsychological assessment, despite preschool children having a high risk of first stroke occurrence (Armstrong et al., 1996; DeBaun et al., 2012) and a greater executive burden due to the adaptive requirements of their disorder (Tarazi et al., 2007). A targeted family-focused intervention in the early years for families of children with SCA may have a positive impact on early executive development. Children who have SCA may even be more susceptible to the effects of family factors. Previous research has shown family function to be associated with rates of behavioural problems in children with SCA, but not in their typically developing siblings (Brown, Buchanan, et al., 1993; Thompson et al., 1999). Previous research has found that parents of adolescent patients tend to report more negative home environments than preschool age children, a decline in family functioning that could be addressed through family intervention (Barakat et al., 2007). However, given the possible bi-directionality of the association of family function and EF deficits in children, the next step is to undertake experimental research to confirm the role of family functioning in the development of EF skills through intervention studies that focus on specific family factors such as those identified in the current study.

Family intervention programs are costly to implement, both in terms of funding and time, but could have huge long-term benefits if effectively delivered, both for the child and their parents, as well as alleviating longer-term pressure on health and education services. Daniel and colleagues recently implemented the first family-based intervention in families of school age children with SCD that aimed to improve academic performance over a six-month period (Daniel
et al., 2015). However, they did not find any significant improvements over time, which can partly be attributed to the poor power due to a high rate of attrition. Nevertheless, they still conclude that with the right intervention, a focus on family functioning for children with SCA is a worthwhile avenue for the future.

6.3.5.3 Conclusions
In recent years, researchers in SCA have shifted their attention to a more biopsychosocial model of child development (Gustafson et al., 2006; King et al., 2014). In the current study, I looked at predictors of EF in preschool age children with SCA for the first time and found that positive family functioning was associated with better executive performance in preschool children with SCA, with some evidence for an additional role of SES in attention control. There was a lack of evidence for associations between disease factors and EF. Overall, the results of this study could inform the identification of children with SCA who are most at risk of developing executive difficulties, laying a foundation for future focus on earlier assessment and intervention for EF deficits in SCA.
Chapter 7: Neurophysiological correlates

A neurophysiological investigation of selective auditory attention, an early emerging and foundational executive skill, in preschool children with sickle cell disease
7 Neurophysiological correlates

7.1 Introduction

“Everyone knows what attention is…It is the taking possession by the mind, in clear and vivid form, one of out of what seems several simultaneously possible objects or trains of thought…It implies withdrawal from some things in order to deal effectively with others.”

-William James (1890)

Selective attention is the ability to enhance the processing of relevant stimuli, while suppressing the processing of irrelevant or distracting stimuli (Desimone & Duncan, 1995; Hillyard, Hink, Schwent, & Picton, 1973). The ability to selectively attend and the neural systems that underlie this process, including the anterior cingulate and the prefrontal areas, undergo significant development in the preschool years (Rueda, Posner, & Rothbart, 2004; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005). Accumulating evidence from the past sixty years suggests that these systems are not fully developed until adolescence (Casey, Giedd, & Thomas, 2000). In adults, the selective attention phenomenon described as the ‘Cocktail Party Effect,’ is well recognised. In fact, the ability to differentially process relevant and irrelevant information is present from very early on and is thought to be one of the earlier emerging executive skills that influences the future development of other executive domains (Anderson, 2002; MacCoon, Wallace, & Newman, 2004; Stuss, 1992).

An efficient attentional process means that the relevant information is attended to and can then be applied in the process of learning (Bhatt & Quinn, 2011; Goldstone, Son, & Byrge, 2011). This process is particularly important
in the first few years of life during language acquisition and as a child begins to develop their schema in order to understand the world around them. As well as laying down a foundation for later emerging executive skills, selective attention has also been shown to play a role in other cognitive domains such as language, writing, and mathematics (Engle & Kane, 2004; Stevens & Bavelier, 2012). Selective attention has been described as an important predictor of school readiness and academic achievement (Duncan et al., 2007; Rueda, Checa, & Rothbart, 2010).

### 7.1.1 The development of neurophysiological correlates of selective auditory attention

Hillyard and colleagues first identified the ERP index of selective auditory attention in adults (Hillyard et al., 1973). Adults typically show an early positivity (P1) followed by a negative component (N1) at about 100 milliseconds (ms). This has been demonstrated in many different ways in the intervening years (Nager, Estorf, & Münte, 2006). The underlying neurophysiological components of selective attention in the context of noisy, ecologically valid environments are well studied in adults (Hopfinger, Luck, & Hillyard, 2004) but in the past decade there has been a greater focus on how this process develops from early childhood. It has been posited that the ability to selectively attend to stimuli is present from early in life but that the speed and efficiency of these processes increase with age (Ridderinkhof & van der Stelt, 2000).

In more recent years, research with young children has shown a difference in the morphology of the ERP in the context of selective auditory attention. Instead of the P1-N1-P2 response typically seen in adults, children tend to show an elongated broad positivity that starts at approximately 100 ms (Sharma, Kraus, McGee, & Nicol, 1997). Table 7.1 shows a summary of studies that have investigated the EFP in children and figure 7.1 shows difference in ERP morphology with increasing age. It has been speculated that the positivity in developmental populations may be the opposite
polarity of the N1 response observed in adults (Albrecht, Suchodoletz, & Uwer, 2000), while others have argued that this response shows evidence for an absence of the N1 in children (Ponton, Eggermont, Kwong, & Don, 2000). Coch and colleagues contend that the absence of the N1 response in children may be due to saturated auditory environments, or paradigms that have competing sources or auditory demands, similar to real life situations (Coch et al., 2005).
Figure 7.1 (A) Karns et al., (2015) show the developmental transition from the EFP to the adult P1-N1-P2 response and (B) Sanders et al., (2006) show the attention effect differences between preschool children and adults.

This positive developmental peak has since been described as the early frontal positivity (EFP)(Lackner et al., 2013). ERP research has shown that
children as young as three years can selective attend to one auditory source while ignoring another (Sanders et al., 2006; Sanders & Zobel, 2012). Preschool children (3-5 years) have been shown to produce a broad positivity from 100-300ms while 6-8 year olds show a shorter positivity from 100-200 ms. The extended attention effect in younger children could reflect a prolonged effect of attention on neural processing and/or the variability between and within children in the latency of the effect (Stevens & Bavelier, 2012).

Karns, Giuliano, & Neville (2015) recently investigated how the neural processes of selective attention, in the context of noisy, ecologically valid, environments, transitions from the EFP of preschool to the adult response and found that the P1-N1 complex emerges in early adolescence (Karns, Isbell, Giuliano, & Neville, 2015). Initial evidence of the earlier P1 can be observed from 10 years of age but is not present in younger children (Karn et al., 2015; fig 8.1. B). The P1-N1 complex has a protracted developmental time course (Ponton et al., 2000) and these changes in functional development likely parallel the slow development of the fronto-parietal network (Yurgelun-Todd, 2007). Karns et al., (2015) postulated that these changes reflect a range of brain development processes including synaptic proliferation, pruning and physical alterations to the underlying anatomy, which likely affect the dipole orientation of the neural response, as well as myelination affecting processing speed. Further complex processes, such as changes in oscillation frequency and cortical response variability, need to be considered as well (Segalowitz, Santesso, & Jetha, 2010; Strait et al., 2014). In a visual selective attention task using functional MRI, Casey and colleagues found that children showed a greater pattern of pre-frontal brain activity in a go-nogo paradigm when compared with adults, potentially indicating that children recruited more brain tissue to perform the same task (Casey et al., 1997).
7.1.2 The development of the neurophysiological correlates of selective attention in the context of developmental disorders

One study found that preschool children with specific language impairment (SLI, n=12) showed deficits in selective attention when the early frontal positivity was compared with typically developing (TD) children (n=12) on an ecologically valid dichotic listening task, despite no group differences in behaviour (Stevens et al., 2006). Specifically, they found no evidence of sensorineural modulation with attention in the children with SLI who processed both the attended and unattended streams in the same way, leading the authors to suggest that the children with SLI had a filtering deficit in attentional processing, rather than distractor suppression. Gomes and colleagues looked at auditory selective attention in school age children with (n=15) and without (n=15) attention deficit hyperactive disorder (ADHD) on a dichotic listening task that involved responding to presented sounds (Gomes et al., 2012). Children with ADHD showed poorer target detection and on inspection of individual datasets, they showed an absent or inconsistent difference waveform response. A similar pattern has emerged for the development of visual attention in ADHD, where one study showed that there was also an absence of the EFP in a visual selective attention task in a group of school age children with ADHD when compared to TD children (Jonkman, Kenemans, Kemner, Verbaten, & Van Engeland, 2004). The authors hypothesized that the absence of the early visual EFP may be due to an early filtering deficit. In another auditory selective attention ERP study using an auditory oddball paradigm with preschool children born preterm, Hövel and colleagues found that better cognitive task performance and a higher gestational age were associated with shorter P1 latencies and more positive P1 mean amplitudes (Hövel et al., 2014).
7.1.3 Relationship between the EFP and psycho-socio-environmental factors

Children with low socio-economic status show reduced selective attention in neural processing specifically related to a reduced ability to filter irrelevant information (Stevens et al., 2009; Stevens, Paulsen, Yaseen, & Neville, 2015). Stevens et al., (2009) found that maternal education was predictive of distractor suppression in 3-8 year olds (n=32). Recent research has speculated about the potential role of family functioning in the development of the early frontal positivity (Isbell, Wray, & Neville, 2015). Neville and her team found that an intervention that combined attention training for children with training for parents was more effective in changing in the underlying neurophysiological attention effect than attention training only(Neville et al., 2013). This is a particularly interesting avenue for research given that family environment is hypothesized to moderate the effects of SES on cognitive development and was found to be an important predictor of EF in Chapter 7. However, the effects of family factors on the development of neurophysiological markers of EF remain to be investigated.

7.1.4 Relationship between the early frontal positivity and cognition

Attention has previously been described as an important element in the acquisition of non-verbal abilities. Isbell et al., (2015) found that larger positive attention effects in their cohort of preschool children (n=124) were related to non-verbal IQ as measured by the Stanford Binet test. Additionally, associations between the EFP and other measures of EF have corroborated its role in early executive attention. One study showed a significant relation between higher mean EFP amplitudes in the unattended condition and poorer parent ratings on the BRIEF in school age children (Lackner et al., 2013). In a similar paradigm in adults, a greater P1 amplitude was associated with better visual working memory capacity (Giuliano, Karrns, Neville, & Hillyard, 2014).
These findings were replicated with children in a similar study where individual differences in the ERP markers of attentional control were linked to visual short term memory capacity in a group of 10-year-old children (Shimi, Kuo, Astle, Nobre, & Scerif, 2014). Children with more adult-like neural responses had greater visual memory capacity. So far, there has been no attempt to look at associations between the EFP and behavioural tasks of selective attention, despite the EFP being described as a neurophysiological marker of this specific executive component.
<table>
<thead>
<tr>
<th>Paper/Year</th>
<th>Population</th>
<th>No. of Electrodes</th>
<th>Time-windows explored</th>
<th>Minimum events</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isbell et al., (2015)</td>
<td>TD low SES 40-67 months (n=124)</td>
<td>32</td>
<td>100-200</td>
<td>75</td>
<td>More robust attention effect associated with better non-verbal functioning</td>
</tr>
<tr>
<td>Karns et al., (2015)</td>
<td>TD 3-5 (n=20), 10 (n=19), 13 (n=19), 16 year olds (n=18) and adults (n=20)</td>
<td>24</td>
<td>-</td>
<td>none</td>
<td>Gradual transition of early frontal positivity to P1-N1 complex in adolescence</td>
</tr>
<tr>
<td>Strait et al., (2014)</td>
<td>TD 3-5 years (n=24) 7-13 years (n=28) 18-35 years (n=22)</td>
<td>16 (for children) 30 (for adults)</td>
<td>90-130ms (preschool)  only</td>
<td>180 total (for preschool)</td>
<td>Preschool children have equivalent cortical response variability to attended/unattended conditions whereas older children/adults have less variability in response to attended conditions</td>
</tr>
<tr>
<td>Study</td>
<td>Group Details</td>
<td>ERP Time Window</td>
<td>ERP Amplitude</td>
<td>ERP Profile</td>
<td>Findings</td>
</tr>
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<td>-------</td>
<td>---------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Lackner et al., (2013)</td>
<td>TD 12-14 years (n=48)</td>
<td>121</td>
<td>65-160</td>
<td>75</td>
<td>A larger ERP in unattended condition was associated with poorer executive function</td>
</tr>
<tr>
<td>Stevens, Lauinger, &amp; Neville (2009)</td>
<td>3-8 year olds from low and high SES families (n=32)</td>
<td>29</td>
<td>100-200</td>
<td>78</td>
<td>Both the higher and the lower maternal education preschoolers showed a single, broad positivity peaking around 150 ms. Low SES children had a reduced ability to filter irrelevant information (i.e. to suppress the response to sounds in the unattended channel).</td>
</tr>
<tr>
<td>Sanders, Stevens, Coch, &amp; Neville (2006)</td>
<td>TD 3-8 years (n=43)</td>
<td>29</td>
<td>100–200 ms, 200–300 ms, and 300–450 ms</td>
<td>40</td>
<td>Broad positivity between 100 and 200ms, amplitude of this positivity was larger at anterior and medial sites between 100 and 200. Positive attention effect over anterior regions continued into 200–300 ms time window. Evidence positive attention effect over anterior regions remained in the 300–450ms epoch.</td>
</tr>
<tr>
<td>Stevens, Sanders, &amp; Neville (2006)</td>
<td>3.6-8.8 year old children with and</td>
<td>29</td>
<td>100–200 ms</td>
<td>49</td>
<td>TD children showed a larger positivity to probes in the attended channel, children</td>
</tr>
</tbody>
</table>
without specific language impairment with SLI showed no evidence of attentional modulation during this time window. The SLI group showed a smaller response to attended stimuli, independent samples. This suggests that the SLI deficit in selective attention was associated specifically with deficits in signal enhancement, as opposed to distractor suppression. Individual amplitude variability.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range</th>
<th>Sample Size</th>
<th>Age</th>
<th>Latency</th>
<th>Morphology</th>
<th>Topography</th>
<th>Description</th>
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<tr>
<td>Coch, Sanders, &amp; Neville, 2005</td>
<td>6-8 years olds</td>
<td>n=22</td>
<td>29</td>
<td>100-250</td>
<td></td>
<td></td>
<td>Morphologically dissimilar ERP and different topography adults. Both groups showed attention effects by 100ms.</td>
</tr>
<tr>
<td></td>
<td>adults (n=22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ponton, Eggermont, Kwong, &amp; Don, 2000</td>
<td>5-20 years</td>
<td>n=118</td>
<td>30</td>
<td></td>
<td>30 (no unattended condition)</td>
<td></td>
<td>Age-related latency decreases and abrupt changes in P1 amplitude age 10 differ by scalp location.</td>
</tr>
<tr>
<td>Sharma, Kraus, McGee, &amp; Nicol, 2000</td>
<td>6-15 years (n=86)</td>
<td>Fz electrode</td>
<td>50-150</td>
<td></td>
<td></td>
<td></td>
<td>Child’s response characterised by broad P1 at 100ms that reduces in latency and</td>
</tr>
<tr>
<td>Year</td>
<td>Description</td>
<td>Amplitude up to 20 years.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>(single channel, no unattended condition)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ms = milliseconds
7.1.5 Neuroimaging and Neuropsychological studies of children with SCD

SCD results in a global pattern of diffuse brain injury, thought in part to be secondary to chronic anaemia and hypoxia (Baldeweg et al., 2006; Kawadler et al., 2013; Steen, Emudianughe, et al., 2005). These subtle differences observed in imaging studies are noted even in the absence of any evidence of silent infarction. The frontal lobes have a protracted period of development in comparison to other brain regions and are thought to be the regions most susceptible to pathology in SCD (Brown et al., 2000; Watkins et al., 1998). They are known to play a prominent role in the brain network underlying executive skills, the cognitive area most affected in children with SCD (Hogan, Telfer, Kirkham, & de Haan, 2013; Watkins et al., 1998). Neurocognitive deficits have been reported to appear early in development and impact school readiness, and with the appropriate measures these deficits are detectable in the early years (Hogan et al., 2013; Noll et al., 2001; Steen et al., 2002; Tarazi et al., 2007; Thompson et al., 2002).

Older children and adult patients with SCD with no evidence of MRI pathology are still at risk for executive deficits (Schatz, Finke, et al., 2002; W. Wang, Enos, Gallagher, Thompson, Guarini, Vichinsky, Wright, Zimmerman, & Armstrong, 2001). This may be a result of chronic anaemia and hypoxaemia causing neurocognitive impairment secondary to cerebral injury that is undetectable by standard magnetic resonance imaging studies (Vichinsky et al., 2010). Amongst other executive deficits, Vichinsky et al., (2010) found specific selective attention deficits on the Map Search and Telephone Search selective attention tasks of the Test of Everyday Attention (Ridgeway, Robertson, Ward, & Nimmo–Smith, 1994) in a sample of adults with SCA (N=160) as compared to matched controls (N=57), despite no evidence of MRI pathology.

Neuroimaging techniques such as transcranial Doppler, diffusion tensor imaging, and magnetic resonance imaging are useful tools in the
determination of disease-related alterations in the brain structure but tell us little about differences in brain function (Bernaudin et al., 2000). There is an abundance of behavioural evidence in older children and adults for specific executive deficits in SCD (see Chapter 1). However, the use of ERP and other EEG techniques offer another window into potential differences in executive skills on a neuronal level. Functional MRI is difficult to apply in young children, and to the author’s knowledge, has never been applied in older children with SCD to explore executive deficits. ERP measures, however, have recently been used in two studies with older children with SCD. Although it has not been previously applied in younger children in this patient population, ERP methodology offers an appropriate tool for use in preschool aged children with SCD.

To the author’s knowledge, only two published studies have previously used ERPs to look at EF in older children with SCD (Colombatti et al., 2015; Hogan, Vargha-Khadem, et al., 2006). Hogan et al., (2006) looked at ERP components related to performance monitoring in children between the ages of 11 and 23 with SCD with (n=11) and without (n=11) evidence of silent lesions and found that children with SCD showed some electrophysiological evidence for executive deficits in comparison to controls (n=11) even in the absence of stroke (figure 7.3). They also administered a battery of executive tasks where both the sickle cell groups showed significantly poorer scores on a number of tasks, including selective attention. Colombatti et al., (2015) investigated the P300 using an auditory oddball paradigm in 12 children with SCD (ages 6 to 15 years) and found that two patients did not evidence the P300 response and that the response was more protracted in the frontal areas and more variable than the typically developing children, with differences in the cortical sources (figure 7.2). Beyond the mentioned studies, there have been no published investigations into the development of neurophysiological indices of cognitive functioning in children with SCD, despite the well-established literature illustrating cognitive deficits using neuropsychological assessment in older children. Specifically, there has been no investigation of EF on a behavioural level or a neurophysiological level in
preschool-age children with SCD. As a result, there is currently no available information on when and how the executive deficits observed in school age children emerge or whether they can be prevented or ameliorated. The previous two chapters (Chapter 5 and Chapter 6) have delineated the emerging pattern of executive deficits on a behavioural level in preschool children with SCD; however it is still unknown whether these differences are detectable on a neural level. This is important to know because ERPs more directly reflect the activity of the underlying cortex in response to the specific EF skill under measurement and allow for the detection of precise differences in processing. ERPs also have high temporal resolution, are not prone to examiner bias, and offer the opportunity to conduct a more robust investigation of EF using a multi-level methodology (Astle & Scerif, 2009).
Figure 7.2 Low resolution brain electromagnetic tomography shows variable responses and prolonged activation of frontal cortex in children with SCD. Children with SCD divided into those with more typical (red) and poorer (green) P300 response. Image reproduced from Colombatti et al. (2015).
Figure 7.3 ERP differences between SCD patients with frontal stroke (SCD-FL), SCD patients without stroke (SCD-C), and controls on the 2-choice response task (CRT) and the 4-CRT. A reduction of the correct-response negativity (CRN) and error-related negativity (ERN) difference was due to a significant reduction of the ERN in the SCD-FL group. Dashed lines represent ERP to correct trials and solid line represents error trials. Image reproduced from Hogan et al. (2006).
7.1.6 The Present Study

The current study extends the work of the ERP studies described in the previous sections of this chapter by investigating the neurophysiological indices of EF in preschool children with SCD in comparison to a group of typically developing (TD) children. This study will focus on an ERP component related to attention control, a skill that involves the prefrontal cortex and the anterior cingulate cortex, as this domain is thought to both develop at a faster rate and to influence the development of other executive domains, including performance monitoring (Anderson, 2002). The current paradigm was chosen as it has been previously applied to elicit well characterised neural indices of attention control in this age range with typically developing preschool children (Sanders, Stevens, Coch, & Neville, 2006), other patient populations (e.g. Stevens, Sanders, & Neville, 2006) and in relation to behavioural measures of EF (Lackner et al., 2013). Based on (a) the performance of the current patient group on behavioural executive tasks in Chapter 6 (b) previous behavioural reports of EF and selective attention (Tarazi et al., 2007; Vichinsky et al., 2010), and (c) the two previously published ERP studies in SCD (Colombatti et al., 2015; Hogan et al., 2006), it is predicted that the SCD group will show deficits in the selective attention task. Similar to a cohort of children with SLI (Stevens et al., 2006), it is hypothesized that the children with SCD will show evidence for poor sensorineural modulation with attention.

7.2 Aims

The aim of this chapter is to explore potential differences in the neurophysiological underpinnings of selective auditory attention in preschool children with SCD. It is hypothesized that the children with SCD will show diminished neural modulation with attention. Given that the ERP response elicited in this task is an internal and measurable aspect of cognitive control (Anokhin, Heath, & Myers, 2004; Van Beijsterveldt & Van Baal, 2002), a second aim, is to look at associations between neural modulation and behavioural tasks. It is hypothesized that, based upon previous research (e.g.
Isbell et al., 2015), that the children with the poorest executive scores on the neuropsychological assessments will show less pronounced and more variable responses and less differentiation between the attended and unattended conditions. Finally, based on the findings of Chapter 6 and previous research it is hypothesised that markers of disease severity will not be predictive of the neurophysiological response in children with SCD (due to their stable clinical state and lack of infarct), and that poorer socio-economic status (SES) and less positive family functioning will be associated with less pronounced and more variable ERP responses.

7.3 Method

7.3.1 Procedure

7.3.1.1 ERP methodology

7.3.1.1.1 Stimulus design and presentation

Fifteen short stories from Aesop’s classical fables (www.librivox.org) were edited to make the language and content more age-appropriate and were re-recorded in a male and female voice. The sound recordings were edited using Audacity (http://audacity.sourceforge.net) to remove gaps longer than 100 ms and to compress the files in order to make them comparable in terms of loudness. During the recording sessions, the narrators were instructed to keep their tone and pitch at a consistent level throughout each story. These steps were taken to ensure that some stories were not more appealing than others and so that they only differed in timbre. Each story was up to one minute in duration. Pure tone burst of white noise with a length of 500ms were randomly inserted into the attended and unattended streams and were the same loudness as the story being attended. The inter-stimulus-interval was 1.5 seconds to ensure no overlap between trials. Images on the screen corresponded with the story that the child was instructed to listen to with an arrow that pointed in the direction of the channel that they should have been
tuning into. Custom images were generated using a drawing application to match each story.

Stimuli were presented through age-appropriate adjustable headphones. Tests showed that the headphones did not induce electrical artefacts above background noise. The auditory and visual task stimuli were presented using a script programmed via Matlab 2012 R2012b (The MathWorks, MA) using Psychtoolbox V3 (Kleiner et al., 2007). Stimuli were presented on a Dell Optiplex (Dell Inc., TX) computer screen running Windows XP. Auditory stimuli were transmitted via a Creative Sound Blaster Express sound card with a low latency driver. The offset latency for auditory stimuli was measured to be 23ms on average using an EGI latency-testing device.

7.3.1.1.2 Recording and Set-up
Data was obtained and recorded using NetStation V4.1.2 (Electrical Geodesics Inc., OR) on Mac OS 10.3.9 software. A NetAmps 200 amplifier and HydroCel Geodesic Sensor Nets were used (Electrical Geodesics Inc., OR). These sensor nets provide advantages over alternative sensor net models, as they do not require washing the child’s hair afterwards or scalp abrasion so the process is less invasive and they are quicker to apply (Johnson et al., 2001). EEG was recorded from 128 electrodes and digitized at 250 Hz with a bandwidth of 0.1-100 Hz. A ground electrode was in place and the vertex electrode (Cz) was used as an online reference (data were later re-referenced offline using an average reference). Channel impedances were adjusted where necessary and appropriate to levels below 50kΩ. In young children, a balance needs to be maintained by the researcher between acquiring good impedances across the scalp and sustaining the compliance of a child who may grow frustrated during an extended period of preparation time. An electroculogram was recorded for the detection of eye-related artefacts during the analysis stage. Electrodes were positioned above and below both eyes.
7.3.1.1.3 Task Protocol

The EEG session took place in the London Babylab at the Wolfson Assessment Centre, UCL Institute of Child Health. The testing session took place as part of a larger battery of tasks as described in this thesis. Typically the child completed approximately one hour of behavioural tasks, including the WPPSI-III-UK (see Chapter 5 for further task description and group results), so that verbal IQ could be obtained and the researcher could build a rapport with the pre-schooler. The child then had a snack break for as long as required (typically 15-20 minutes) before the researcher showed them pictures of children wearing the sensor net “hats” and gave them the opportunity to feel the sensor net and ask any questions. If the child was hesitant about the apparatus, the parent/guardian was asked to try on a larger net so that they could see what it looked like. The researcher then made a game of “who has the biggest head?” to obtain the head measurements for the sensor net so that the correct size sensor net could be chosen. Children were required to have a verbal IQ greater than 75 and to pass the training phase in order to proceed to the ERP task (two patients were excluded due to low verbal IQ, one also has a SLI diagnosis).

The full session, including net preparation, typically lasted thirty minutes. The child was sat on a comfortable seat behind a divider (to minimize distractions) and the parent typically left the room during the session to minimize noise in the data collected. The child watched a cartoon for approximately five minutes while the net was correctly set-up and positioned. This was followed by a training session where the researcher interacted with the participant in order to gauge their understanding of ‘Left’ and ‘Right.’ An arrow sign was used and the child was instructed to touch the ear that corresponds with the side that the arrow was pointing towards (an understanding of direction is not necessary as long as the child understands that they are to listen to the ear that the arrow points towards).

After the initial training phase, the child undertook a practice session with two
popular nursery rhymes and the researcher asked him or her questions about the song that they were cued to listen to. Once the researcher was satisfied that the child understood the rules, the testing session began. Participants were cued to selectively attend to one of two simultaneously presented stories that differed in location (left/right), voice (male/female), and content. There were up to 14 story blocks. At the beginning of each story the child heard “Are you ready?” and the researcher pressed a key for the session to proceed. After each story the child was asked questions relating to the attended story. Once the researcher had established whether the child was attending to the correct story, a button was pressed and the task was continued. The researcher noted story answers and bad trials (e.g. observed excessive movement, removal of headphones/sensor net) on a response sheet. If the child expressed a request to end the testing session after a period of time, the researcher asked if they would like to do one more story and then terminated the session if the child did not agree.

7.3.1.1.4 ERP Processing and Analysis

A criterion of a minimum of 25 artifact-free trials in each condition after all pre-processing steps was imposed. This figure is within the range of minimum number of trials (15-40) required in similar ERP studies with young children (Coch et al., 2005; Haan, Pascalis, & Johnson, 2002; Sanders et al., 2006). It has been recommended that studies with young children should include at least ten to twenty trials per condition (DeBoer et al., 2007) to obtain a reliable estimation of the ERP component under investigation (Cuevas et al., 2014). Each child completed up to 14 sessions so participants had up to 160 events (12 to 15 per story session) before processing. Children were reminded to fixate on the screen and to sit still between each story in order to maximize the number of artefact-free trials and were offered a teddy bear to hold “so he could also watch the images appearing on the screen’ if they struggled to stop movement. Data from individuals who did not meet this
criterion was excluded from further analysis (six patients; four controls). To further improve signal-to-noise ratio, several channels were combined for channel-level analyses based on previous reports (Coch et al., 2005; Sanders & Zobel, 2012; Strait et al., 2014). Four electrode groupings (figure 7.4) are defined based on previous studies with similar age groups and paradigms (e.g. Coch et al., 2005; Sanders et al., 2006; Isbell et al., 2015) and a topographical investigation of the current population.
Figure 7.4 The Geodesic Sensor Net 128 channel layout in accordance to the 10-20 system of electrode placement. Data were averaged across four channels at each site to increase the signal-to-noise ratio. The four channel cluster sites are located over the mid frontal, left frontal, right frontal, and frontocentral sites and are illustrated in black, green, orange, and purple respectively. Channel selection was based on previous research using similar age ranges and paradigms (e.g. Sanders & Zoebel, 2012; Stevens, Sanders & Neville, 2006).

7.3.1.1.5 ERP Processing Pipeline
EEG recordings were exported from Netstation for processing and analysis in EEGLAB (Delorme & Makeig, 2004). “Bad” story trials (where the child was
not participating in task, moving excessively, or attending to incorrect side) were manually removed. The EEG was digitally filtered with finite impulse response (FIR) filters. Data was filtered at a high-pass frequency of 0.1Hz and a low-pass frequency of 30Hz in EEGLAB 11.0.3 (Delorme et al., 2011). The EEG signal was epoched at 200 milliseconds before the stimulus event (allowing for a 200 millisecond baseline) to 600 milliseconds after stimulus presentation. Automatic epoch rejection of bad epochs occurred at a threshold of plus or minus 100 microvolts. Data were baseline corrected. The average voltage of the 200 milliseconds segment before stimulus onset was set as the baseline. This segment represents ‘zero voltage’ and is subtracted from every channel in the epoch. Visual inspection was used to remove artefacts such as eye blinks, saccades, muscle activity, and skin potentials (Luck, 2005). The data were re-referenced from the vertex reference to an ‘average reference’ montage. The time window of interest (100 to 300 milliseconds) was chosen based on a review of the relevant literature for this age range in similar tasks (Sanders et al., 2006; Sanders & Zobel, 2012; Stevens et al., 2009) and examination of the current data. Trials were averaged together to acquire a single averaged segment for the ignore and attend condition for each participant. The grand averages of each condition for both the patient and the comparison groups were analyzed. Grand averages were also computed for three year olds, four year olds, and five year olds separately in order to ensure that the expected developmental trends were observed.
7.3.1.2 Cognitive
In addition to the WPPSI-III-UK\textsuperscript{7}, children completed the scrambled memory task and two selective attention tasks; the NIH toolbox (NIHTB) test of attention control as well as the Doggie Deletion Preschool Task (DDTP; see Chapter 5 for further task description and results). The scrambled memory measure used was the number of consecutively correct trials. Poorer scores in the NIHTB task reflect longer reaction time and incorrect responses, while more omissions on the DDTP purportedly reflect poor application of attention and commissions is related to poorer management of response conflict. Parents completed the BRIEF-P questionnaire (see Chapter 5 for further task description and results), where a higher score indicates poorer parent-reported EF. The BRIEF-P was not completed for one of the patients and the working memory task was not administered to six of the control children due to task changes during the piloting of task (they completed a pilot six box version not included in analysis; see chapter 4 for further details on task validation). Some of the participants did not complete the paper-based DDTP task (two patients and nine control children) due to task modification in the pilot phase (seven control children), timing issues (two patients/one control child), and experimenter error (one control child), and five of the control children did not complete the NIHTB task due to timing or equipment issues.

7.3.1.3 Medical and Socio-environmental factors
Medical information for the patients was retrieved from hospital databases (number of admissions in previous year and cerebral blood flow velocity) and measured on the day of testing (haemoglobin levels and oxygen saturation). Parents completed the family environment Scale (FES; see Chapter 5 for further task description and results) and socio-economic status was based on

\textsuperscript{7} See Chapter 2 for further details on each cognitive task
income approximations based on postcode (measured on a scale from one to five; see Chapter 2 for full population descriptives). Family functioning data was missing for two of the control children and one patient and SES data was missing for three of the control children.

7.3.2 Participants

Twenty-four patients and 38 typically developing children participated in the EEG part of the study. Thirty-four usable datasets were available for analysis after data collection and pre-processing steps (12 patients and 22 comparison children). The following section delineates the reasons for EEG data loss. Final groups were matched (using Pearson's Chi-Square for category comparison and independent t-tests for comparison of continuous variables) for age, full scale IQ, socioeconomic status, and gender (Table 7.2), although only 32% of the comparison group was matched for ethnicity (Black British).

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8 This chapter includes one child with sickle cell disease who has a HbSC genotype in order to increase power in the investigation of group differences.
Table 7.2 Group descriptives for final group of usable datasets

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Group (n=12)</th>
<th>Control Group (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years; SD; range)</td>
<td>5.0</td>
<td>4.4</td>
<td>.1</td>
</tr>
<tr>
<td>FSIQ (mean; SD; range)</td>
<td>101.2</td>
<td>109.0</td>
<td>.1</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>10</td>
<td>.4</td>
</tr>
<tr>
<td>Socioeconomic</td>
<td></td>
<td></td>
<td>.7</td>
</tr>
<tr>
<td>Status (by income)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No information</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maternal Education</td>
<td></td>
<td></td>
<td>.5</td>
</tr>
<tr>
<td>Secondary level</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Third level</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>No information</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

7.3.2.1 EEG Attrition

Figure 7.5 illustrates the reasons for data loss. Unfortunately, the EEG software would not operate on seven separate occasions, which meant that 7 children, 11.3% of the population was lost due to system error. Nine children (14.5%) either refused to participate in the task or removed sensor net and headphones during the recording session before sufficient data could be collected for analysis. One of the comparison children had thick braids that meant that the apparatus could not be applied successfully for data collection. A second comparison child was born extremely pre-term and so was excluded.

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9 A new EEG system was installed in the London BabyLab after the cessation of the current study in order to avoid this issue in future investigations.
from analysis. Additionally, one of the patients had specific language impairment (SLI) and one patient did not pass the training phase.

![Diagram showing data flow and reasons for attrition/data loss during data collection and analysis.](image)

**Figure 7.5** Data flow illustrating reasons for attrition/data loss during data collection and analysis

### 7.3.2.2 Task descriptives

There were no group differences between the total number of completed story trials, number of correctly attended story trials, number of event before pre-processing and final number of events (Table 7.3).
Table 7.3 No group difference between behavioural task performance or number of usable events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of trials completed Mean (SD)</td>
<td>10.7 (3.7)</td>
<td>10.8 (3.2)</td>
<td>.922</td>
</tr>
<tr>
<td>Percentage of correct/attended trials Mean (SD)</td>
<td>82.5 (18)</td>
<td>89.7 (17)</td>
<td>.265</td>
</tr>
<tr>
<td>Number of events before processing Mean (SD)</td>
<td>107.5(35)</td>
<td>123.4(38)</td>
<td>.171</td>
</tr>
<tr>
<td>Number of events after processing Mean (SD; N)</td>
<td>81 (35; 12)</td>
<td>86 (23; 22)</td>
<td>.632</td>
</tr>
</tbody>
</table>

7.3.3 Data Analysis
The frontomedial electrode grouping was chosen from the four clusters of interest for further analysis based on the findings of previous studies and topographical data observed in the current population. Analysis of variance (ANOVA) was used to evaluate whether the attention effect varied as a function of group. The mean amplitudes for the early frontal positivity were analysed using a two-way univariate ANOVA with group (SCD or TD) and condition (attended vs unattended) as the between-subject factors and the mean amplitudes at the frontomedial site as the within subject factor. Overall group differences for effect attended and unattended conditions were further explored across the four frontal clusters of interest using a MANOVA. Non-parametric comparisons of group when divided by age were conducted using Mann-Whitney Tests due to small numbers. Pearson’s correlations were used to look for associations between neurophysiological responses and disease and socio-environmental factors, and performance on neuropsychological tasks. Shapiro-Wilk tests showed that scores on the DDTP were not normally distributed so Spearman’s correlations were used to compare with the EFP. Similar to Karn et al. (2015), significance levels of p < .1 are reported as trends in the current study, as the EFP amplitudes are small and variable in young children.

7.4 Results

7.4.1 Group differences in Early Frontal Positivity

As expected, the comparison group showed a broad positivity peaking at approximately 150-200 ms post-stimulus onset; however this was not observed for the SCD children who showed a less attenuated and inconsistent response (see figure 7.6). Consistent with previous studies, the typically developing children showed the attention effect to be largest at the frontomedial site in comparison to the other three sites of interest, however
this did not reach significance (F(2.2,46.19)=2.164,p=.10), whereas the patients did not seem to show as strong an effect for the attended condition any of the sites (see figure 7.7). As illustrated in figure 7.6, the attention effect is observed at the four anterior and central sites of interest for the comparison children, although it is most evident at the main cluster of interest, the frontomedial site, however it is not observable for the patients at any of the sites of interest.

There was a trend for the main effect of group on mean amplitudes at the frontomedial site (F(1,64) = 2.3,p=.11) while the interaction between group and condition was near significant (F(1,64)=14.7, p=.09). The control children showed a significant difference in the mean peak between the attended and unattended condition (t=2.2, p=.04) but this was not observed for the patients (t=.60, p=.56).

To further explore the individual mechanisms underlying attention modulation in this task, the enhancement of the peak in the attended condition and the peak suppression in the unattended condition, further analysis compared the two groups on these two processes separately, as undertaken in similar studies (Stevens et al., 2009; 2006). Significant group differences were observed between groups for amplitude in the attended condition at the frontomedial site with the comparison children showing larger mean amplitudes (t=2.2, p=.03), but no group differences were observed for the unattended condition (t=-.12,p=.91). Table 7.4 shows that, although there was also a trend for greater amplitudes for the comparison children in the attended condition on the other sites, this did not reach overall significance (F(4,29)=1.72, p=.16) while there was no trend observed at any site for the unattended condition. Nevertheless, the pattern for larger amplitudes in the attended condition for the comparison children, as seen in previous studies (Table 7.1) and their absence in the patient group, suggests that the patient group has difficulties with signal enhancement (Stevens, Sanders, & Neville, 2006) rather than distractor suppression (Stevens et al., 2009) in the attention
modulation process.

7.4.2 The “Attention Effect” and removal of outliers

The attention effect, or the mean amplitude difference between the attended and the unattended condition, has been previously explored in this age range as an index of attention control (Isbell, Hampton Wray, & Neville, 2015). Near significant group differences were observed for the magnitude of the attention effect (attended-unattended) at the fronto-medial site ($t=1.8$, $p=.07$). As seen in previous studies with this young age range (e.g. Stevens, Sanders, & Neville, 2006), there is variability within each group. Figure 7.8 shows the size of the attention effect for each participant, illustrating greater variability in the younger children. The figure indicates that five patients (42%) and three comparison children (14%) had attention effects greater than one standard deviation below the mean for comparison children.

Group analyses were repeated to ensure that the outliers in the negative range for the attention effect in the comparison group (figure 7.8; all three year olds, suggesting more variability in the youngest children) and the main outlier in the patient group were not having effect on the group differences explored in the previous section. Results revealed that once these outliers were removed, the previous near significant ANOVA effect between group and condition became significant ($p=.01$) and the significant difference between the attended and unattended condition for the comparison children became stronger ($p=.01$); however this difference remained non-significant for the patients. The post-hoc group difference observed for the attended condition also increased in significance ($p=.013$) although the lack of a group difference for the unattended condition remained the same. Finally, the group difference for the attention effect (attended-unattended) reached significance ($p=.006$).

To further explore the effect of age on group differences, both groups were
divided into three age ranges (three year olds; SCA=3, TD=8, four year olds; SCA=2, TD=7, and five year olds; SCA=7, TD=7) for separate comparisons. Results showed that although the five year olds still had a significant group difference for the attended condition (U=8, p=.03), this was not significant for the three (U=10, p=.77) and four year olds (U=3, p=.33). The group difference for the attention effect still held for the four year olds (U=3, p=.05) with a trend for the five year olds (U=13, p=.13) but not the three year olds (U=11, p=.92). These results must be interpreted with caution due to the small group sizes for the three and four year old age ranges.
Figure 7.6 Grand average ERP plots showing attended (green) and unattended (purple) waveforms for the SCD group over the right frontal (A), left frontal (B), centrofrontal (C), and frontomedial (D) sites and for the typically developing children over the right frontal (E), left frontal (F),
centrofrontal (G) and frontomedial (H) sites, showing differences in the early frontal positivity (shaded grey area).

**Figure 7.7** Topographic two dimensional voltage maps show scalp-potential distributions averaged over a 200ms time-window indicating magnitude and ranges of ERPs elicited for A: Attended condition, B: Ignored condition and C: the Attention effect (difference wave; attended-unattended) for SCA patients and D: Attended condition, E: Ignored condition, and F: Attention effect for typically developing children at 100-300ms. Red depicts the highest amplitude in voltage distribution. Maxima corresponding to frontal effects are evident for the typically developing children in the attended condition (D) but are not as
perceptible for the control children (A). A larger attention effect or difference wave in the frontal region can be observed for the controls (F) than for the patients (C).

**Table 7.4** Mean amplitude of the early frontal positivity (100-300ms) in the medial frontal, left frontal, right frontal, and central sites for both conditions.

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>Medial frontal M (SE)</th>
<th>Left frontal M (SE)</th>
<th>Right frontal M (SE)</th>
<th>Frontocentral M (SE)</th>
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</thead>
<tbody>
<tr>
<td>SCA</td>
<td>Attended</td>
<td>-.229 (.57)</td>
<td>.381 (.47)</td>
<td>-.071 (.59)</td>
<td>.386 (.41)</td>
</tr>
<tr>
<td></td>
<td>Unattended</td>
<td>.249 (.49)</td>
<td>.462 (.43)</td>
<td>.282 (.38)</td>
<td>.649 (.43)</td>
</tr>
<tr>
<td>Comparison</td>
<td>Attended</td>
<td>1.637 (.58)</td>
<td>1.389 (.48)</td>
<td>.662 (.29)</td>
<td>1.234 (.49)</td>
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<tr>
<td></td>
<td>Unattended</td>
<td>.167 (.46)</td>
<td>.369 (.57)</td>
<td>.282 (.37)</td>
<td>.555 (.41)</td>
</tr>
</tbody>
</table>

Significant group differences (p< .05) are shown in red and trends for group differences (p<.1) are shown in green bold.
Figure 7.8 The size of attention effect from 100-300ms for individual participants with age denoted by colour. The black line indicates the mean attention effect for typically developing children.
7.4.3 Associations with markers of SCA severity and socio-environmental factors

7.4.3.1 Medical and socioeconomic factors

There were no associations between the attention effect and markers of disease severity for the patient group (Table 7.5). No association was observed between the early frontal positivity and the family environment composite score across the whole population. Individual family factors were explored further, with some evidence for a potential association between more expression and conflict and a greater early frontal positivity in the attended condition across both groups (Table 7.6). However after the significance value was adjusted to $p<.005$ to account for multiple comparisons, this did not reach statistical significance. No associations with SES were observed and there was no significant difference between maternal education groups (university or secondary school only) for the patients ($t= .551$, $p=.59$) or the controls ($t=- .147$, $p=.88$) for the unattended condition.
Table 7.5 No significant relations observed between the disease and environmental variables and the neurophysiological correlates of attention control

<table>
<thead>
<tr>
<th></th>
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<td>Condition</td>
<td>Effect</td>
<td>Condition</td>
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<tr>
<td>A&amp;E admissions</td>
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<tr>
<td>CBFV</td>
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<td>.087</td>
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<td>Hb</td>
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<tr>
<td>SpO2</td>
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<tr>
<td>FES</td>
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<td>.174</td>
<td>-.113</td>
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Table 7.6 No significant relations between family factors and the neurophysiological correlates after Bonferroni correction

<table>
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</thead>
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<td>Unattended Condition</td>
<td>Attention Effect (attend-unattend)</td>
<td>Attended Condition</td>
<td>Unattended Condition</td>
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<td>Unattended Condition</td>
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<td>Cohesion</td>
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<td>.129</td>
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<td>Expression</td>
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<td>-.164</td>
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<td>.363*</td>
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<td>-.074</td>
<td>.249</td>
<td>.404</td>
<td>.109</td>
<td>.354</td>
<td>.491**</td>
<td>.043</td>
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<td>-.113</td>
<td>.329</td>
<td>.156</td>
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<td>Achievement</td>
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<td>-.041</td>
<td>.017</td>
<td>.086</td>
<td>-.1</td>
<td>-.091</td>
<td>.048</td>
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<td>Intellectual-culture</td>
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<td>-.159</td>
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<td>Active-rec</td>
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<td>Moral-religious</td>
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<td>-.542</td>
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<td>.074</td>
<td>.103</td>
<td>.011</td>
<td>-.223</td>
<td>-.211</td>
<td>.097</td>
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<td>Organization</td>
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<td>-.002</td>
<td>.099</td>
<td>.104</td>
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</table>
7.4.3.2 Associations with cognitive measures

A recent study found a relation between the early positivity attention effect and non-verbal IQ (Isbell et al., 2015) in preschool children from low SES backgrounds. However, in the current study there was no relation between performance IQ and the attention effect (attended-unattended) but when looking at the attended condition only a greater positivity was significantly associated with performance IQ ($r=0.483$, $p=0.004$; fig. 7.9). When the groups were separated, this association remained significant for the patients ($r=0.619$, $p=0.040$) but became a non-significant trend for the control children ($r=0.415$, $p=0.005$). Table 7.7 show the correlations performed for the EF tasks. No significant correlations emerged for the BRIEF-preschool or the NIH inhibitory control task. There was a trend ($r=0.481$, $p=0.06$) observed between a greater attention effect and better visual working memory capacity for the TD children, but not for the patients.
Associations with omissions and commissions on the DDTP were explored and it was found that children with larger peaks in the unattended condition made more omissions across both groups (rho=.465, p=.02, n=23; fig. 8.10) and for the TD children (.583, p=.036) and patients separately (.717, p=.045). No associations with commissions on the DDTP were observed. The significance of the DDTP findings did not change when outliers were removed, however this became non-significant after Bonferroni corrections adjusted significance value to p=.01.

**Figure 7.9** Associations between the EFP for the attended condition and performance IQ
Figure 7.10 Associations between the EFP for the unattended condition and number of omissions on the DDTP.
Table 7.7 Associations between the EF variables and the neurophysiological correlates of attention control

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients</th>
<th>Controls</th>
<th>Total</th>
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</thead>
<tbody>
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<td>Attention Effect (attend-unattend)</td>
<td>Attention Effect (attend-unattend)</td>
<td>Attention Effect (attend-unattend)</td>
</tr>
<tr>
<td></td>
<td>Attended Condition</td>
<td>Unattended Condition</td>
<td>Attended Condition</td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>.341</td>
<td>-.270</td>
<td>-.008</td>
</tr>
<tr>
<td>Working Memory CC</td>
<td>.091</td>
<td>.390</td>
<td>.481</td>
</tr>
<tr>
<td>DDTP Omissions*</td>
<td>.150</td>
<td>.717*</td>
<td>.149</td>
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<tr>
<td>DDTP Commissions*</td>
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<td>-.603</td>
<td>.186</td>
</tr>
<tr>
<td>NIH Inhibitory Control</td>
<td>.242</td>
<td>.174</td>
<td>.023</td>
</tr>
</tbody>
</table>

*Spearman's correlations used due to non normal distribution of the DDTP variables; *p<.05
7.5 Discussion

Previous research with preschool children in special populations who have known executive deficits has found evidence for altered neural processing in the early attention modulation process (Stevens et al., 2006; 2009). Here, I extend this research to children with SCD. The main finding was that children with SCD show a less pronounced amplitude to probes in the attended stream and have a poorer ‘difference score’ or attention effect. This study provides novel evidence for specific deficits in attention modulation on the early neurophysiological response of children with SCD. These results align with the behavioural findings of poorer EF, particularly attention control, in the current patient group (see Chapter 5). The current findings are also in line with the two previous ERP studies in SCD that found more diminished and variable executive ERP responses (Colombatti et al., 2015; Hogan et al., 2006). Even the youngest typically developing children in the current study showed attention modulation at 100 ms similar to previous studies, whereas, even at five years old, the children with SCD did not evidence this. This finding specifically pinpoints a deficit in signal enhancement to attended stimuli rather than an issue with distractor suppression.

7.5.1 Group differences in Early Frontal Positivity and the “Attention Effect”

Results showed that typically developing children had a significantly greater response to stimuli in the attended condition. This difference was also observed when the five year olds were investigated separately; however this did not remain significant for the three or four year old children when analysed separately, potentially due to the small number of patients in these groups. The current study showed that there was no difference between groups in the amount of trials completed or the amount of correctly attended stories, despite the difference in the underlying neural processes. Stevens, Sander, & Neville
(2006) reported similar findings for their cohort of children with SLI, who also showed equivalent behavioural performance. Hogan et al. (2006) also reported no group differences in task performance on their performance-monitoring task in children with SCD despite differences in neurophysiological response.

Although more attenuated EFPs were anticipated for children in the attend condition, the lack of any significant response was not expected. However previous research on auditory attention allocation in children with autism and ADHD has also found it to be absent, attenuated, or inconsistent in multiple studies (Donkers et al., 2015; Gomes et al., 2012; Jonkman et al., 2004; Loiselle, Stamm, Maitinsky, & Whipple, 1980), even when compared with TD children. Additionally, children with SCD are also at a higher risk for neurodevelopmental disorders such as ADHD and autism (Berkelhammer et al., 2007; Lance, Comi, Johnston, Casella, & Shapiro, 2015).

The lack of a measurable EFP may suggest that the patients are allocating limited attention resources are less automatic in the allocation of resources, or alternatively that there is a dampening of information, more limited activation, or immature neural synchronization (Gilley, Sharma, Dorman, & Martin, 2005). Thus, the children with SCD may have less established control structures or neural sources of attentional modulation and the lack of neurophysiological modulation reflects poorly attuned attentional control. Additionally, the EFP is a small response so inconsistent modulation could be filtered out with noise, particularly as the current study included fewer events than previously reported studies (e.g. Sanders et al., 2006). Strait et al., (2014) did not find different responses between the attended and unattended conditions for their cohort of TD preschool children, concluding that, as attention control gradually emerges in this age range, it would not be unusual for its effects on neural processing to be inconsistent or barely distinguishable, particularly in patient populations.
The findings suggesting an early filtering attention deficit are similar to preschool children with SLI, who also show a diminished neural response to stimuli, even when performing the task as directed (Stevens et al., 2006). Shafer and colleagues found that TD children contributed attentional resources to speech even when directed to visual cues but that the children with SLI did not (Shafer, Ponton, Datta, Morr, & Schwartz, 2007). This is an interesting finding as potential language-processing deficits have been previously highlighted in the sickle cell literature and indeed one of the participants in the study was excluded due to having an SLI diagnosis (Steen et al., 2002). Unfortunately, due to the design of the study, children with previous diagnosis of developmental disorders such as SLI and children who did had a verbal IQ less than 75 (and therefore could not follow task instructions) were excluded from the study. A recent Brazilian study showed a small but statistically significant reduction of the interpeaks I–V, in the brainstem auditory evoked response in adolescents with SCD which could be suggestive of impaired transmission from the brainstem potentially causing poor cortical representativeness and cognitive control, particularly in crowded environments (de Castro Silva, Magalhães, Toscano, Gandolfi, & Pratesi, 2010). As suggested for children with ADHD this could mean that the development of these earlier subcortical regions could have an impact on the later development of frontal, higher cognitive processing regions (Gomes et al., 2012). Gomes et al. reported that a “virtually” absent neurophysiological response for selective attention in children with ADHD might reflect reduced information in the early processing stages. A higher incidence of peripheral and central auditory impairment has been reported for SCA (Forman-Franco, Karayalcin, Mandel, & Abramson, 1982). One study reported poorer auditory discrimination and language in kindergarten children with SCD (mean age 5.6 years) on the Developing Skills Checklist when matched with classroom controls (Steen et al., 2002) which the authors suggested could be attributable to hearing loss, auditory processing deficits, or deficits in auditory attention. Finally it must be acknowledged that a higher rate of epilepsy has been reported in SCD (Ali, Reid, Fraser, MooSang, & Ali, 2010) and a recent SCA
study found that pathological EEG was a predictor of poor attention performance in children with SCD, however the study included children with cerebral infarction (Ruffieux et al., 2012). The prevalence of pathological EEG in preschool children with SCD and its association with attention in the absence of stroke has not previously been investigated.

7.5.2 Associations with markers of disease severity and socio-environmental factors

No relationship was observed between markers of disease severity and the EFP for the children with SCD. However, the lack of findings may have been hampered by the small patient group size or due to the inclusion of only clinically stable patients and the exclusion of children with prior MRI investigations for brain lesions, reducing the amount of variability in disease severity. Colombatti et al. (2015) also found a lack of correlation between disease severity (as measured by lesion volumes, TCD velocity, haemoglobin levels, and rates of acute chest syndrome and vaso-occlusive crisis) and the P300 response in their group of patients with SCD, concluding that cognitive impairment may instead be attributed to diffuse neuronal network damage as a result of the accumulating effects of chronic hypoxia since infancy on the development of the frontal executive systems. Previous research has demonstrated an effect of lower SES on the development of the EFP (Stevens et al., 2009). However, no associations with SES were observed in the current study. This could be attributed to the measures of SES used (i.e. maternal education and income estimates based on postcode) and the incomplete income dataset for TD children. Of note, a difference between this study and previous investigations of the EFP in preschool children was that this population was more ethnically representative. Previous studies largely recruited Caucasian children (e.g. Karns et al., 2015). There was no relation between the family functioning composite score and the EFP response; however there was some evidence for a potential influence of the family
expression and conflict domains on attention control. The considerable amount of variability in the neural processes across this age range, as previously reported for preschool-age children, could have reduced the likelihood of observing relations between the EFP and disease or environmental factors. Preschool children as a cohort may have contributed to noisier ERP data, reducing the signal to noise ratio and consequently, the statistical power to detect stronger associations.

7.5.3 Associations with behavioural measures of executive functioning

Associations between the ERP task and behavioural performance were explored for the whole group and for the patient and comparison group separately. A recently published study showed a relation between the early positivity attention effect and non-verbal IQ (Isbell et al., 2015) in preschool children from low SES backgrounds, while additional studies showed a relationship between the EFP in the unattended condition and the BRIEF in young adolescents (Lackner et al., 2013) and between the P1 and visual working memory in adults (Giuliano et al., 2014) on similar paradigms. These associations were investigated using similar tasks in the current population revealing similar findings for non-verbal IQ and working memory but not for parent reports on the BRIEF-P. There was an association observed between non-verbal IQ and the EFP for the attended condition, but not for the attention effect, the amplitude difference between the attended and unattended condition, as previously reported (Isbell et al., 2015). The lack of an association between the GEC and the EFP as observed by Lackner et al., (2013) could be due to a difference in scales between the preschool and the school-age version of the BRIEF, a stronger relation emerging over time or to less mature ERP morphology in the younger children. The association between the EFP and working memory was observed for the typically developing children but not for the patients. This may be because the associations between neural processes of attention and performance could be
weaker in certain populations such as young children who potentially produce nosier datasets as well as a more variable response.

Associations with the EFP were only observed for one of the two attention control tasks, where children with larger peaks in the unattended condition made more omission errors on the DDTP. Missing data could contribute to the lack of relation with behaviour performance on the NIHTB task. Behavioural tasks measure multiple steps of cognitive processing whilst ERP measures have the advantage of elucidating a specific process, which could also make it more difficult to draw associations between the two domains. The selective attention behavioural tasks were also limited as they were both visual tasks, an auditory task may have been more informative for direct comparison.

7.5.4 Further investigations

Typically, attrition rates in EEG research are high for toddler and preschool children. EEG studies with two- and three-year-old children are reported to have attrition rates of 30% to 45%, due to refusal to wear the EEG cap, cap removal during the session, or excessive movement/EEG artefact (Cuevas et al., 2012a; Morasch & Bell, 2011; Wolfe & Bell, 2007). Attrition rates have been reported to drop to as low 20% by age 4 as children become more tolerant of the apparatus and display less movement during the testing session (Wolfe & Bell, 2004, 2007). The attrition rate of the current study was 45.2%, which is almost within the previously reported attrition rate for young children, despite the system issues encountered during the study. Future studies in young children with SCA should consider this attrition rate when calculating population sizes.

A broader variety of probe sounds would have been useful to determine the effect of different sounds but as the inclusion of a wider range of stimuli would require a longer task running time to obtain a usable number of trials for analysis, this was not possible for the current study. It was established during piloting that fifteen minutes of task running time was feasible for preschool-age children to complete, particularly given that the children were also expected to complete a range of behavioural tasks. However, future studies
that employ less tasks could extend this paradigm to include linguistic probes as well as standard tones, as research has shown that these stimuli can affect the neurophysiological response differently (Karns et al., 2015). Future studies must consider the potential effects of task design on the neurophysiological findings. The current study included a series of 14 story trials with a break between each story and some engagement with the examiner in order to establish whether the child was attending to the correct story. The “attended” ear also switches between trials. Previous studies have used the less trials (e.g. four) and longer story times (e.g. Coch et al., 2005; Karns et al, 2015). To this end, it may be that our paradigm required different executive demands such that the child had to switch between ears more frequently but only had to listen for shorter periods of time. However, the similar response topography and ERP morphology in the TD children is evidence to support the utility of the more child-friendly set-up developed for this study.

The neural sources underlying the current findings need to be further investigated. In the current study, the topographic maps in figure 7.7 seem to show more frontally distributed positive activity in the attended condition than the children with SCD. Future research could make use of complementary EEG techniques such as dipole source localization for the EFP that could create source models to further identify more reliable sources of the underlying activity (Jonkman et al., 2004). Future studies could also investigate the global field power of the EFP, which calculates the variance of brain activity across all electrode sites and allows for the comparison of potential topographical differences between groups (Shafer, Ponton, Datta, Morr, & Schwartz, 2007). Another arena of EEG research that has been gaining more momentum in executive preschool research over the past few years, and has yet to be applied to the current paradigm, is event-related synchronization and changes in task-related EEG power and coherence (Swingler, Willoughby, & Calkins, 2011; Wolfe & Bell, 2007). Finally, another potential methodological avenue that could be applied to
investigate the lack of a EFP in the patient group would be to compare the EFP amplitude with the non-zero pre-stimulus baseline (Urbach & Kutas, 2006). Given the reports for a higher incidence of auditory processing and epilepsy reported patients with SCD, future studies should incorporate a more objective method of screening for pathological EEG and auditory deficits.

An advantage of the current paradigm is that it can be applied across a wide range allowing for the developmental tracking of neural markers of attention (Kral et al., 2015; Strait et al., 2014). Thus, future studies should apply this paradigm in older school-age children and adolescents to investigate the differences in the developmental trajectory of the response, as well as to ascertain whether the lack of response in the current study is a developmental delay that eventually catches up with TD children or whether it is an early indicator of an alerted course of functional neural development. Additionally, there is currently no published evidence of classical attention ERP paradigms such as the auditory oddball paradigm in infants and young children with SCD. Future research applying this paradigm with young children with SCD will help elucidate whether the early attention deficit in the current study is also evident in more basic attention experiments, or unique to the complex environment in the current study that requires the exertion of more executive control.

7.5.5 Intervention studies for the EFP

Selective attention can be improved in preschool children with intervention (Diamond et al., 2007). Intervention may allow for better recruitment of neural systems important for selective attention. Recent research suggests that ERPs can be used to index executive improvements in interventions with preschool children (Espinet, Anderson, & Zelazo, 2013; Rueda et al., 2012). Examining the neural systems underlying attention can provide an on-line index of the selective auditory attention process that requires no overt or behavioural response and can identify different mechanisms that give rise to similar problems on a behavioural level. Studies have shown that the EFP
attention effect can be enhanced through targeted interventions. Neurocognitive intervention studies for preschool children with SLI, poor socio-economic status, and literacy problems suggest that selective auditory attention may be amenable to intervention at this early stage (Neville et al., 2013; Stevens et al., 2012; figure 7.11). Strait et al., (2015) has also found that musical training can support the maturation of neural markers underlying auditory attention during development. More recently, Isbell (2015) found that children with two copies of the long 5HTTLPR gene initially had more attenuated neural response to probes that significantly improved, in comparison to children with other genotypes, after a targeted eight-week intervention, suggesting a complex gene versus environment interaction in the success of interventions for individual children(Isbell, 2015). Future research should consider using the EFP as an end point measurement for intervention in young children with SCD, who may show a more typical response with intervention.
Figure 7.11 Intervention studies showing improvements in the early frontal positivity modulation and attention effects for i) children at risk (AR) for reading difficulties in comparison to on-track (OT) children (Stevens et al., 2012) and (B) a greater effect on the neurophysiological response (as well as
having wider-reaching consequences for cognition in the children and parent behaviour) for a combined parent behaviour and child attention 8 week intervention study (PMC-A) than a more child focused intervention (ABC) and no intervention (HS-alone; Neville et al., 2013).

7.5.6 Conclusion
Taken together, these findings contribute to the elucidation of differences in the development of the neural underpinnings of selective attention in preschool children with SCD. Children with SCD specifically show poorer signal enhancement with attention in comparison to TD children. Further research is warranted to investigate potential differences in source localization and to determine whether group differences would be evident on other attention paradigms, such as the oddball paradigm, in preschool children with SCD. Future applications of the current paradigm in older children with SCD is also required in order to determine whether this group difference can still be observed. Nevertheless, the current study provides initial evidence for altered neurophysiological response to selective attention in children with SCD, particularly pinpointing a lack of signal enhancement, and also contributes further evidence for the relationship between behavioural performance and neural markers of attention. Although no effects of disease severity or SES was observed in the current study, the investigation of family factors extends our current understanding of EFP development in young children, and the current study provides a platform for future neurophysiological investigations in children with SCD, as well as TD children.
Chapter 8: General Discussion and Conclusions
8 General Discussion

The research pursued in this thesis arose from two major gaps in the research literature; a lack of validated measures of EF for preschool-age children and the absence of knowledge of executive development in the preschool years in children with SCD, a cohort of children with known executive difficulties by school age. This thesis built upon previous research in the development of novel executive tasks for preschool children that can be easily replicated. The researcher also developed norms for the Preschool Executive Task Assessment, the first ecologically valid task of EF created for preschool children\(^\text{10}\). Executive development was investigated for the first time in preschool children with SCA. The researcher investigated different domains of EF so that a profile could be established that illustrated patient performance in specific domains of functioning when compared to a matched comparison group. Additionally, other domains that have been previously implicated in the sickle cell literature, such as sleep and family functioning, that have known influences on executive development in typically developing children, were explored. Predictors of EF in preschool children with SCA, including markers of disease severity and socio-environmental variables, were explored in order to contribute to the mixed literature observed for cognitive outcomes in older children. Finally, the neurophysiological indices of attention control, the earliest emerging executive domain, were explored in preschool children with SCD for the first time, adding to the sparse literature for ERP research in children with SCD. Only two previous studies with older children looked at aspects of EF using ERP methodology. In this concluding chapter, the main findings of this thesis are summarised. Study limitations and potential implications for future research and clinical practice will also be discussed.

\(^{10}\) The researcher has since won a Grand Challenges Award to create a training video for this task so that clinicians and researchers can use it worldwide. The researcher has also submitted a grant application for the development of a B version of the task.
8.1 Aims

There were two main objectives in the current thesis, and in the current section I briefly describe how these aims were met.

8.1.1 To develop a valid battery of executive functioning measures for preschool children

To this end, a multi-method approach was adopted, where different methodologies were combined. The researcher successfully developed and validated behavioural tasks of EF that could be applied from 36 to 72 months without ceiling or floor effects during the pilot phase. The Doggie Deletion Task for Preschoolers, the Scrambled Memory task, and the Preschool Executive Task Assessment, were all found to be reliable and valid measures of attention control, working memory, and general EF, respectively. All of the tasks were developed based upon the existing research literature. The task protocol is well documented so that other researchers can easily replicate the assessments. This thesis overcomes some of the issues encountered when the researcher began her thesis work; many executive tasks administered to preschool children in published studies were not assessed for validity and reliability and were designed, administered and scored differently across studies, resulting in a lack of continuity, comparability and consistency in research within this domain. This thesis also developed the first ecologically valid task of EF for preschool children so that functional support and scaffolding can be provided for teachers and caregivers in the promotion of executive development. The researcher entered into collaboration with Dr Christine Berg in the U.S. who had previously developed ecologically valid tasks of EF for school-age children with and without SCD, in the design and development of the PETA. As well as piloting and validating this task, the researcher normed the PETA in a large population so that normative scores could be obtained and so that the task could be readily translated into other research and clinical settings. The researcher also developed an age-appropriate ERP measure of attention control, building upon previous ERP
research. Chapter 3 details the validation process for each behavioural task, while Chapters 2 and 7 describe the development of the ERP task in detail. In conclusion, all of the design criteria discussed as part of Aim 1 in the introduction of this thesis were met.

8.1.2 To establish whether there are observable executive deficits in preschool children with SCA and the potential impact of disease-related and other relevant factors

Specific executive deficits were identified in preschool children with SCA, for the first time (Chapter 5). The children with SCA showed a poorer EF profile with a trend for lower scores across multiple measures, and significantly poorer EF performance observed for particular EF domains. Attention control and switching were observed to be significantly impaired in the children with SCA, while working memory and processing speed remained relatively preserved at this early stage. On a more ecological level, parents of children with SCA did not report more executive problems; however the PETA revealed specific executive deficits during the completion of an every-day multi-step task. Additionally, neurophysiological evidence for altered neural processing of selective auditory attention was presented for the first time in the only ERP study to date conducted with pre-school age children with SCD. Taken together, these findings present evidence for detectable executive deficits at this early stage of development. Chapter 6 looked at predictors of performance across the behavioural measures of EF, and found that positive family functioning emerged as the most important contributory factor to stronger general executive performance at this early stage of development in this patient population. Other factors such as parent-reported sleep problems, CBFV and SES contributed to specific domains of EF. Sleep played a role in the domain of goal setting, while CBFV contributed to cognitive flexibility, and SES contributed to the variability in attention control. Interestingly, no factors of interest independently contributed to the domain of information processing. There was also a lack of differences observed for processing speed between
the patients and the matched controls in Chapter 5, which suggests that poorer processing speed in older children may be a result of long-term disease-related factors. Overall, the findings of these studies provide a platform for action in terms of future research but also in terms of clinical provision and policy change. The evidence provided in this thesis belies the idea that specific executive deficits cannot be reliably detected in the preschool years and imparts the first strong argument for neuropsychological assessment in preschool children with SCD before they enter the school system. Not only will early assessment contribute to bridging the achievement gap frequently observed for children with SCD, but it will also provide clinicians with a baseline of ability for those children who may later experience stroke, potentially even preventing future stroke occurrence.

### 8.2 Specific Findings

The hypotheses for each chapter, whether they were supported, and the evidence for each research question are outlined in Table 8.1.
### Table 8.1: Specific hypotheses and specific findings within each experimental chapter

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Hypothesis</th>
<th>Supported?</th>
<th>Specific Results</th>
</tr>
</thead>
</table>
| 3: The development and validation of measures of EF for three to five year olds | To develop tasks that validly and reliably assess aspects of EF from 36 to 72 months | Yes (3/4) | - The PETA was found to be a reliable and valid ecological assessment of EF in preschool children  
- The DDTP was found to be a reliable and valid assessment of sustained attention in preschool children  
- The Scrambled Boxes task was found to be a reliable and valid assessment of working memory in preschool children  
- The Circle-tracing and Bear/Dragon tasks were not found to reliably measure inhibition of pre-potent and on-going responses across this age range |
<p>| 4: An investigation of the children with SCA in the current study with a particular focus on factors known to other than disease status may be different | Factors relevant to EF | Yes (2/4) | - There was no differences between groups for IQ or for temperament (apart from discomfort) |</p>
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Sample and Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>have a potential impact on executive development in the children and the matched comparison group</td>
<td>- The children with SCA had a higher rate of parent-reported sleep problems and parents reported poorer family functioning</td>
<td>- Statistically significant differences for performance on the switching task (EF Scale for early childhood) and the attention control tasks (NIH Inhibitory control and DDTP) as well as differences observed on the PETA.</td>
</tr>
<tr>
<td>5: Investigating the early development of EF in children with SCA using measures that tap specific components as well as measures that look at EF in a more ecologically-valid way</td>
<td>Children with SCA will show poorer performance on executive tasks as observed in studies of older children</td>
<td>- There were no significant performance differences on the processing speed and working memory tasks or in parent reports of EF, although there was a trend for slightly poorer performance in the patient group.</td>
</tr>
<tr>
<td>6: An investigation of factors that contribute to poorer EF in preschool children with SCA</td>
<td>Poorer parent-reported family functioning and more sleep problems in the patient group</td>
<td>- Poorer family functioning was more predictive of general EF outcomes than disease, sleep and SES factors.</td>
</tr>
</tbody>
</table>
children with SCA will have more of an influence on executive outcomes than markers of disease severity.

- For specific EF domains; family functioning was the strongest predictor of cognitive flexibility (CBFV showed a near significant effect), age and sleep were the greatest predictors for goal setting, family functioning was the greatest predictor of attention control (followed by SES), however no factors independently contributed to information processing.

| 7: A neurophysiological investigation of selective auditory attention, an early emerging and foundational executive skill, in preschool children with SCA | 1: Children with SCD will show diminished neural modulation with attention. | 1: Yes | 1: Children with SCD specifically show poorer signal enhancement with attention in comparison to typically developing children. |
| | 2: Children with the poorest executive scores on behavioural tasks will show less controlled EFP | 2: Yes (partially) | 2: There were no associations observed with the BRIEF-P or the NIH Inhibitory Control task but there were associations observed for performance on the DDTP. A relation with behavioural performance on the working memory task was only observed for the |
responses and less
differentiation between
the attended and
unattended conditions.

3: Poorer SES and less
positive family
functioning will be
associated with less
mature ERP responses
but there will be no
relation with markers of
disease severity.

typically developing children.

3: There was no evidence for an association
between the EFP and disease markers or sleep
and family functioning.
8.3 A Critical Review

There are some limitations in this thesis. Most limitations have been stated in the discussions of the relevant experimental chapters, however the limitations relevant to the thesis as a whole will be discussed here.

8.3.1 Participation, Representativeness, and Attrition

Data loss or attrition is noted at different points in this thesis whereby not all of the children who attended the London Babylab completed all of the measures. This was largely due to technical issues in the case of the ERP study and the NIHTB computerised measure. Length of assessment battery may have also been an issue, particularly for the younger children, despite the opportunity for numerous breaks. However, the task battery was developed and shortened during the pilot phase and typically a whole visit would last for less than four hours, including breaks. Compliance was an issue only for the ERP task where some children did not like wearing the net; however this overall was within the range of normal compliance levels typically reported for preschool children. This study allowed for a holistic assessment of executive development in preschool children with SCA and the application of multiple measures allowed for the development of a profile of strengths and weaknesses to contribute to the sickle cell literature, which previously had no information on general executive development, or the development of specific executive domains in preschool children with SCD.

Another limitation is that some questionnaires were not completed or returned by parents or teachers. For the parents who attended the laboratory, English was typically not their first language and it took a longer period of time to fill out the four study questionnaires with assistance sometimes required from the researcher. However, the researcher ensured that time was available throughout the assessment day to answer any questions parents had about the questionnaire measures and the number of questionnaires not returned was minimised. Additionally, not all teachers completed the EF questionnaire
in the validation study for the PETA. This was mainly due to the work burden that many teachers reported. The researcher gave the teachers an additional month to fill out the questionnaires after study completion.

The representativeness of the patient group must also be considered. This thesis mainly focused on patients with a HbSS genotype as it is the most typically reported genotype for SCD in the UK and is typically associated with a greater burden of medical and neurocognitive issues, including a higher risk for stroke. One patient with HbSC was recruited initially due to error in referral but was included in the ERP chapter to increase power. Patients with SCD typically encounter socioeconomic disadvantage and it may be that patients from higher SES backgrounds are more likely to participate in research. However, participation rates were high and the researcher minimised the burden of study participation by making testing days available seven days a week, organising taxi pick-up and drop-off, encouraging parents to bring siblings who could be entertained in the play room and by offering a gift voucher and reimbursing refreshments and lunch costs incurred. The study had a small sample size, due to the nature of clinical research in a restricted age range of a relatively rare condition. The patient population was estimated for Chapters 4 and 5 from a power calculation at the start of the PhD but the numbers were not adequate for sufficient statistical power in Chapter 6. The sample size limitation lay in the size of the matched comparison group for some of the domains reported in Chapter 5. Children that were matched for ethnicity and SES were challenging to recruit. The researcher attended local clinics and support groups to recruit age-matched relatives of patients as well as advertising the study in local schools and libraries based in the same boroughs that patients were recruited from as well as Sickle Cell charities and African Heritage groups. Community support groups for parents of children with SCD were not well attended. Parents and nurse specialists informed the researcher that this was mainly due to the stigma associated with SCD in some cultures. The researcher had additional comparison children datasets recruited during the pilot phase that were matched for age, IQ, and SES (appendix 6) but were not included in the main analysis due to the emphasis
in the behavioural sickle cell literature on the importance of ethnicity-matched comparison children (Barbarin & Christian, 1999; Richard & Burlew, 1997). However, despite a small comparison group for some of the tasks, the children are matched for ethnicity, SES, age and IQ, which greatly reduces the likelihood of group differences that may have been influenced by extraneous variables other than disease status and strengthens the findings reported in Chapter 6 and Chapter 7.

### 8.3.2 Methodological Considerations

It would have been useful to include a visual ERP task and auditory behavioural tasks of attention control as Chapter 7 compared auditory performance on the ERP task with visual performance on behavioural tasks. The different modalities for both types of measures could have influenced the relationship observed between the ERP and the behavioural performance. However, there are no auditory attention and working memory behavioural tasks or visual attention ERP tasks reported in the literature for this age range so the researcher did not pursue these avenues of investigation, choosing instead to build upon and develop previously reported measures. The lack of standardised data for the newly developed behavioural tasks in this thesis, Scrambled Memory and the DDTP, must also be noted. However, an aim of this thesis was to develop and validate executive tasks so that, similar to the PETA, they can be standardised in a larger population, and be more informative in future studies with patient populations. It would have been of interest to include non-executive tasks, such as episodic memory, as control measures in the thesis however due to the length of the testing battery, priority was based on the assessment of executive functions.

Another limitation of this study is the reliability of markers of disease severity and SES. The patients in this study did not undergo MRI as part of this study due to their young age so it may be that some of the patients had silent stroke that was undetected. However, as MRI scans were not feasible in this young population to rule out brain pathology (due to the young age of the population
we did not apply for ethical permission for MRI), exclusionary criteria included patients who previously underwent MRI investigations for suspected brain pathology. The study included some patients who were being treated by regular transfusion or hydroxyurea, which could have influenced their cognitive performance. However, treatment status is noted throughout the thesis and did not impact any findings. No significant associations were observed between the disease biomarkers and the behavioural or ERP measures, which may be due to the reliability of disease measures used for the patient group. Haemoglobin was measured on the assessment day but for the few cases that this was not possible, the most recent clinical reading was obtained from patient notes. Most recent TCD measures varied in the length of time from the assessment day. It may have been more reliable to obtain an average of haemoglobin and TCD values across the three most recent clinical assessments similar to some previous reports. However patient non-attendance rates in the clinic where patients were recruited was high and some of the patients did not have regular notes for these medical variables. The socio-economic variables may also not have been the most informative markers; maternal education was divided into two categories but could have been more informative with a more finely scaled scoring system; however as the school system experienced by some parents in Africa was different to the UK system, a two-category variable was deemed more appropriate. Additionally, home postcode was used as an indicator of SES, however it could have been more informative to collect other demographic information from parents such as actual house income. It would have been useful to have more information on parent-child interaction and maternal well-being as the family environment scale gives an overview of family dynamics but these psycho-social variables have also found to be important in other studies looking at the development of EF in preschool children.

8.3.3 Particular Strengths

Despite the limitations discussed in the previous section, this study had several strengths. This study validated executive tasks for preschool children and developed and normed the first ecologically valid task of EF for preschool
children. For the first time, this study investigated EF in preschool-age children with SCD using age-appropriate measures and a well-matched comparison group. Another strength of this study is the investigation of factors that contribute to EF at this young age and the incorporation of family, sleep, and SES variables, as well as disease status. This study was also the first investigation of attention control in SCD using ERP methodology, and the first study to use ERP methodology to look at any aspect of cognition in preschool children with SCD. Previously, no other studies have use a matched comparison group to look at IQ in preschool children with SCA or investigated temperament in children with SCA using the CBQ. This study also gives an overview of family functioning in young families with SCA in the UK and the rates of parent-reported sleep problems in preschool children with SCD in the UK.

8.4 Practical Implications

The practical implications of this chapter can be divided into two general domains: the implications for executive assessment in typically developing preschool children and children at-risk for executive difficulties, and the implications for the treatment and planning for children with SCA.

8.4.1 Implications for executive assessment in preschool children

Five tasks were developed and tested for their validity and reliability for measuring executive development in three to five year olds in Chapter 3. Four behavioural measures that tapped specific executive skills and one measure that analysed general EF from an ecological perspective were assessed. The tasks that tapped specific domains of EF, namely attention, working memory, and impulse control, were developed based on the existing literature. The design of these tasks was adapted from studies that had used similar non-validated measures in an attempt to measure these EF constructs in young children. The working memory task and sustained attention task were found to be valid and reliable measures of these domains and can be
readily applied in other studies with preschool children based on the materials developed in this thesis. The impulse control tasks encouragingly showed age effects for performance but were not sensitive to subtle increments in ability and require further development and adaption. This was surprising for the Bear & Dragon task, which has been administered frequently, albeit in many different formats, to this age range. The circle-tracing task had not been previously administered in this age range but the children understood instructions and future studies could adapt the current methodology to be more age-appropriate. Although not all of the developed task methodologies were validated, the approach adopted in this thesis aims to promote better standards for task design and validation in future studies with preschool children. By creating validated methodologies that can be easily replicated by other research groups, future research will develop a better understanding of executive development in typically developing preschool children and patient groups at-risk for executive dysfunction.

An ecologically valid method of executive assessment for preschool children, the Preschool Executive Task Assessment, was developed as part of this thesis. There are no other performance-based tools that measure EF in an ecologically valid away for preschool-age children in the literature to date (Burgess et al., 2006; Rabbitt, 2004). This task allows EF to be captured during a multi-step task using a micro-analytic approach that incorporates quantitative and qualitative scoring of different aspects of EF as well as providing an overall composite score. This task provides a potential advantage over existing timed or pass/fail measures that tap specific executive domains as it measures executive skills in an integrated way that mirrors real-life performance on a multi-step task. This task was adapted from versions developed for older children and adults with executive problems and is useful in a clinical and research context as it directly informs of the functional impact of executive deficits. A child’s performance on the measure can inform targeted, jargon-free support for children with executive difficulties.
as it demonstrates where a child struggles in an everyday task\textsuperscript{11} and what level of support they may require\textsuperscript{12}.

Finally, this study has implications for the application of ERP methods with pre-school populations. There has been a lack of ERP research in the preschool years, as this age range provides an inherent challenge due to their rapidly developing language and behavioural control. ERP methodology is more commonly applied in young infants, who can be easily distracted during the EEG net application, and in school-age children who can easily follow instruction and be motivated to participate (de Haan, 2002). The design of the current study was developed based upon the methodology used with preschool children by Helen Neville and colleagues to measure attention control (Sanders et al., 2006). There are few other groups that look at executive development in preschool populations using ERP methodology. This study demonstrates that with the appropriate task design modifications, such as the inclusion of a practice phase and child-friendly instructions, ERP methodology can be a useful tool to investigate the neurophysiological underpinnings of EF in preschool children. The findings of this study also corroborate the development of the ERP component in preschool children, the Early Frontal Positivity, reported in studies from Neville’s laboratory, as a similar trajectory of development was observed in the typically developing children in the current cohort. In conclusion, the methods developed in this thesis contribute to the future assessment of EF in preschool children.

\textsuperscript{11} For example, it may be that the child struggles to initiate or complete a task independently, has poor working memory and has to keep referring back to the picture book, has poor processing speed so takes a longer time to complete each step, is more distractible so finds it difficult to remain on task, or has poor sequencing skills and finds it difficult to move from step to the next.

\textsuperscript{12} For example, it may be that for one child they need a general verbal cue only so the adult only needs to ask what happens next, while another child may require a direct cue and so the adult tells them what they are supposed to do next. A third child may require physical assistance or demonstration in order to understand how they will achieve a goal.
8.4.2 Implications for treatment and planning for children with SCA

This was the first study to investigate the development of executive functions in preschool children with SCD and the findings of this study emphasise the importance of early neuropsychological assessment of executive skills in children with SCD. The patients in this thesis showed a poorer executive profile in comparison to the well-matched controls. Poorer EF was not associated with disease severity and findings provide strong evidence for the previous reports that have called for early neuropsychological assessment in children with SCD before they enter the school system (Glass et al., 2012), particularly as EF is strongly linked to school readiness and academic achievement. A focus on early assessment will improve outcomes for young children with SCD by informing early interventions and restricting the achievement gap that is frequently reported, particularly as executive problems are the most commonly reported specific deficits in older children with SCD (Jeffrey Schatz, Finke, et al., 2002). It will also potentially indicate children who are most at-risk for future stroke as well providing information for a baseline of ability for those children who later experience stroke (White et al., 2006). This study also found that, although parents were not yet reporting significant differences in EF as observed in studies of older children, specific deficits were observable on a behavioural and neurophysiological level during assessment. These differences were particularly notable for the areas of attention control and cognitive flexibility which are not as frequently reported as other domains, such as processing speed and working memory, in older children and adults with SCD. Notably, the patients’ performance for working memory and processing speed was still comparable to their peers, despite the commonly reported difficulties for older children and adults (Vichinsky et al., 2010). During the PETA, poorer performance in certain functional aspects of task performance such as task completion and distractibility were observed, which may mean that children with SCD may need more support attending to the task at hand to follow it to completion. As the comparison group were well
matched to the patients for age, IQ, SES, and ethnicity, the findings of this study are particularly compelling. In particular, the group matching for general cognitive functioning, which has been reported to decrease with age in older children, ensured that successful task performance was not driven by general cognitive ability. The findings of this study have implications for the future assessment of executive functions in children with SCD in research and clinical settings.

Poorer family functioning and sleep behaviours, both factors that are associated with poorer EF in typically developing children (Karpinski et al., 2008; Schroeder & Kelley, 2010), were reported for the children with SCA. These non-disease related factors, particularly family functioning, were observed to have a greater impact on EF development in the patients than disease and SES related factors. These findings have been previously reported for EF development and for the development of other cognitive domains in older children with SCD (Tarazi et al., 2007) and have implications for the development of interventions for preschool children with SCA. To date, no intervention studies for children with SCD have used EF as a primary endpoint of interest. There has been little emphasis on neuropsychological interventions in children with SCD (Drazen et al., 2014). One study with older children with SCD found improvements in EF after a sleep intervention, while the first study to apply a family-focused intervention, a one day problem-solving workshop for disease management, with the aim to improve academic achievement in school-age children, was inconclusive due to high attrition rates (Daniel et al., 2015; Marshall et al., 2009). Previous ERP studies in at-risk preschool populations have already shown that executive improvements can even be observed at a neural level following early-targeted intervention (Espinet et al., 2013; Rueda et al., 2012). These studies provide an additional impetus for the development of interventions that promote EF and healthy brain development in young children with SCD. Executive interventions targeted at preschool-age children with SCD may have a greater impact on long-term outcomes due to the malleability of the frontal lobes during this
rapid period of early development (Melby-Lervåg & Hulme, 2013; Sonuga-Barke & Halperin, 2010).

Despite the need for the development of educational policies and interventions for executive dysfunction in children with SCA being reiterated in the literature (Gold et al., 2008; Hijmans, Grootenhuis, et al., 2011; King, DeBaun, & White, 2008; Ruffieux et al., 2011; Smith et al., 2013), these needs cannot be implemented until appropriate methods of assessment for young children are further developed and applied in the research and clinical context. The development of EF assessments for preschool children in the current thesis may also have clinical implications that extend beyond SCA to address early development in other clinical populations known to have high rates of executive difficulties.

8.5 Theoretical Implications

This thesis contributes to the theory of executive dysfunction in SCA. There have been multiple studies that have provided evidence for EF deficits in patients with SCA, contributing to the development of a theory for EF dysfunction in SCA. However there are some issues with this theory. One issue is that there has been a mixed focus across studies in terms of the specific EF skills investigated, which has contributed to mixed findings. A second issue is the restricted age ranges and patient populations assessed; most studies have focused on children that are school age or older due to lack of appropriate assessment, which we have attempted to address in Chapter 3, and have largely focused on children who have stroke who show more severe and general EF problems than children with SCA who do not have stroke. A third problem is that most studies have combined sickle genotypes and have not used matched control groups. As discussed throughout this thesis, factors such as IQ, SES, sleep problems and family functioning can all contribute to executive dysfunction and must be taken into consideration when using a comparison group in a study of EF.

Finally, the underlying cause of EF dysfunction in children with SCA who do not have stroke is still debated. Recent research in SCA from the past decade
has used neuroimaging, neurophysiological, and neuropsychological measures to gain a better understanding of how the brain develops differently in children with SCA, while an emerging literature has begun to focus on the impact of environment on EF development in this patient population. However, many questions remain in our quest to understand the complex interactions between brain, behaviour, and environment in the context of neurocognitive development of this patient population.

The main findings of this study show that preschool children with SCA have different developmental trajectories of EF that may be particularly sensitive to their early family context and that the underlying neural bases of EF also shows developmental differences. Clinical stroke, most commonly in the frontal and parietal lobes, occurs in 10% of children with SCA by the end of their second decade and evidence of silent stroke is also most frequently reported in the fronto-parietal regions (Moser et al., 1996; Ohene-Frempong et al, 1998). However, even in the absence of stroke, bilateral cortical thinning and reduced white matter integrity resulting from chronic hypoxemia in frontal, parietal and temporal lobes is reported for patients with SCA.

Due to the impact of chronic hypoxia and anaemia on the protracted development of the neural systems important to EF, children with SCA may be particularly susceptible to EF deficits, and thus more vulnerable or less resilient to additional factors, such as poor sleep and family functioning as found in Chapter 4, known to impact EF development in typically developing children. Behavioural differences between the patients and the matched controls on EF tasks in Chapter 5 were also supported by differences on the ERP task of attention control in Chapter 7. There have been different theories proposed, such as the skill learning account, maturational account, and the interactive specialisation account, to describe the development of EF and its underlying neural bases (figure 8.1). The interactive specialisation account postulates that EF development is dependent upon connectivity between different brain regions (Johnson, 2011). This account may be most applicable
to SCA as white matter integrity is reported to be affected in older children even when there is no evidence of stroke, and white matter connections are important to integrate information between different brain regions in circuits related to specific EF skills (Charlton et al., 2006). Various studies have shown evidence for reduced bilateral white matter density in children with SCA who have no evidence of stroke (Baldeweg et al., 2006; Kawadler et al., 2013; 2015), with one study reporting potential associations between white matter integrity and processing speed in children with SCA (Scantlebury et al., 2011). There is an accumulating evidence base that suggests a relation between white matter growth and integrity and executive functions (Kraus et al., 2007; Nagy, Westerberg, & Klingberg, 2004). One study found that when they compared patients with SCA who had frontal stroke (n=11, mean age=18.3 years) to patients with SCA without frontal stroke (n=11, mean age =18.3 years and healthy control children (n=11, mean age = 17.7 years) on an ERP task of performance monitoring, the error-related negativity amplitude was significantly diminished in the patients with stroke, but reduced (non-significant) amplitudes were also reported for the control group. This is similar to the diminished amplitudes observed for the patients on the ERP paradigm in Chapter 7 who may have reduced connectivity or white matter integrity, and so a reduced or less efficient ability to recruit important early attention regions, as compared to the typically developing children. The interactive specialisation account may also offer an explanation for the lack of differences in processing speed and working memory deficits previously reported for older children with SCA in the current cohort, as well as the lack of more complex EF differences reported by parents. It may be that connections are not as established or refined in this younger population for these higher-order regions. The cognitive profile of children with SCD who show decreases in general cognition over time as well as deficits in EF has been compared to patients with early treated phenylketonuria who also show a similar pattern of reduced microstructural white matter integrity (Antenor-Dorsey et al., 2013; Schatz, Finke, et al., 2002).
The results of this study can also build upon Anderson’s theoretical model of EF development. In Anderson’s model, basic EF skills emerge first that lay down the foundation for and are then used in combination with later emerging EF skills (Anderson, 2002) so specific EF abilities ‘come on-line’ at different points of development. The findings for specific deficits in the domains of inhibitory control and switching in Chapter 5 did not translate to the composite scores on the PETA and the BRIEF-P or working memory and information processing, perhaps reflecting the combination of EF skills that these measures report and the developmental stage of the children (Garon et al., 2008; Garon et al., 2014). For example, it has been historically theorized that the storing and retention of information in working memory is a basic capacity that enhances with development. However, the improved ‘memory capacity’ could be attributed to more efficient information processing or the employment of recall strategies which means that an integrated relationship between memory, processing speed and EF, and thus increased neural connectivity between regions, is responsible for this developmental progression (Anderson, Northam, & Wrennall, 2014).

One aspect that Anderson’s neuropsychological theory of EF development and Johnson’s interactive specialisation of neurocognitive development do not emphasise is the impact of environment of neurocognitive development. Chapter 6 showed that family functioning played a particularly important role in EF development for patients with SCA. Despite the important role for genetic processes in neurocognitive development, the role of the environment must not be understated, particularly considering the protracted development period that underlies the development of the brain bases of EF and the evidence for the influence that protective processes, such as positive parenting, can have on this development (Belsky & de Haan, 2011; Kim-Cohen, Moffitt, Caspi, & Taylor, 2004; Lenroot et al., 2009).
Figure 8.1. Working memory development and its proposed underlying brain regions for three theories of the neural bases of cognitive development. DLPFC = dorsolateral prefrontal cortex, SUPAR = superior parietal cortex, VLPFC = ventrolateral prefrontal cortex. A: Improvement in working memory is due to the maturation of additional areas (i.e. DLPFC and SUPPAR). B: Improvement due to refinement of connections between brain areas (VLPFC, DLPFC, SUPPAR). C: Improvement due to changes in recruiting more low level system (i.e. VLPFC) to more high level or complex systems (DLPFC and SUPPAR). Adapted from Crone & Ridderinkhof (2011).

8.6 Recommendations for Future Research
The ultimate goal of this research is to improve the long-term outcomes for preschool children who have early signs of executive deficits, particularly
children with SCD, by developing novel assessments that can inform the development of interventions. Further work is required to develop and refine EF assessment in preschool children (Anderson, 2002). The EF tasks developed in the study require future development. The PETA requires the development of a B version, as it is important that the task remains novel to control for practice effects in the investigation of developmental trajectories and the impacts of intervention. The Scrambled Memory and DDTP tasks require further validation in a larger population and other patient populations with known EF deficits. Behavioural tasks that measure auditory attention and working memory in preschoolers are also required so that modality specific deficits can be elucidated. There still remains a lack of ERP studies that look at aspects of EF in preschool-age children despite the utility of ERP as a method to investigate the neural underpinnings of cognitive development. Future studies should focus on the development of ERP methodology designs appropriate for tapping specific executive skills in young children.

SCD is the most common and fastest growing genetic disorder in the UK with approximately 1 in 2,000 births. The findings of this study provide evidence for early neuropsychological assessment in all children with SCA before they start school. It is recommended that neuropsychological assessment, with a particular focus on EF, becomes part of standard clinical care in the UK. The awareness and clinical care of SCD has improved greatly in recent years. In 2009, regular routine TCD screening from two years of age was introduced into UK clinical practice, with the aim of predicting and reducing stroke occurrence (Dick, 2008). However, there is room for further improvements and the introduction of early neuropsychological assessment could have an impact on both medical and neurocognitive outcomes for children with SCD (Daly et al., 2011; White et al., 2006). Previous reports have called for a focus on EF in cognitive rehabilitation in SCD, and as EF declines with age in

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13 The researcher has recently submitted a small grant to develop, validate, and standardize a B version of the PETA
children with SCD, early assessment and intervention is essential to address difficulties before the achievement gap grows between children with SCD and their peers (Kral et al., 2001; Ruffieux et al., 2013; Wang, 2007). Children with SCD have been reported to have poorer school readiness (Chua-L et al., 1993; Steen et al., 2002). Several studies have called for early neuropsychological assessment to assess school readiness in children with SCD (Bonner, Schumacher, Gustafson, & Thompson Jr, 1999); however, this study, for the first time, provides evidence of poorer EF which has been strongly associated with school readiness in children with SCD, bolstering the case for early neuropsychological assessment in preschool children with SCD. The promotion of EF can compensate for the reported decline in IQ that is observed over time for patients with SCD and EF skills are also associated with better disease management and social and adaptive functioning (Johnson, 2012b; Jeffrey Schatz, Finke, et al., 2002; Steen, Fineberg-Buchner, et al., 2005). Early EF assessment will inform targeted intervention to improve the quality of life for children with SCD and provide a baseline for cognitive ability for children who may later experience the cognitive sequelae of stroke.

Evidence is emerging to suggest that some neurocognitive deficits in SCA may be alleviated by medical interventions, including the use of hydroxyurea, blood transfusion and bone marrow transplantation, further emphasising the need for holistic neurocognitive assessment as a core component of care in young children with SCA and a focus on cognition, particularly EF, as an important study outcome (Kassim & DeBaun, 2014). The determination of what interventions will be most effective in children with SCD is the next avenue for investigation. For example, in a preschool child with SCA who has indicators of OSA, a sleep intervention, such as the removal of their adenoids and tonsils may be best suited\textsuperscript{14}, while a child who does not have indications of clinically significant OSA may benefit from a family-based intervention that

\textsuperscript{14} The researcher has recently submitted a grant as the named research worker to investigate this question
could promote executive development based on the strong case for the importance of family functioning in the patient group. Only one study has applied a family intervention in families with older children with SCA; however, it did not focus on aspects of family function highlighted in this thesis, instead focusing on problem-solving for disease management, and experienced high rates of attrition (Daniel et al., 2015). Future intervention research is required that focuses on family interventions that promote cognitive development in families with young children with SCD (Neville et al., 2013), specifically for the domains of family supportiveness and conflict, which were more negatively reported in the families with SCD in the current study.

8.7 Final Conclusions

Reliable and valid tasks of EF appropriate for preschool children were developed and validated. The battery of tasks was used to traverse a previously unchartered area of research: EF in preschool children with SCD. This thesis presents evidence for poorer executive performance in the patients with SCD, particularly in the domains of attention control and switching. Evidence for poorer attention control in the patients was also observed on a neuronal level using ERP methodology. The impact of poorer family functioning on EF development was observed across multiple domains of EF, with some evidence for an influence of other factors such as sleep problems and CBFV on specific executive domains. Considering children with SCD have higher rates of sleep problems and parents report poorer family dynamics than their typically developing peers, the impact of these factors on executive development warrants further investigation.

8.8 Post-doctoral Research

The researcher is continuing to work on projects arising from and related to the current thesis work. A small Grand Challenges grant has allowed for the
development of a training video for the PETA and a grant has been submitted to develop and standardise a B version of the task. The researcher has co-written and submitted a grant as the named research worker to look at the impact of a sleep intervention on EF in preschool children with SCA and OSA to Action Medical Research for Children. The researcher is also currently working as a research associate on two related projects; looking at the development of cognition in children diagnosed with epilepsy in infancy (EPIPEG) and investigating the neurocognitive impact of a sleep intervention on patients over eight years with SCD (POMS: Phase 2 randomised controlled trial of auto-adjusting continuous positive airways pressure).

8.9 Key Points

- Executive functioning can be reliably and validly measured in three to five year olds
- Ecological assessment is an important asset to an assessment protocol in order to establish the functional implications of executive deficits and to guide support
- ERP methodology can be utilized to measure executive functioning on a neural level in preschool children if the task is appropriately adapted
- Poorer family functioning is reported by parents of young children with SCA, particularly in the domains of supportiveness and conflict
- Preschool children with SCA have higher parent-reported indications of sleep-disordered breathing in comparison to matched controls
- Preschool children with SCA who are otherwise healthy show poorer executive functioning, specifically in the domains of switching and attention control
- Family functioning plays an important role in the promotion of EF in children with SCA and should be a focus for intervention
- Preschool children with SCD show evidence of diminished neurophysiological modulation on a task of selective auditory attentio
9 Appendices

9.1 Ethical approval letters

National Research Ethics Service Approval

13 August 2013

Professor Fenella Kirkham
Professor of Paediatric Neurology and Consultant Paediatric Neurologist
UCL Institute of Child Health
Neurosciences Unit
4/5 Long Yard
London, UK
WC1N 2AP

Dear Professor Kirkham,

Study title: Development of processing speed and attention in young children with and without sickle cell disease.

REC reference: 135.0.0962
IRAS project ID: 119518

Thank you for your letter of 29 July 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Dr Ashley Totenhofer, nrescommittee.london-bloomsbury@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.
Research and Innovation Approval

Professor Fenella Kirkham
UCL Institute of Child Health (ICH)
Neurosciences Unit

Dear Professor Fenella Kirkham

PROJECT TITLE Development of processing speed and attention in young children with and without Sickle Cell Disease
Protocol version 1
Protocol date 24th April 2013
R&D Reference 12NR27
Funder CHRAT Studentship
Sponsor ICH (UCL)

This project has been granted Management Approval by the R&I Office.

Approval Conditions:

You must submit an annual report which will be sent to you by the R&I office when it is due.

The PI must inform the R&I office of any changes to the start and end dates of the project, or if there are any changes to the protocol or personnel. At the end of the study the PI will be sent a final report form to complete and return to the R&I Office.

Please contact the Joint R&D Office if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Yours sincerely,

Dr Thomas Lewis
Research Management and Governance Officer
Joint R&D Office

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Non NHS/JCHR&D Approval 12NR27 Professor Fenella Kirkham
Approval for amendment of protocol to collect normative data for PETA

Health Research Authority
National Research Ethics Service

NRES Committee London - Bloomsbury
HRA NHS Centre Manchester
Barlow House 3rd Floor
4 Mindmill Street
Manchester
M1 3DZ

Tel: 0161 625 7815
Fax: 0161 625 7299

20 November 2014

Professor Fenella Kirkham
Professor of Paediatric Neurology and Consultant Paediatric Neurologist
UCL Institute of Child Health
Neurosciences Unit
4/5 Long Yard
London, UK
WC1N 2AP

Dear Professor Kirkham

Study title: Development of processing speed and attention in young children with and without sickle cell disease
REC reference: 13/LO/0962
Amendment number: Modified Amendment 1
Amendment date: 10 November 2014
IRAS project ID: 119518

- The proposed amendment is to collect the behavioural part of the protocol with a cohort of 94 typically developing children on school sites.

Thank you for submitting the above amendment, which was received on 11 November 2014. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter dated 30 October 2014 refers).

The modified amendment was reviewed at the meeting of the Sub-Committee held on 19 November 2014. A list of the members who took part in the review is attached.

Ethical opinion

There were no ethical issues raised.

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.
Research Approval for Recruitment of patients at Barts Health NHS Trust

FINAL R&D APPROVAL
13 February 2014
Dr Paul Telfer
Barts Health NHS Trust
4th Floor Pathology and Pharmacy Building
80 Newark Street
Whitechapel
London E1 2ES

Dear Dr Telfer,

Protocol: Development of processing speed and attention in young children with and without sickle cell disease.
ReDA Ref: 009505
REC Ref: 13/LO/0962

I am pleased to inform you that the Joint Research Management Office for Barts Health NHS Trust and Queen Mary University of London has approved the above referenced study and in so doing has ensured that there is appropriate indemnity cover against any negligence that may occur during the course of your project. Approved study documents are as follows:

<table>
<thead>
<tr>
<th>Type</th>
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<tr>
<td>Protocol</td>
<td>1</td>
<td>24 April 2013</td>
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<tr>
<td>Participant Information Sheet - Parent</td>
<td>2.0</td>
<td>10 July 2013</td>
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<td>Participant Consent Form - Parent</td>
<td>2.0</td>
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<tr>
<td>Participant Information Sheet - Child</td>
<td>2.0</td>
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<td>Participant Consent Form - Photography / Video Recording</td>
<td>2.0</td>
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<td>Participant Brochure</td>
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Please note that all research within the NHS is subject to the Research Governance Framework for Health and Social Care, 2005. If you are unfamiliar with the standards contained in this document, or the BH and QMUL policies that reinforce them, you can obtain details from the Joint Research Management Office or go to: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

You must stay in touch with the Joint Research Management Office during the course of the research project, in particular:
• If there is a change of Principal Investigator
• When the project finishes
• If amendments are made, whether substantial or non-substantial
Researcher Letter of Access to Barts Health NHS Trust

Barts Health NHS

Our ref: LOA-UR

Michelle Downes
PhD Student
Developmental Cognitive Neuroscience Unit
Institute of Child Health
University College London
30 Guilford Street
London
WC1N 1EH

30th January 2014

Dear Miss Downes

Letter of access for research

This letter confirms your right of access to conduct research through Barts Health NHS Trust for the purpose and on the terms and conditions set out below. This right of access commences with immediate effect and ends on 14th October 2015 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Barts Health NHS Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Barts Health NHS Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Barts Health NHS Trust, you will remain accountable to your employer University College London but you are required to follow the reasonable instructions of Dr Paul Telfer, Consultant in this NHS organisation or those given on his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to cooperate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.
9.2 Study consent and recruitment documents

Consent Forms

Main Study Consent Form (V2 10.7.2013)

A look at how Sickle Cell Disease can affect Thinking Skills
Consent/Assent for parent v2 10.07.2013

Please read each of the following statements and initial the boxes before signing the form.

1. I confirm that I have read and understand the information sheet (V.2; 10.07.13) for the above study.

2. I have had the opportunity to consider the information and ask any questions.

3. I understand that my participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without our medical care or legal rights being affected.

4. I will allow the research team to access relevant medical information via my child’s consultant.

5. I wish for my child to take part in the research study looking at neuropsychological function.

6. I will allow the research team to record audio/video to be analysed at a later time.

7. I wish for my GP to be informed of my participation in this study.

8. I agree for anonymous findings to be used in future studies.

9. I understand that relevant sections of my child’s medical notes and data collected during the study may be looked at by individuals from the Sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child’s records.

Participant’s Name

Name of Guardian Date Signature

Name of Person taking consent Date Signature

Chief Researcher Date Signature

UCL Institute of Child Health, Neurosciences Unit, London WC1N 1EH
Tel: +44 (0)20 7599 4116 Fax: +44 (0)20 7430 0032
www.icn.ucl.ac.uk

Working in partnership with
Great Ormond Street Hospital for Children NHS Trust
The child first and always
Video Consent From (V2 10.7.2013)

CONSENT TO PHOTOGRAPHY OR VIDEO RECORDING
Video consent V2 10.07.2013

Our policy for recording of photography or video is in line with the Data Protection Act, which gives you the right to control future use of photographs or video recordings taken of you.

We confirm that the video recording and the storage of the resulting images will take place in line with the ICH policy for making use of illustrative records, and we will take the appropriate photographs in a dignified manner.

This consent limits their use to the research or teaching purposes as outlined below and should it be desired to use your video in any other way—for example, in a textbook or for advertising purposes, we will seek your specific permission to do so.

Researcher’s Name:
Researcher’s Signature:

CONSENT

In view of this explanation (please initial as appropriate)

☐ I consent to their use in student projects or theses
☐ I consent to their use for teaching purposes
☐ I consent to the video being shared in an academic domain for educational purposes

Signature of Parent:
Date:
A Look at Thinking Skills
Consent/Assent for parent (pre-school) V.2; 31.10.14

Please read each of the following statements and initial the boxes before signing and returning the form to your child's school in the enclosed envelope.

1. I confirm that I have read and understand the information sheet (V.2; 31.10.14) for the above study.

2. I have had the opportunity to consider the information and ask any questions.

3. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason.

4. I wish for my child to take part in the research activity that will take place for up to 20 minutes at their preschool/school.

5. I agree for anonymous findings to be used in future studies.

Participant's Name

Participant's Date of Birth

Participant's Gender

Participants' ethnicity

Any relevant medical information/special requirements?

Name of Guardian

Date

Signature

Name of Person receiving consent form

Date

Signature

UCL Institute of Child Health, Cognitive Neuroscience and Neuropsychiatry Section,
London WC1N 1EH
Tel: +44 (0)20 7599 4116    Fax: +44 (0)20 7430 0032
www.ich.ucl.ac.uk

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**Information sheets**

**Parent Information Sheet for Patients (V2 10.7.2013)**

**A look at how Sickle Cell Disease can affect Thinking Skills**

*Participant information sheet SCD for parent v.2 10.07.2013*

**Why is this study being done?**
We invite you to participate in this study because your child is between 3 and 5 years and has previously been treated for sickle cell disease at Barts Health NHS Trust.

Our aim is to develop ways to detect cognitive difficulties related to sickle cell disease before children enter the school system. We will look at thinking skills in preschool children with and without sickle cell disease.

**Who is conducting the study?**
This project is being carried out by researchers from the Institute of Child Health at University College London.

**Who can take part?**
We would like to invite children between the ages of 3 and 5 with and without a diagnosis of sickle cell disease.

**What will my child have to do?**
The research will take up to 3 hours of your and your child’s time. During this time, your child will have lots of chances to have snack breaks and resting periods.

The testing session will be divided into three parts. Firstly, we will look at intelligence using a test that involves your child doing some tasks that involve pictures and words. Then your child will play some short games such as sorting cards. Each game will measure a slightly different function, such as planning or attention. Finally, your child will engage some tasks that involve looking at videos and listening to stories. Brain wave tasks involve wearing a funny hat that sends brain waves to a machine.

Your child’s oxygen saturation, haemoglobin and carbon dioxide levels will also be monitored using a pulse oximeter, a machine that has small tubes which can be placed close to the nose as well as an end placed on the finger for a few minutes.

**What will I have to do?**
While your child is engaged in tasks with the examiner, you will be asked to fill in some short questionnaires which will ask you about your child’s sleeping, behaviour, and overall well-being.

You will present for the testing session but we ask that you do not help or interrupt your child while they are doing tasks or playing games.

**What will you do with the information that you collect from my child?**
All information collected as part of the study will remain completely confidential and anonymous. If you decided you would like your child to take part and they are also happy to participate, they will be
assigned a number. Your personal information will be stored securely in a locked filing cabinet within the Institute of Child Health.

The results of this study will be used as part of a PhD project, and may be published in peer reviewed scientific journals or presented at conferences. No names, addresses or any identifying information will be used in any of these reports.

**Who will know that we are taking part?**

Only the research team and your child's GP will know you are taking part. When your child joins the project, we will inform your GP that he/she is participating in this study.

**What are the benefits of my child taking part in this study?**

There are no direct benefits of the study other than a fun experience for your child. The tasks will be presented alongside a sticker reward system so that your child can track their progress. We can also offer to take a picture when they wear the funny brainwave hat and every child will receive a thank you gift. Your travel costs will also be reimbursed.

If I decide to let my child take part, are there any risks involved?

Neuropsychological assessment can be a fun and enjoyable experience for children; but, there is the chance that your child will get bored and restless. If a break does not help the situation, we can stop the assessment at any point.

It is possible that your child will not feel comfortable wearing the hat that looks at brain waves. They will first be shown a teddy with the hat on and the hat will be presented in a fun way but if he/she still does not want to wear it, we can stop the assessment. If your child does not like the pulse oximeter, we can stop the measurement.

**Video/Photo recordings**

Video footage will be taken during some of the behavioural tasks. This recording will be completely confidential and will only be accessed by the research team. It will be stored securely along with other information that we collect. If you would prefer not to have any video recording of your child, then you can indicate this on the consent form. You may also be asked for a photo or a video recording of your child while participating in the study to be used for educational/teaching purposes. This will involve a separate photo/video recording consent form that you can decide not to sign. This will not affect your child’s treatment or participation in the study.

**Who is funding this study?**

We are funded by the Child Health Research Appeal Trust (CHRAT). This foundation supports research at the Institute of Child Health and Great Ormond Street Hospital for Children. This study is being done as part of an educational project for a PhD.

**Does my child have to take part?**

No. Participation in this study is completely voluntary. If you decide not to participate it will not affect the care that your child receives. If you decide to take part, you are free to withdraw at any point, and again this will not affect your child’s care in any way.

**Who should I contact if I would like to take part?**

Your participation in this study is voluntary. If you decide to take part, please contact a member of the research team:

UCL Institute of Child Health, Neurosciences Unit,
London WC1N 3JF
Tel: +44 (0)20 7997 4126 Fax: +44 (0)20 7997 4052
www.ucl.ac.uk

Michello Downes, PhD student on G207 005 2644 or at michello.downes@ucl.ac.uk.

If you agree to participate you will be asked to sign a consent form. Before you do this, please ensure you have fully read this information sheet and that you have had the opportunity to ask questions.

**Who do I contact with any questions?**

If you have any questions or concerns about the study, contact:

Dr Feneila Kirkham
fenelia.kirkham@ucl.ac.uk
Tel: 0238 070 4765, Mobile: 0706 808 8079

If you have questions or concerns about your privacy and the use of your protected health information, please contact the Data Protection Officer for the Institute of Child Health, Tel: 020 3549 5111. If you wish to complain during the study you can contact PALS at Great Ormond Street Hospital NHS Trust in person, by phone on 020 7929 7662 or by email at pals@gosh.nhs.uk. The normal National Health Service complaints procedure would be available to you.

**Thank you for reading this – please ask any questions if you want to.**
Participant Information Sheet for Children (V2 10.7.2013)

This study involves doing some tasks and games. We are inviting lots of children, with and without sickle cell to take part. We want to see how different people use their brains in different ways!

What will I be asked to do?
If you want to take part in our study you will be doing three types of things:
1. You will play some games and puzzles!
2. You will watch some videos!
3. You will listen to some stories while wearing a funny hat just like the EEG hat in the picture!

Parent Information Sheet for Phase Two School Recruitment (V 31.10.14)
Recruitment documents

Study Brochure (V2 10.7.13)

Study Poster (V2 10.7.13)
Ethically Approved recruitment notice for on-line and e-mail use (V2 10.7.13)
Are you and your child interested in participating in our study?

Thinking Skills in Preschool Children

If your child is between 2 and 5 years, we would like to hear from you.

The study looks at the development of thinking skills in preschool children.

We are inviting you and your child to visit us at the Institute of Child Health for a series of stimulating, enjoyable and engaging tasks. These will involve playing games, solving puzzles and completing tasks while we look on and observe your child's thinking. We aim to make this a fun experience for your child and there is plenty of opportunity to ask questions.

The visit will take up to 2 hours at a time that will suit you and your child.

If you are interested in taking part, you can contact the research team by phone or email at the details below for further information.

Tel: +44(0) 20 7905 2644
Email: ich.babylab@ucl.ac.uk or michelle.downes@ucl.ac.uk

UCL INSTITUTE OF CHILD HEALTH

9.3 FES Approval letter
9.4 DDTP Task Documents

Doggie Deletion Task for Preschoolers: Instructions

Task Introduction and Development

This task was developed based on a task used to measure attention in preschool-age children (Corkum et al., 1995). Custom dog stimuli were designed to vary only in position. The child undergoes a teaching phase and a practice phase with shapes before the testing phase. This is to ensure that they can hold and use the bingo stamper successfully and can understand the task instructions. The aim is to stamp the
target stimuli as cued by the image on the top of the page. The original design of the task was not suited to some typically developing 3 year-old pilot children. The task was modified so that the examiner terminates the task if a child remains off-task for greater than a 20 second block. Omission/commission errors and time to completion/termination are coded.

Design

Training phase: The preschooler is taught to identify the target pictures and to use a washable, self-inking bingo stamper to mark each target (in a 2 × 6 array).

Practice phase: This is continued until the preschooler accurately identifies all targets and makes no errors of commission. This phase consists of two pages upon which the target ([30]: triangle) and distracter ([90]: circle, square, diamond, and octagon) are arranged in a 10 × 6 array. After successful completion of the training phase, the child can continue onto the test phase.

Test Phase: This contains 8 pages; each page consisted of a 10 × 6 array of target ([120]: standing dogs) and distracter ([360]: four identical dogs varying in position only). The target picture is located at the top and centre of each page for the child’s reference. The pictures are randomly organised, with 15 targets and 45 distracters in each array.

Motor Speed Phase: This phase is to be administered last. The child is asked to start at the dog circle and end at the dog’s house circle, going as fast as they possibly can.

Administration Instructions

Training Phase:
Examiner: In this game, you have to stamp all the shapes down here that match the one up here (point to top centre triangle).
Examiner marks triangle in top row with bingo stamper.

Examiner: ‘Child’s name’ do you want to have a go at stamping the shapes down here (point to bottom row) that match the shapes up here?

Once child stamps the two triangles successfully, move to practice phase.

**Practice Phase:**

Examiner: Now ‘Child’s name,’ we have two more pages of shapes. This time you have to stamp all the shapes that look like this one all by yourself. Remember that you don’t need to stamp the shape at the top here (point to centre top triangle) because this is just there to remind you what ones you need to stamp. Any questions?

Examiner: Great. Start at the top and go as quickly as you can without missing any and let me know when you are done! When you are finished the first page, move to the second page and keep going until the end.

*If the child makes 6 or more consecutive errors, return to training phase for further instruction.

*Examiner: Look at the shape here, what one here (points to row) matches this one up here (points to top centre triangle).

*Once child understands task, they should resume practice phase until end. If 6 or more further consecutive errors are made, terminate task. Examiner must note the total time, whether the child needed to return to training phase, and why the task was terminated early. Examiner should proceed to motor speed phase.

On successful completion of practice phase, move to test phase.
Test Phase:

So “child’s name” do you have any pets at home or do you know anyone who has a pet? What pet? What is his name? Well see on this page we have a picture of my pet dog ‘Jaydee.’ There is also some other dogs but they are not standing up like this one. Look, some of them are sitting down and some are facing in another direction. We have eight pages this time and I want you to stamp all the doggies that look like this one. Once you finish this page, keep going until you reach the end.

If a child is off-task for a 20 second block, examiner offers a cue.

Examiner: Remember, you have to go as fast as you can until the end, only a few more pages to go.

Off-task = 1. Attempting to engage with examiner/parent
2. Begins to scribble/draw picture
3. Stops and stares
4. Gets up from table and walks around room/picks up something else
i.e. the child is doing anything but actively seeking out the targets

After initial cue, there are three potential outcomes:

1. Child returns to task and completes to end.

2. Child attempts to engage examiner in conversation where the following response is acceptable:

Examiner: Remember you have to do this is fast as you can without any help from me.

3. Child returns to task but goes off-task for a further 20 seconds at which the examiner immediately terminates task and stops timing. Examiner should proceed to motor speed phase.
4. Child refuses to return to task at which point the examiner terminates task and stops timing. Examiner should proceed to motor speed phase.

Motor Speed Phase:

Examiner: Well done! Now we are going to do my favourite bit. I want you to trace this line as fast as you can to get the dog from here (point) to here (point). Wait until I say go as I am timing how fast you can go! Are you ready? GO!

Scoring

The amount of omissions, commissions, and time to completion should be coded along with whether a cue was offered or not during the testing phase. Time to complete motor phase should also be coded.

In cases where child does not complete task to end, the examiner still codes the omissions, commissions, and time to completion but adjusts or pro-rates scores by dividing by the number of pages attempted.

Doggie Deletion Task for Preschoolers: Score Sheet

Practice C/O: Practice Time: Practice cues?:

Task Completion Time:

Commission: Omission:

Motor Speed Task:
Off task for 20 seconds?: Once/Twice/None

*CUES: Response to “I am done”-“You have to stamp all of the doggies on all of the pages” Response to participant skipping page/skipping 2 pages when turning/not
### 9.5.1 PETA Manual Excerpt

Full Manual >50 pages available from michelle.downes@ucl.ac.uk

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**PETA Manual Contents**

- Acknowledgments & Contact Information
- Introductory Letter
- Manual
-Introduction
  Rationale
  Key features
  Background
  Description of task
  Psychometric features

-Basic Administration
  Material Placement
  Administration
    Step1: Pre-task Questionnaire
    Step2: Initiation
    Step3: Adding green circle
    Step4: Adding red circle
    Step5: Adding yellow circle
    Step6: Adding antennae
    Step7: Adding red stamp
    Step8: Let stamp dry 1 minute/timer use
    Step9: Adding blue cloud and eyes/mouth
    Step10: Cutting the grass and bending it
    Step 11: Avoidance of dangerous situations
    Step12: Completion
    Step13: Post-task Questionnaire

-HELPFUL HINTS
  Administration
  Cueing

  Cueing system
  How to cue
  When to cue

-Troubleshooting

  Children's behaviour

  Illustrations of potential errors
    a. Video Error
    b. Timing Error

  Incorrect set-up
  Examiner cueing Error

  Potentially ambiguous situations
  Potentially difficult parent behaviours

-Scoring

  1. Total cues
2. Total score
3. Total Time
4. Highest level
5. Executive subdomains

-Cueing Script
Step1: Pre-task Questionnaire
Step2: Initiation
Step3: Adding green circle
Step4: Adding red circle
Step5: Adding yellow circle
Step6: Adding antennae
Step7: Adding red stamp
Step8: Let stamp dry 1 minute/timer use
Step9: Adding blue cloud and eyes/mouth
Step10: Cutting the grass and bending it
Step11: Avoidance of dangerous situations
Step12: Completion
Step13: Post-task Questionnaire

-Additional Information
-Equipment Guide
-Checklist
-Scoresheets (attached separate)
-Sample Recipe Book (attached separate)

PETA Manual Introductory Letter

Dear Researcher,

Thank you for your interest in using this ecologically valid task of executive functions designed for children aged 3 to 5 years 12 months.

Included in this pack, you will find a manual which will guide you through administering and scoring the task and show you how to set-up successfully. You will also find a ‘recipe book’ guide and a score sheet as well as a checklist. The task training video is available on request. In exchange for use of these materials, we ask that you make available your data so that we can create standardised scores and develop this assessment even further.
The PETA is a formal cognitive task and requires strict adherence to the instructions in terms of administration and scoring, this is important in order to increase the validity of the assessment. The administrator must avoid bias in terms of a child’s ability to perform the task as this will affect how they cue and consequently score the assessment. The administrator must also be careful that the parent fills out questionnaires of executive functioning/behaviour beforehand if they are to be present as observing the assessment may influence their responses. It is also crucial that the researcher has practiced administering the task several times and that they video record themselves until they are confident that they can administer the task without any errors. By recording yourself, you may observe subtle gestures or supports that you were not aware that you were doing in this unnatural structured context.

Please cite this measure as:


If you would like further information about this measure or have any questions, please contact michelle.downes@ucl.ac.uk. We hope that you enjoy administering the task and welcome any feedback that you may have. Please gain permission from Michelle Downes or Christine Berg before sharing this assessment pack.

All the best,

Michelle & Christine
9.6 Executive functioning: Extended control group

This supplementary section includes additional appropriately matched children who are matched on all factors (age, IQ, SES, gender) except for ethnicity. In this section the ethnicity-matched children are combined with twelve other typically developing children who were assessed by the researcher in the London Babylab during Phase one to form a larger control group in order to draw further comparisons with the patient group performance on each task.

TableS1 inhibitory Control and Processing Speed: Group means for the NIHTB tasks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=20) M(SD)</th>
<th>Ethnicity Matched Controls Only (n=13) M(SD)</th>
<th>p</th>
<th>Controls (n=23) M(SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Inhibitory Control Age adjusted SS</td>
<td>92.38(22.6)</td>
<td>98.45(21.8)</td>
<td>.38</td>
<td>102.13(18.6)</td>
<td>.07</td>
</tr>
<tr>
<td>NIH Processing Speed</td>
<td>80.28(12.71)</td>
<td>85.9(14.9)</td>
<td>.27</td>
<td>85.4(14.2)</td>
<td>.69</td>
</tr>
</tbody>
</table>
**Table S2 Attention:** Group differences for DDTP variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCA Group</th>
<th>Ethnicity Matched</th>
<th>p</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>Controls Only</td>
<td>M (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Tested</td>
<td>22</td>
<td>12</td>
<td></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>N Passed</td>
<td>18</td>
<td>11</td>
<td></td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Commissions</td>
<td>77.9 (111.2)</td>
<td>13.6 (22.7)</td>
<td>.04</td>
<td>11.5 (19.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Omissions</td>
<td>22.9 (22.9)</td>
<td>26.7 (30.4)</td>
<td>.73</td>
<td>26.4 (27.6)</td>
<td>.65</td>
</tr>
<tr>
<td>Time to Complete</td>
<td>12.1 (4.9)</td>
<td>11.06 (4.2)</td>
<td>.52</td>
<td>10.6 (4.0)</td>
<td>.34</td>
</tr>
<tr>
<td>Motor Speed</td>
<td>51.9 (13.7)</td>
<td>46.6 (8.3)</td>
<td>.54</td>
<td>46.6 (8.3)</td>
<td>.26</td>
</tr>
</tbody>
</table>
**Table S3 Cognitive Flexibility:** Group means for EF Scale for Early Childhood

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=20)</th>
<th>Ethnicity Matched Controls Only (n=12)</th>
<th>p</th>
<th>Controls (n=16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switching Score/no. of correct trials</td>
<td>46.6 (14.4)</td>
<td>56.9(9.7)</td>
<td>.046</td>
<td>56.9(9.1)</td>
<td>.003</td>
</tr>
<tr>
<td>Highest Level</td>
<td>4.3</td>
<td>5.6(1.2)</td>
<td>.011</td>
<td>5.6(1.1)</td>
<td>.001</td>
</tr>
</tbody>
</table>

**Table S4 Working Memory:** Group means for variables on the Scrambled Memory Task

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCA Group (n=22)</th>
<th>Ethnicity Matched Controls Only (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>Total Number of Trials</td>
<td>14.68(3.92)</td>
<td>14.64(3.99)</td>
<td>.98</td>
</tr>
<tr>
<td>Required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consecutively Correct Trials</td>
<td>5.63(2.21)</td>
<td>5.28(1.49)</td>
<td>.67</td>
</tr>
</tbody>
</table>
10 References


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