Altered neurophysiological processing of auditory attention in preschool children with sickle cell disease

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Running Title: Neurophysiological processing in sickle cell disease

Abstract
Objective: Sickle cell disease is a genetic red blood cell disorder that often leads to stroke and executive dysfunction in school-age children and adults. This study aimed to characterise the development of the neural correlates of selective attention, an early component of executive function, in preschool children with sickle cell disease.
Methods: Auditory event-related potentials were recorded while children attended to a story stream in one ear and ignored a second story in the other ear interchangeably.
Twelve patients (mean age = 5.5, 7 males) and 22 typically developing children (mean age = 4.4, 10 males) were included in the final analyses. Results: By 100 ms, more positive ERP amplitudes were observed for attended relative to unattended stimuli in typically developing children but not those with sickle cell disease, suggesting deficits in the ability to focus attention. Reduced attention effects were associated with lower performance IQ. Conclusion: There are deficits in early attention modulation in young children with sickle cell disease.

**Key words:** Sickle cell disease, Neuropsychology, Attention, Developmental Disabilities, Academic Functioning

**Abbreviations:** ERP=event related potential, MRI=magnetic resonance imaging, SCD=sickle cell disease

Sickle cell disease (SCD) is a blood disorder that can result in a global pattern of diffuse brain injury, thought in part to be secondary to chronic anaemia and hypoxia (Baldeweg et al., 2006; Steen et al., 2005). Clinical stroke, a focal neurological event lasting more than 24 hours, and silent stroke, which results in small lesions that can only be observed through structural magnetic resonance imaging (MRI), are commonly reported in patients with SCD, but volumetric differences can also be observed in quantitative
imaging studies even when structural MRI appears normal (Jordan & DeBaun, 2017; Land et al., 2015). The frontal lobes have a protracted period of development and the fronto-parietal regions, supplied by the internal carotid artery and the middle and anterior cerebral arteries, are most commonly affected by stroke in SCD (Ohene-Frempong et al., 1998). There is also evidence for abnormal cerebral blood flow despite normal MRI (Prohovnik, Hurlet-Jensen, Adams, De Vivo, & Pavlakis, 2009). As a result, the frontal lobe and its connections are thought to be the most susceptible areas to SCD related pathology.

The frontal cortex plays a prominent role in the brain network underlying executive skills, the cognitive domain most affected in children with SCD with or without visible tissue injury (Hogan, Telfer, Kirkham, & de Haan, 2013; Schatz, Finke, Kellett, & Kramer, 2002; Wang et al., 2001; Watkins et al., 1998). Neurocognitive deficits appear early in development impacting IQ and school readiness, however the developmental trajectory of executive skills in children with SCD compared with their peers remains unclear (Hogan et al., 2013; Noll et al., 2001; Steen et al., 2002; Tarazi, Grant, Ely, & Barakat, 2007; Thompson, Gustafson, Bonner, & Ware, 2002).

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 to target stimuli and ignore irrelevant environmental information is present from early in life but the speed and efficiency of these processes increase with age (Ridderinkhof & van der Stelt, 2000). Selective attention and the neural systems that underlie this process undergo significant development in the preschool years (Rueda, Posner, & Rothbart, 2004; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005). As well as laying down a foundation for the development of later emerging
executive skills, selective attention also plays a role in other cognitive domains such as language, writing, and mathematics (Engle & Kane, 2004; Stevens & Bavelier, 2012), and is an important predictor of school readiness and academic achievement (Duncan et al., 2007; Rueda, Checa, & Rothbart, 2010). Few studies have attempted to study selective attention skills in detail in SCD. A recent study found specific selective attention deficits on the Test of Everyday Attention in a sample of adults with SCD as compared to matched controls, despite no evidence of MRI pathology (Vichinsky et al., 2010). Many developmental models of executive function depict it as a process of simpler skills, such as selective attention, emerging first which are then bootstrapped into more complex executive skills (Anderson, 2002). Understanding when deficits emerge may be a first step to preventing potential snowballing effects of early skill deficits impacting the emergence of more complex skills.

The use of event-related potential (ERP) and electroencephalography (EEG) techniques offers a window into potential differences in the brain functions underlying executive skills such as selective attention. EEG is the measurement of continuous electrical activity in the brain while the ERP is a voltage change that is time-locked to a specific stimulus. An ERP is acquired by averaging multiple trials so that the EEG signal of interest can be isolated from other brain activity (Taylor & Baldeweg, 2002). ERP components are averaged waveforms that have been attributed to a certain cognitive or sensory process (Downes, Bathelt, & de Haan, 2017). ERPs have high temporal resolution, are not prone to examiner bias, and offer the opportunity to conduct robust investigations of executive functions using a multi-level methodology (Astle & Scerif, 2009).

Hillyard and colleagues first identified the ERP index of selective auditory attention in adults using a dichotic listening task where the adults were instructed to
pay attention to a series of tones presented in one ear and to ignore tones in the other ear (Hillyard et al., 1973). In response to these tones, adults typically show an early positivity (P1) followed by a negative component (N1) at about 100 milliseconds and a second positivity (P2) at approximately 200 milliseconds (Nager, Estorf, & Münte, 2006). Selective attention is observed in adults as a larger N1 for the attended stimuli relative to the unattended stimuli.

Instead of the P1-N1-P2 response observed in adults, children tend to show an elongated broad positivity that starts at approximately 100 milliseconds in the same conditions (Sharma, Kraus, McGee, & Nicol, 1997). ERP research using dichotic listening paradigms has shown that children as young as three years can selectively attend to one auditory source while ignoring another (Sanders et al., 2006; Sanders & Zobel, 2012). In response to probe stimuli, preschool children from 3-years-old have been found to produce a broad positivity that extends from 100 to approximately 300 milliseconds while 6 to 8-year-olds show a shorter positivity from 100 to 200 milliseconds (Sanders et al., 2006). This positivity is observed to have larger amplitudes in response to attended stimuli. The extended effect in younger children could reflect a prolonged influence of attention on neural processing and variability between and within children (Stevens & Bavelier, 2012). In a recent study, the transitions from the neurophysiological response observed in young children to the adult P1-N1-P2 response was investigated and it was found that the P1-N1-P2 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 (Karns et al., 2015). The P1-N1-P2 complex has a protracted developmental course and changes in functional development likely reflect the slow development of the fronto-parietal network (Ponton et al., 2000; Yurgelun-
The aim of this study is to explore potential neurophysiological differences in selective auditory attention in preschool children with SCD using an ecologically valid dichotic listening paradigm that was developed based on previous studies with preschool children (Isbell et al., 2016; Sanders et al., 2006). It is hypothesised that children with SCD will show less pronounced amplitudes as compared to the typically developing children in the attended condition and thereby demonstrate less of an attention effect. 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). 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 secondary aim is to look at associations between neural modulation and performance on behavioural tasks of non-verbal IQ and executive attention. It is hypothesised that the children with the poorest executive scores on the neuropsychological assessments will show the smallest attention effect in the ERP response.

Methods

Participants

Patients were informed of the study by their consultant haematologist at XXX during their routine clinical visit if they met the inclusionary criteria. Inclusionary criteria for the patient group and the control group included being aged between 36 and 72 months, fluent in English, and no history of stroke, brain MRI investigations, known neurological issues, other disorders, or pre-term delivery. A diagnosis of SCD based on genotype was required. The participation rate for patients was approximately 85%. Reasons for non-participation included unavailability or a lack of response after
referral. Three families cancelled the scheduled session. Control children were recruited through the same clinics as the patients and through local advertisement. Twenty-four patients (23 HbSS genotype and 1 HbSC genotype; FSIQ=98.8) and 38 typically developing control children (FSIQ=108.7) were recruited. All children spoke English as their first language. Mean averaged maximum velocity in the middle cerebral artery for patients at the most recent clinical visit was 155.3 (21.3) cm/sec; no patients had abnormal transcranial Doppler recordings (velocity >200 cm/sec). Five patients were currently on blood transfusion, four patients were being treated with hydroxyurea, and no patients reported experiencing current pain.

Thirty-four EEG datasets were available for analysis after pre-processing (12 patients (1 HbSC) and 22 comparison children; Table 1). Two patients and five controls were excluded due to EEG system error. Additionally, two patients and five controls were excluded due to removal of sensor net and/or headphones during the session. One control child had thick braids that prevented successful application of the apparatus. It was disclosed during assessment that a control child was born extremely pre-term and so was excluded from analysis. Additionally, one patient was diagnosed with SLI between recruitment and assessment, and one patient did not pass the training phase due to poor comprehension of instruction. Six patients and four controls were removed for not meeting the minimum criteria of 25 stimuli per condition after pre-processing. Final groups, including 12 patients and 22 control children, were matched for age, full scale IQ, socioeconomic status, and gender (Table 1), although only 36% of the control group was matched for ethnicity (Black British).

Selective auditory attention task

The ERP paradigm and processing pipeline was piloted with adults and two preschool-age children. Several measures were taken to make this task more age
appropriate including the development of training and practice phases. Custom static low-detail visual cues for on-screen presentation were developed to match the story to be attended. Arrows were created for on-screen presentation to reduce memory load. Fifteen short stories from Aesop’s classical fables were adapted to be age-appropriate. All stories were recorded in a male and a female voice so that the child was always attending to a male and a female voice concurrently, helping them to differentiate between the two auditory streams. Sound recordings were edited using Audacity software to remove gaps longer than 100 ms and to make the recordings comparable for loudness. Story narrators were instructed to keep their tone and pitch at a consistent level.

Auditory and visual stimuli were presented through age-appropriate adjustable headphones and on a Dell Optiplex (Dell Inc., TX) computer screen running Windows XP using a script programmed via Matlab 2012 R2012b (The MathWorks, MA) and Psychtoolbox V3 (Kleiner et al., 2007). The child watched a cartoon while the net was positioned. This was followed by a training session. The child was instructed to touch the ear that corresponded with the side that the arrow on the screen was pointing towards. After the training phase, the child undertook a practice session before EEG recording 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. The stimuli of interest, pure tone bursts of white noise with a length of 500ms, were randomly inserted into the attended and unattended streams at the same loudness level as the stories. At the beginning of each story the child heard “Are you ready?” and the researcher pressed a key to proceed. After each story, the child was asked questions relating to the attended story. The offset latency for the pure tone bursts of white noise was measured as 23 milliseconds using the EGI
latency-testing device. There was a maximum of 14 story trials that were each up to one minute in duration. The inter-stimulus-interval was 1.5 seconds. If the child expressed a request to end the testing session, the researcher asked if they would like to attempt one more story trial and terminated the session if the child did not agree.

Table 2 shows the average number of story trials completed for each group.

ERP Recording and Analysis

EEG data were 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 EEG was recorded using the Electrical Geodesics sensor net system 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. Channel impedances were adjusted where necessary and appropriate to levels below 50kΩ. An electroculogram was recorded for the detection of eye-related artefacts. Electrodes were positioned above and below and to the side of both eyes.

Offline, data were filtered with finite impulse response filters 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 (the pure tone bursts of white noise) to 600 milliseconds after stimulus presentation. Automatic epoch rejection of bad epochs occurred at a threshold of plus or minus 100 microvolts. The average voltage of the 200 milliseconds segment before stimulus onset was set as the baseline. 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 montage. The time window of interest (100 to 300 milliseconds) was chosen based on a review of the relevant literature for this age (Coch et al., 2005; Karns et al., 2015; Sanders, Stevens, Coch,
Neville, 2006; Sanders & Zobel, 2012; Stevens, Sanders, & Neville, 2006; Stevens et al., 2009). The mean peak amplitude for this time window was investigated. Trials were averaged together to acquire a single averaged segment for the *ignore* and *attend* condition for each participant. A criterion of a minimum of 25 artefact-free trials in each condition after all pre-processing steps was imposed. This figure is within the range of minimum number of trials required in similar ERP studies with young children (Coch, Sanders, & Neville, 2005; de 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 to obtain a reliable estimation of the ERP component under investigation (Cuevas, Cannon, Yoo, & Fox, 2014; DeBoer, Scott, Nelson, & de Haan, 2007). Each child completed up to 14 story 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 to maximize the number of artefact-free trials and were offered a teddy bear to hold if they struggled to stay still. To further improve signal-to-noise ratio, several channels were combined for channel-level analyses (Coch et al., 2005; Sanders & Zobel, 2012; Strait, Slater, Abecassis, & Kraus, 2014). Four electrode groupings (figure 1) are defined based on previous studies with similar age groups and paradigms and a topographical investigation of the current population (Coch et al., 2005; Sanders et al., 2006; Isbell et al., 2016).

Wechsler Preschool and Primary Scale of Intelligence

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-UK) (population mean=100, SD=15) was administered to obtain IQ (Wechsler, 2002). The IQ scores for the final groups were slightly higher than the original group means for both groups although executive scores were similar in the final group (Table 1) to that
observed for the original groups. Children were required to have a verbal IQ greater than 75 to proceed to the ERP task. This threshold was implemented to ensure that children could comprehend task instruction. The chosen cut-off was based on language cut-offs used in similar studies that used ERP paradigms to investigate attention in preschool-age children (Stevens, Lauinger, & Neville, 2009).

NIH toolbox test of attention control

The standardised NIH toolbox (NIHTB) test of attention control (population mean=100, SD=15) was administered. Poorer scores in the NIHTB task reflect longer reaction time and incorrect responses. The NIHTB task has been validated from three years of age (Zelazo et al., 2013). Five control participants had missing NIHTB data due to technical difficulties during data collection.

Doggie Deletion Task for Preschoolers

The Doggie Deletion Task for Preschoolers (DDTP), a revised cancellation task, was also used to measure attention control (Byrne, Bawden, DeWolfe, & Beattie, 1998). More omissions and commissions on the DDTP reflect poorer attention control. The DDTP task was previously developed with typically developing children at the XXX (Downes, Kirkham & de Haan, 2014).

Procedure

Ethical approval was obtained from the XXX NHS committee and site-specific approval was obtained from XXX. Written informed consent was obtained from each parent and verbal assent was obtained from each child. The testing session took place in the XXX. All consent procedures and data collection was conducted in English by the same researcher (MD). All children first completed the WPPSI-III-UK, followed by the DDTP and the NIHTB test of attention control, in that order. After a
scheduled break the child then completed the EEG session, which lasted approximately 30 minutes.

**Results**

**ERP Behavioural Results**

There were no group differences between the total number of completed story trials, number of correctly attended story trials, number of events before pre-processing or final number of events (Table 2).

**Group differences**

As expected, the control group showed a broad positivity peaking at approximately 150-200 ms post-stimulus onset. However, this was not observed for the patient group who showed a less pronounced and inconsistent amplitude (figure 2).

Overall group differences for attended and unattended conditions were further explored across the four frontal clusters of interest using a multivariate analysis of variance (ANOVA). Consistent with previous studies, the control group showed the attention effect (a larger response to the attended signal) to be greatest at the frontomedial site in comparison to the other three sites of interest, however this did not reach significance ($F(2.2,46.19) =2.164, p=.10$). In contrast to the control group, the patients did not show as strong an effect for the attended condition at any of the sites (see figure 3). The control group 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 ($t=.60, p=.56$). The frontomedial electrode grouping was chosen from the four clusters of interest for further analysis. Mean amplitudes were analysed using a two-way univariate ANOVA with group (patient vs control) and condition (attended vs unattended) as the between-subject factors and the mean amplitudes at the frontomedial site as the within subject factor. The two mechanisms underlying attention
modulation in this task, enhancement of the amplitude in the attended condition and suppression of the amplitude in the unattended condition, were analysed. Significant group differences were observed between groups for amplitude in the attended condition at the frontomedial site with the control group showing larger mean amplitudes ($t=2.2$, $p=.03$), but no group differences were observed for the unattended condition ($t=-.12$, $p=.91$). Table 3 shows that, although there was greater mean amplitudes for the control group in the attended condition on the other sites, this did not reach significance ($F(4,29)=1.72$, $p=.16$) and there was no trend observed at any site for the unattended condition.

The Attention Effect and removal of outliers

Near significant group differences were observed for the magnitude of the attention effect (the difference between the attended and unattended conditions) at the fronto-medial site ($t=1.8$, $p=.07$). Group analyses were repeated to ensure that the three outliers in the negative range for the attention effect in the control group (all three-year-olds- suggesting more variability in the youngest children) and the main outlier in the patient group were not having effect on group differences. The group difference for the attention effect (attended-unattended) reached significance ($p=.006$) after removal of outliers. The post-hoc group difference observed for the attended condition also increased in significance ($p=.013$) although the lack of a group difference observed for the unattended condition remained the same.

Associations with cognitive measures

There was no relation observed between performance IQ and the attention effect using Pearson’s correlations although a greater positivity in the attended condition was significantly associated with performance IQ ($r=.483$, $p=.004$; figure 4 A). When the groups were separated, this association remained significant for the patients ($r=.619$,
p=.040) but became a near significant trend for the control children (r=.415, p=.055). Associations with omissions and commissions on the DDTP were explored using Spearman’s correlations (as scores were not normally distributed) 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; figure 4 B) and for the control group (rho=.583, p=.036) and patient group separately (rho=.717, p=.045). No associations with commissions were observed. The significance of the DDTP findings did not change when outliers were removed. No significant correlations emerged for the NIH attention control task.

Discussion

Previous research with preschool children in special populations who have known executive deficits has found evidence for altered neural processing in auditory attention modulation (Stevens et al., 2006; 2009). Here, we extend this research to children with SCD. The main finding is that children with SCD show a less pronounced positive amplitude to stimuli in the attended stream and have a poorer ‘difference score’ or attention effect. This study provides novel evidence for specific deficits in attention modulation in the neurophysiological response of young children with SCD. These results align with the behavioural findings of poorer executive function, particularly attention control, in older children with SCD (Daly, Kral, & Tarazi, 2011).

The current findings are also in line with two previous ERP studies in SCD that found more diminished and variable ERP responses on tasks of executive skills (Colombatti et al., 2015; Hogan et al., 2006). Hogan and colleagues measured ERP components related to performance monitoring in children with SCD between 11 and 23-years-old, with and without evidence of silent lesions, and found that children with SCD showed some evidence for executive deficits in comparison to typically
developing controls, even in the absence of stroke, as demonstrated by a reduced error related negativity amplitude which reflects reduced unconscious processing of errors (Downes, Bathelt, & de Haan, 2017). They also administered a battery of behavioural executive tasks where both sickle groups showed significantly poorer scores across several domains, including selective attention. Colombatti and colleagues investigated the P3 using an auditory oddball paradigm in children with SCD between 6 and 15-years-old who had no history of stroke. The P3, a positive ERP component that reflects information processing during tasks that involve attending to and discriminating between target stimuli and distracting stimuli, was found to be more protracted and variable in the children with SCD.

In the present study 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, highlighting the sensitivity of ERPs to processing differences. Stevens, Sander, and Neville (2006) reported similar findings for their cohort of children with specific language impairment (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 neurophysiological differences.

The pattern for larger amplitudes in the attended condition for the control group, and their absence in the SCD patient group, suggests that the SCD group had difficulties with signal enhancement rather than distractor suppression in attention modulation (Stevens et al., 2009; Stevens, Sanders, & Neville, 2006). Although attenuated ERPs were anticipated for patients in the attended condition, the lack of any significant response was not expected. 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, even when compared with typically developing children (Donkers et al., 2015; Gomes et al., 2012; Loiselle, Stamm, Maitinsky, & Whipple, 1980). The lack of a response in the attended condition may suggest that patients are allocating limited attention resources, are less automatic in the allocation of these resources, or alternatively, that there is a dampening of information, more limited activation, or immature neural synchronization (Gilley, Sharma, Dorman, & Martin, 2005). Thus, children with SCD may have less established neural sources of attentional modulation and the lack of neurophysiological modulation reflects poorly attuned attentional control.

In the current study, there was an association observed between non-verbal IQ and the ERP amplitude in the attended condition, but not for the attention effect. A relation between the attention effect and non-verbal IQ has been reported in preschool children from low SES backgrounds, while additional studies have shown a relationship between the ERP amplitude in the unattended condition and parent-reports of executive function (Isbell et al., 2016; Lackner et al., 2013). Associations with the ERP were only observed for one of the two attention control tasks in our battery, where children with larger peaks in the unattended condition made more omission errors. Missing data or differences in task demands could have contributed 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 breaking down these steps into a series of components, which makes it more difficult to draw associations between the two. The behavioural attention tasks were also limited as they were both visual; an auditory task may have been more informative for direct comparison.

Limitations
One limitation of this study is the lack of neuroimaging, which means that although patients with a known history of stroke were excluded, some children may have had undetected silent stroke. Another limitation of this study is the small population. Nevertheless, the current patient population size was larger than the only previous published ERP studies in SCD (Colombatti et al., 2015; Hogan et al., 2006).

A further limitation of this study was the high attrition rate, which resulted in only 34 datasets in the final analysis, representing only 55% of the children recruited for the study. High attrition rates of up to 45% in EEG and ERP studies are typical for this age range and are related to refusal to wear the EEG cap and excessive movement during the session ( Cuevas et al., 2012; Morasch & Bell, 2011; Wolfe & Bell, 2007). Finally, as observed in previous ERP attention studies with this young age range, there was variability within each group (Isbell et al., 2016; Stevens, Sanders, & Neville, 2006). Five patients (42%) and three children from the control group (14%) had attention effects greater than one standard deviation below the control group mean. Noisy ERP data in younger participants could have precluded the detection of stronger relations with behavioural measures.

Future Investigations

An advantage of the current paradigm is that it can be applied across a wide age range allowing for the developmental tracking of neural markers of attention (Kral et al., 2015; Strait et al., 2014). Future studies should apply this paradigm in older school-age children and adolescents to ascertain whether the lack of response in the current study is a developmental delay that eventually catches up over time or whether it is an early indicator of an altered 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 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 stimuli in the current study that require the exertion of more executive control. It is important to determine the role of early attention deficits in the development of well-established later executive deficits in older children with SCD (Schatz & Roberts, 2007). Similar to Barkley’s developmental model of executive function for children with ADHD, where primary deficits in inhibition are proposed to have knock-on effects for later emerging executive domains, it may be that poor attention control in young children with SCD impairs the emergence of higher-order executive functions (Barkley, 1997).

Recent research suggests that ERPs can be used to index improvements in cognitive interventions with preschool children, potentially indicating better recruitment of neural systems important for selective attention (Espinet, Anderson, & Zelazo, 2013; Isbell et al., 2016; Neville et al., 2013; Rueda, Checa, & Cómbita, 2012; Stevens et al., 2012; Strait et al., 2015). Future research should consider using ERP responses in dichotic listening tasks as an end point in treatment trials of young children with SCD.

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. Further research is warranted to investigate potential differences in source localisation and to determine whether group differences would be evident on other attention paradigms, such as the oddball paradigm. 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 an altered neurophysiological response to selective attention in children with SCD, pinpointing a lack of signal enhancement, and also contributes further evidence for the relationship between behavioural performance and neural markers of attention.
Acknowledgments

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List of Figure Legends

**Figure 1: Electrode sites**

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.

**Figure 2: ERP waveforms for both groups**

Grand average ERP plots. Plots show 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 area of interest (shaded grey area).

**Figure 3: Topographical maps for both groups**

Topographic two-dimensional voltage maps show scalp-potential distributions averaged over a 200ms time-window. Figures indicate magnitude and ranges of ERPs elicited for A: Attended condition, B: Ignored condition and C: the Attention effect (difference wave = attended-unattended) for SCD patients and D: Attended condition, E: Ignored condition, and F: Attention effect for typically developing control 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).
Figure 4: ERP and behaviour

The relations between ERP and cognitive tasks. A: Association between the ERP for the attended condition and performance IQ and B: Association between the ERP for the unattended condition and number of omissions.

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### Table 1: Group Descriptives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Group (n=12)</th>
<th>Control Group (n=22)</th>
<th>P-value</th>
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<td>102.3 (17.5) (n=17)</td>
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<td>DDTP omissions</td>
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<td>23.4 (15.7) (n=13)</td>
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<td>DDTP commissions</td>
<td>72.8 (121.6)</td>
<td>12.03 (21.7) (n=13)</td>
<td>.1</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>10</td>
<td>.4</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black British</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>White British</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian British/Other</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic Status (by income)</td>
<td></td>
<td></td>
<td>.7</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>
</tbody>
</table>
Maternal Education

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Patient Group</th>
<th>Control Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary level</td>
<td>5</td>
<td>7</td>
<td>.5</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>

Pearsons’s Chi-Square used for category comparison and independent t-tests for comparison of continuous variables. FSIQ=full scale IQ VIQ=verbal IQ PIQ=performance IQ* Some of the participants did not complete the paper-based DDTP task due to task modification in the pilot phase (seven control children), timing issues (two patients/one control child), and experimenter error (one control child). Five of the control children did not complete the NIHTB task due to equipment issues.

**Table 2: Group comparison on behavioural task performance and number of usable events**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Group</th>
<th>Control Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of</td>
<td>10.7 (3.7)</td>
<td>10.8 (3.2)</td>
<td>.92</td>
</tr>
<tr>
<td>story trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>completed Mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage correct/attended story trials</td>
<td>82.5 (18)</td>
<td>89.7 (17)</td>
<td>.27</td>
</tr>
<tr>
<td>Number of events</td>
<td>before processing</td>
<td>Mean (SD)</td>
<td>Number of events</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td>107.5 (35)</td>
<td>123.4 (38)</td>
<td>.17</td>
<td>81 (35; 12)</td>
</tr>
</tbody>
</table>
Table 3: Mean amplitude of the early frontal positivity (100-300ms) in the medialfrontal, left frontal, right frontal, and central sites for both conditions. Significant group differences (p< .05) are shown in bold and trends for group differences (p<.1) are shown in italics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>Medial frontal</th>
<th>Left frontal</th>
<th>Right frontal</th>
<th>Frontocentral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M (SE)</td>
<td>M (SE)</td>
<td>M (SE)</td>
<td>M (SE)</td>
</tr>
<tr>
<td>Patient</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>Control</td>
<td>Attended</td>
<td>1.637</td>
<td>1.389</td>
<td>.662 (.29)</td>
<td>1.234 (.49)</td>
</tr>
<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>
Table 4: Associations between the behavioral variables and the neurophysiological correlates of attention control

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patient Group</th>
<th>Control Group</th>
<th>Total Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Attended Condition</td>
<td>Unattended Condition</td>
<td>Attended Condition</td>
</tr>
<tr>
<td></td>
<td>Attention Effect (attended - unattended)</td>
<td>Attention Effect (attended - unattended)</td>
<td>Attention Effect (attended - unattended)</td>
</tr>
<tr>
<td>DDTP Omissions*</td>
<td>.150</td>
<td>.517</td>
<td>.717*</td>
</tr>
<tr>
<td>DDTP Omissions*</td>
<td>.192</td>
<td>-.268</td>
<td>-.603</td>
</tr>
<tr>
<td>NIH Inhibitor Control</td>
<td>.242</td>
<td>.485</td>
<td>.174</td>
</tr>
</tbody>
</table>
*Spearman’s correlations used due to non-normal distribution of the DDTP variables;

*p<.05