

Adaptive Functioning and Time Processing in Children with Tourette Syndrome

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Thesis Declaration Form

I 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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Overview

This thesis focuses on behavioural outcomes in children with Tourette syndrome (TS).

Part I is a systematic review of the literature on aggression in TS. The aim of the review is to better understand aggression in TS and specifically to determine the impact of ADHD symptoms on aggressive behaviour in TS. The impact of these findings will support families and clinicians in knowing the risk factors, and potentially best treatment approaches, for behaviours that challenge in TS.

In Part II, adaptive functioning, or the ability to apply one's cognitive abilities to achieve day-to-day tasks, is examined in children with TS. Time processing, or the ability to process time intervals, is increasingly becoming known as one of the brain's most important basic functions and has been shown to be impaired in multiple neurodevelopmental conditions. An experimental time measure is used in this study to investigate the impact of time processing on adaptive functioning outcome in TS. This was a joint project with DCLinPsy Trainee, Lara Harris.

In the final portion of this thesis, Part III, the research process is critically appraised, and challenges that arose in the process are highlighted. This includes a reflection on broader themes relating to working with children with TS, application of the study findings, and future directions for research.

Impact statement

This thesis on children with Tourette syndrome (TS) provides insights into factors that lead to positive outcomes in TS. TS, which is characterised by movement and vocal tics, is known as a neurodevelopmental condition in which children show highly variable behavioural outcomes and levels of impairment in day-to-day functioning. Compared to neurodevelopmental conditions that tend to co-occur with TS, such as Autism Spectrum Condition (ASC) and Attention Deficit/Hyperactivity Disorder (ADHD), TS aetiology and interventions are far less investigated in the literature. This results in insufficient understanding and resources to manage the condition in community mental health services, resulting in families needing to travel far to specialist services around the country in order to get support.

The research in this thesis shows several significant findings. The first is that a comorbidity of ADHD significantly increases a child's likelihood of portraying aggressive symptoms, including anger outbursts, oppositional or delinquent behaviours. The next important finding is that the level of independence of children with TS is significantly impaired compared to the general population. Several factors contribute to these difficulties including the ability to hold and manipulate information in mind (working memory) and inattention and hyperactivity. Another important factor that was assessed is a child's ability to process how much time has gone by, both in very short intervals (under one-second) and longer intervals (over one-second). We found that the ability for a child to automatically process very short time frames can predict how independent that child will be in their day-to-day functioning, and especially predict their socialisation skills.

The clinical impact of our findings is the opportunity for new intervention pathways to support children and families impacted by TS. Clinicians should primarily assess for the co-occurrence of ADHD symptoms and consider the need for their treatment prior to the onset of treatment for TS. This is mainly because many of the behaviours that challenge (that would be targeted in treatment) will likely lessen if the ADHD is sufficiently treated beforehand. Since attention can predict adaptive functioning, the treatment of attention difficulties may also result in an overall improvement in day-to-day functioning. We highly encourage the administration of adaptive measures to get a sense of the child's level of independence and areas of need as this can lead to more suitable treatments depending on their areas of difficulty. Teaching time processing skills is rarely considered as an intervention, however our findings show that accuracy in processing short time periods can predict social independence, and therefore an enhanced ability in this domain may result in benefits of daily function. Future areas to consider for research are the evaluation of time-enhancing interventions to hopefully improve overall functioning.

These findings can contribute to improving overall health and wellbeing in children in the UK and around the world. Aggression and Disruptive Behaviour Disorders have a significant impact on communities. Children who show these difficulties are often labelled as “problem children” or “difficult to teach.” Additionally, recent research has shown that children with TS are more likely to perform poorly in school or be less eligible to transition to secondary school. As such, the investigation of behavioural outcomes in TS can lead to better treatment options in mental health services and will contribute to

improving wider societal concerns around supporting children to stay in school and reach their academic and professional potential.

Table of Contents

Overview	3
Impact statement.....	4
Table of Contents	7
List of Figures.....	12
List of Tables	13
List of Equations.....	13
Acknowledgements	14
Part I: Literature Review	15
Aggression in Children with Tourette Syndrome with and without ADHD Symptoms: A Systematic Review	15
1.1 Abstract.....	16
1.2 Introduction	17
1.2.1 Tourette Syndrome	17
1.2.2 Comorbidity in Tourette Syndrome.....	19
1.2.3 Types of Anger in Tourette Syndrome	20
1.2.3.1 Explosive Outbursts in Tourette Syndrome	20
1.2.3.2 Self-Injurious Behaviour in Tourette Syndrome.....	21
1.2.3.3 Anger and OCD in Tourette Syndrome	22
1.2.3.4 Disruptive Behaviour Disorders in Tourette Syndrome.....	23

1.2.3.5 ADHD and Anger in Tourette Syndrome	25
1.2.4 Objective	26
1.3 Methods	27
1.3.1 Inclusion and Exclusion Criteria.....	27
1.3.2 Data Sources	27
1.3.3 Quality Assessment.....	28
1.3.4 Data Extraction	29
1.3.5 Data Items	30
1.3.6 Summary Measures.....	32
1.3.7 Analysis of Results	32
1.4 Results	35
1.4.1 Study Design.....	35
1.4.2 Diagnostic Criteria.....	36
1.4.3 Results Breakdown	41
1.4.4 The Impact of ADHD on Aggression in TS	41
1.4.5 Greater Aggression and the Incidence of Attention Difficulties in TS.....	46
1.5 Discussion.....	48
1.5.1 What is the Impact of ADHD symptoms on Aggression in TS?	49
1.5.2 Are Attention Difficulties More Pertinent in Aggressive Phenotypes in TS?...	51
1.5.3 Limitations	53

1.5.4 Future Studies	54
1.5.5 Conclusion	55
1.6 References	57
Part II: Empirical Study	70
Time Processing and Adaptive Functioning in Children with Tourette Syndrome....	70
2.1 Abstract.....	71
2.2 Introduction	73
2.2.1 Neurobiology of TS	74
2.2.2 Neurobiology of Time Processing	76
2.2.3 Time Processing in Developmental Disorders.....	77
2.2.3.1 Time Discrimination	78
2.2.3.2 Time Reproduction.....	80
2.2.4 Adaptive Functioning in TS.....	82
2.2.5 Aims.....	83
2.3 Method.....	84
2.3.1 Participants.....	84
2.3.2 Procedure	85
2.3.3 Measures	86
2.3.3.1 Child Performance Measures	86
2.3.3.2 Parent/ Caregiver-Rated Measures.....	89

2.3.4 Statistical Analysis Procedures	90
2.4 Results	92
2.4.1 Neuropsychological and Behavioural Profile of TS	92
2.4.1.1 Adaptive Functioning.....	93
2.4.2 Timing Tasks	95
2.4.2.1 Time Discrimination	95
2.4.2.2 Time Reproduction.....	97
2.4.3 Tics and Timing	98
2.4.4 Cognition and Time	100
2.4.5 Time and Adaptive Functioning	104
2.5 Discussion.....	107
2.5.1 Main Findings	107
2.5.2 Timing in TS.....	108
2.5.2.1 How is Timing Related to Tics?.....	110
2.5.2.2 Cognitive Tasks and Timing	111
2.5.2.3 Adaptive Functioning.....	113
2.5.3 Limitations, Strengths, and Future Research	115
2.5.3.1 Limitations	115
2.5.3.2 Strengths.....	118
2.5.3.3 Future Directions for Research	118

2.5.4 Conclusion	119
2.6 References	120
Part III: Critical Appraisal	132
3.1 Introduction	133
3.2 Understanding TS	133
3.2.1 Spectrum of Difficulties.....	133
3.2.2 Diagnostic Changes and Validity	135
3.2.3 Epigenetics of Neurodevelopmental Disorders	136
3.3 Research Process	137
3.3.1 Selection Bias	138
3.3.2 The Overlap in Clinical and Research	138
3.3.3 Choice of Measures	140
3.4 Implications of Findings and Future Research	141
3.5 Conclusions	143
3.6 References	144
Appendix I: Search Terms.....	148
Appendix II: Quality Assessment.....	150
Appendix III: Child Behaviour Checklist Items.....	152
Appendix IV: HRA Ethical Approval	154
Appendix V: Tourette Action Funding Approval	156

Appendix VI: Parent and Child Information Sheets and Consent / Assent Forms	158
Appendix VII: Individual Trainee Contributions	177
Appendix VIII: Parent and Child Cognitive Report Templates	179

List of Figures

Figure 1.1 Visual Representation of the Search Process	34
Figure 2.2 Visual Representation of Basal Ganglia Output Under Typical Conditions and in TS.....	75
Figure 2.3 Average Number of Intervals Correctly Discriminated in the Sub-second Range	96
Figure 2.4 Average Number of Intervals Correctly Discriminated in the Supra-second Range	97
Figure 2.5 Absolute Reproduction Error (ARE) in the Sub- and Supra- second Ranges	98
Figure 2.6 Tic Severity and Absolute Reproduction Error (ARE) in the Supra-second Range	99
Figure 2.7 Tic Severity and Mean Discrimination Accuracy in the Sub-second Range	100

List of Tables

Table 1.1 Study Characteristics	37
Table 1.2 The Impact of ADHD Phenotype on Aggression in TS	44
Table 1.3 The Co-occurrence of ADHD and Aggression in TS.....	47
Table 2.4 Clinical Characteristics of Participants	92
Table 2.5 Neuropsychological Measures for Clinical Sample Compared to Normative Mean	94
Table 2.6 Correlational Analysis Vineland Adaptive Behaviour Composite (ABC) and Clinical Variables	95
Table 2.7 Pearson’s Correlational analysis between cognitive and clinical variables and reproduction error in the sub- and supra-second domains.....	101
Table 2.8 The Impact of Cognition on Timing: Standardised Beta Coefficients from Linear Regression.....	103
Table 2.9 The Impact of Timing on Adaptive Functioning: Standardised Beta Coefficients from Linear Regression Models.....	106

List of Equations

Equation 2.1 Reproduction Error	89
Equation 2.2 Absolute Reproduction Error	89

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Part I: Literature Review

Aggression in Children with Tourette Syndrome with and without
ADHD Symptoms: A Systematic Review

1.1 Abstract

Aim: The aim of this study is to review the literature on aggression in Tourette syndrome (TS). More specifically it sets out to answer the question: what is the relationship between Attention Deficit/Hyperactivity Disorder (ADHD) symptoms and aggressive symptoms in children with TS?

Method: MEDLINE, PsycINFO, and PsycARTICLES were systematically searched for articles specific to Tourette syndrome and key words including “aggression,” “anger,” “child behaviour disorders,” and “intermittent explosive disorder”. Studies were limited to children under the age of 18. Full articles were then screened to only include studies that reported metrics of inattention/hyperactivity and aggression. All articles published before December 2017 were included.

Results: Fifteen papers were selected for quality assessment and one was later removed. Data was extracted from the remaining fourteen. The studies were of varying quality and methodological approach. The majority of the results showed evidence that aggression, defiance, and delinquency, are significantly elevated in TS cohorts with a comorbidity of ADHD, or in groups with higher levels of ADHD symptoms.

Conclusion: ADHD symptoms and comorbidity were associated with increased aggression in children with TS.

1.2 Introduction

1.2.1 Tourette Syndrome

Tourette syndrome (TS) is a chronic, genetically-based neurodevelopmental disorder that is characterised by motor and vocal involuntary movements or sounds, known as tics. Tic severity is a compiled measure of the number of tics, frequency, intensity, complexity and interference caused by and associated with impairment from tics. Tics peak at around age 10-12 and in most cases decline significantly by late adolescence (Leckman, King, & Bloch, 2014; Tabori Kraft et al., 2012). A review on long-term outcome and prognosis TS studies showed that by early adulthood roughly three-quarters of children with TS have greatly diminished tic symptoms, and more than one-third are tic free (Leckman et al., 2014). A recent prospective follow-up study (Groth, Mol Debes, Rask, Lange, & Skov, 2017) found a significant age-related decline in tics as well as ADHD symptoms and OCD severity in a population of young people with tics. By age 16, 18% of participants were tic-free, and 60% had minimal or mild tics. As such, TS is very much considered a developmental condition.

The Diagnostic and Statistics Manual of Mental Disorders (5th ed.; DSM- 5; American Psychiatric Association, 2013) defines Tourette Disorder, also known as Tourette syndrome, as the presence of multiple motor and one or more vocal tics having been present during the time of illness, for at least one year. It is also required that the onset begins before the age of 18 and that the tics are not attributable to effects of substances or other medical conditions. This diagnostic criteria matches that of the International Classification of Diseases – 10 (ICD-10; World Health Organization, 1992)

which classifies “Combined vocal and multiple motor tic disorder” as a form of tic disorder in which multiple motor and one or more vocal tics is present.

A number of closely-related diagnoses exist; Persistent tic disorder, which was previously known as Chronic Motor or Vocal Tics (CMT) or (CVT) in the DSM-IV-TR (American Psychiatric Association, 2000), have the same criteria as Tourette syndrome but require that the motor and vocal tics were *not* present at the same time. As such, the type of tics, be it motor or vocal, is specified. Provisional Tic Disorder, previously known as Transient Tic Disorder (TTD) in the DSM-IV-TR (2000), is similarly a tic disorder with single or multiple motor or vocal tics, but will have had to be present for less than one year. New categories in the DSM-5 (2013) “Other Specified” and “Unspecified” Tic Disorders classify tic disorders that cause significant impairment to the individual but do not meet the full criteria for other disorders. These diagnoses may be for tic disorders that onset in adulthood or are triggered by drug use. Prior to the DSM-IV-TR (2000), impairment and distress were required as part of the diagnosis, but these criteria have recently been dropped. For simplicity, in this paper, unless otherwise specified by a study, we will be exploring Tourette syndrome (TS).

Aside from the tics themselves, people with TS frequently have one or more co-occurring difficulties that impact their quality of life. It is common for clinical samples of children with TS to show, among others, behaviours that challenge, compulsions, aggression, hyperactivity, and impulsivity. In this study we will be considering the aetiology of some of these behaviours and specifically exploring the impact of comorbidity on the occurrence of aggressive behaviours in TS.

1.2.2 Comorbidity in Tourette Syndrome

The lifetime estimated prevalence of comorbid psychiatric conditions in TS is 85.7% with greater than half suffering from two or more comorbidities (Hirschtritt et al., 2015). It is found that both in clinical settings and in the community, only approximately 10% of people have pure-TS (Robertson, Cavanna, & Eapen, 2015) while the rest have a variety of comorbidities or psychopathologies. The most frequent are: ADHD, which occurs in approximately 60% of clinically referred children (Khalifa & von Knorring, 2005; Zhu, Leung, Liu, Zhou, & Su, 2006), Obsessive Compulsive Disorder (OCD) where comorbidity ranges from 11 to 80% of people (Kumar, Trescher, & Byler, 2016), anxiety disorders (4-38%; Freeman et al., 2000), and disruptive disorders, including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) in 4-44% (Freeman et al., 2000). Because of this, the clinical picture of people with TS is highly heterogeneous with various phenotypic outcomes.

Several studies have found aggressive behaviours to be part of the TS phenotype (Cavanna et al., 2011; Robertson, Althoff, Hafez, & Pauls, 2008; Robertson & Cavanna, 2007). Studies drawn from clinically referred samples suggest 25-70% of individuals with TS report problems with uncontrollable anger that causes significant disruption (Budman, Bruun, Park, Lesser, & Olson, 2000; Robertson et al., 2015; Wright, Rickards, & Cavanna, 2012). These difficulties have been reported worldwide as a leading cause of morbidity which impact on family function and quality of life in TS (Dooley, Brna, & Gordon, 1999; Eapen, Snedden, Črnčec, Pick, & Sachdev, 2016; Freeman et al., 2000; Rizzo, Gulisano, Pellico, Calì, & Curatolo, 2014). As such, it is of clinical significance

to understand the aetiology of the aggression expressed in TS as well as the risk factors for developing aggressive behaviour.

1.2.3 Types of Anger in Tourette Syndrome

Aggressive behaviours in children can be classified as reactive or proactive. Reactive aggression is typically seen as impulsive, spontaneous, and are usually performed in response to high levels of physiological and emotional arousal (White, Jarrett, & Ollendick, 2013). Proactive aggression on the other hand is considered non-impulsive, in which the aggressive behaviour is premeditated and accompanied by limited levels of guilt or physiological arousal (Rosell & Siever, 2015; White et al., 2013).

Aggression in the TS population is predominantly impulsive in nature (Chen et al., 2013; Robertson et al., 2015; Tabori Kraft et al., 2012), however the presentation and aetiology of aggressive behaviour in TS is heterogeneous. Aggression can be categorized as explosive anger outbursts, fits and tantrums, oppositional or disruptive behaviour, as well as self-injurious behaviour (SIB). The presentation of the behaviour may differ based on the TS phenotype, that is, depending on whether the child has pure-TS, or a comorbidity of ADHD, OCD, ODD or CD, or otherwise.

1.2.3.1 Explosive Outbursts in Tourette Syndrome

Explosive outbursts have been extensively researched in TS and appear to be the main form of aggression expressed. Explosive outbursts are also commonly known as “rage attacks” and are severe, unpredictable, and recurrent episodes of anger (Budman, et al.,

2003). These episodes most resemble DSM-5 (2013) criteria for Intermittent Explosive Disorders (IED). Similar to IED, in TS these episodes occur with little provocation and are out of proportion to the stressor. Common triggers include being reprimanded unjustly or a feeling of frustration due to not getting one's way. Explosive outbursts in TS may result in mutilation and destruction of property as well as physical and verbal assault of loved ones, and is usually followed by a sense of remorse.

An exploratory study (Budman, Rockmore, Stokes, & Sossin, 2003) of 48 children with TS presenting for treatment of episodic rage showed that while episodic rage in TS has some signature features, it should not be considered an independent disorder. Rather, a wide range of psychological, biological, and environmental conditions contribute to a loss of control of aggressive impulses in TS.

1.2.3.2 Self-Injurious Behaviour in Tourette Syndrome

Self-injurious behaviour is another form of impulsive aggression that is commonly seen in TS. Unlike what is known as deliberate self-harm, often used as a coping mechanism in times of distress, SIB constitutes acts of harm to oneself without suicidal intent. Studies show that approximately one third of people with TS engage in SIB (Robertson et al., 2015; Robertson, Trimble, & Lees, 1989). This therefore constitutes a significant minority of children with TS.

Freeman (2007) found SIB to be higher in individuals with TS who had a comorbidity of ADHD than TS participants without ADHD. The age of SIB onset in the TS+ADHD group was earlier than the TS-ADHD group. Mathews (2004) explored the

factors contributing to SIB and concluded that mild/moderate SIB may be a separate phenomenon to severe SIB in TS. Mild/moderate SIB was associated with OCD and other obsessive and compulsive symptoms, indicating that mild SIB, such as skin picking and scratching, may fall into the clinical spectrum that lies between complex motor tics and compulsions. On the other hand, severe SIB in TS was associated with variables relating to impulsivity and affect dysregulation, including episodic rages and risk-taking behaviours. This form of SIB was hypothesised to be more similar to the aetiology of SIB in other neuropsychiatric disorders. It was also found that all types of SIB were correlated with tic severity (Mathews et al., 2004; Robertson et al., 2015).

1.2.3.3 Anger and OCD in Tourette Syndrome

The literature has shown a bidirectional relationship between OCD and TS. It has been estimated that between 20-60% of TS patients meet criteria for OCD, while 20-38% of children with OCD report tics (Lewin, Chang, McCracken, McQueen, & Piacentini, 2010). Children with OCD also experience explosive outbursts and rage attacks that can occur in approximately half of the population (Storch et al., 2012), which accounted for greater functional impairment than obsessive compulsive symptom (OCS) severity did.

One study set out to explore the relationship between impulsivity and compulsivity in TS (Kano et al., 2015). In a cohort of 53 participants aged 5-43 with TS, tic severity scores were positively correlated with OCS. Additionally, OCS, not impulsivity, predicted impairments in global functioning. Of OCS symptoms, only aggression had a significant impact on global functioning. Therefore, one must consider

the impact of aggression symptoms in both conditions, particularly when they co-occur in patients.

1.2.3.4 Disruptive Behaviour Disorders in Tourette Syndrome

Aggression is also seen in the context of Disruptive Behaviour Disorders, including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) in TS. A worldwide study (Freeman et al., 2007) estimated a comorbidity of ODD or CD in 12.3% of the TS population.

A diagnosis of ODD in DSM-5 (2013) indicates the person must exhibit one of the following three patterns: angry or irritable mood, argumentative or defiant behaviour, or vindictiveness, lasting at least 6 months. The disturbance should be associated with distress in the individual or others in his or her social context. In a study of 48 children with TS and episodic rage (Budman et al., 2003), 42% met criteria for ODD. Therefore, the form of anger displayed in ODD is slightly different from IED in that they can be impulsive but can also be proactive and vindictive.

Oppositional Defiant Disorder is known to precede CD in development (American Psychiatric Association, 2013) and is informally thought of as a milder version of CD (Robertson et al., 2015). The diagnosis of CD in the DSM-5 (2013) requires a persistent pattern in which the basic rights of others or societal norms or rules are violated. The person will show a combination of behaviours that fall into the following categories: aggression to people, aggression to animals, destruction of property, deceitfulness, and serious violations of rules.

The presentation of CD is heterogeneous with two main types reported in the literature: callous-unemotional, usually known as the aggressive-type and is found to be heritable (Burt, 2012; Frick, 2012; Viding, Fontaine, & McCrory, 2012), and the non-callous type, which is mainly associated with emotional and behavioural regulation difficulties (Frick, 2012). Structural abnormalities, particularly in the form of reduced amygdala volume, are found to be a consistent trait among adolescents with CD, irrespective of the quality of traits (callous-unemotional vs aggressive), age of onset of CD, and presence of ADHD (Fairchild et al., 2011). This study proposes that all types of CD may stem from a dysfunction in neural circuits involved in emotion processing that are established during development. On the other hand, CD and antisocial behaviours are shown to be significantly influenced by a shared environment (Kendler, Prescott, Myers, & Neale, 2003), therefore indicating a complex genetic and environmental risk factor link in CD.

In a study examining the relationship between TS and CD, 578 participants (mean age: 25.4 years) with TS and other related comorbidities, it was found that CD was related to a positive family history of aggressive and violent behaviours (Robertson et al., 2015). Conduct Disorder was also significantly related to the presence of ADHD in TS: 80% of participants with CD and TS also had ADHD. This is in line with previous studies that have shown a high co-occurrence between ADHD and CD / ODD (Carter et al., 2000; Sukhodolsky et al., 2003). Conduct Disorder studies have shown similar associations with ADHD and family history of forensic encounters (Burt, 2012; Viding et al., 2012). This led Robertson et al. (2015) to conclude that the genetic underpinnings of TS are not

responsible for aggressive and violent behaviours, and that TS and CD are not genetically linked.

Although CD and ODD were not found to be correlated with tic severity, the same study showed that greater tic severity in the group was associated with a history of aggressive behaviours (Robertson et al., 2015). Therefore, it is possible that certain types of dysregulated and impulsive behaviours may be overrepresented in cases with more severe tics than mild tics.

1.2.3.5 ADHD and Anger in Tourette Syndrome

ADHD and TS are found to have a close neurobiological and genetic relationship in the literature (Hirschtritt et al., 2015). While most research considers TS and ADHD to be co-occurring conditions, some have suggested that the mechanisms that underlie the disinhibited behaviours (including aggression) in TS are more to do with ADHD comorbidity than TS itself (Robertson et al., 2015). That is, that aggression and impulsive behaviour might not be elevated in the population of individuals with TS without ADHD.

Disentangling ADHD symptoms from aggressive behaviours in TS has resulted in a variety of studies exploring behaviour in two phenotypic groups: TS+ADHD and TS-ADHD (or TS-only). Many studies have now shown that people with pure TS do not significantly differ from healthy-control subjects in their quality of life, emotional liability, and behavioural difficulties, whereas TS+ADHD subgroups show increased incidence of difficulties in these areas. (Eapen et al., 2016; Pollak et al., 2009; Rizzo et al., 2007, 2014; Spencer et al., 1998; Stephens & Sandor, 1999; Sukhodolsky et al., 2003).

A prevalence study of explosive outbursts in TS showed that, within a US sample, ADHD significantly predicted explosive outbursts, while in the Costa Rican sample, ADHD did not significantly predict aggressive behaviour (Chen et al., 2013). A community sample (Kraft et al., 2012) of school-age children (n=8,244) showed that children with TS and hyperactivity show greater symptom severity across several domains of behaviour and overall impairment as compared with TS without hyperactivity. Without hyperactivity, TS participants were at risk of emotional difficulties but not disruptive behaviour. Therefore, given the existing literature, ADHD comorbidity appears to be a contributing factor to aggression in TS.

1.2.4 Objective

Clinically, aggression is known to be a difficulty that many children with TS face. It has also been found that comorbidities in TS cause significant impairment to overall behavioural and emotional functioning in children.

To date, we have not identified any reviews that have systematically considered factors that impact aggression and disruptive behaviours in children with TS. Although it is often understood clinically that children with ADHD comorbidity show more impulsive behaviours, the extent to which ADHD symptoms are associated with aggressive behaviour in TS is unknown.

The aim of this study is to review the literature and evaluate the impact of Attention Deficit/Hyperactivity Disorder (ADHD) comorbidity and symptoms on

aggression in children with TS. Our hypothesis is that anger expression is rooted in the existence of ADHD comorbidity and symptoms.

1.3 Methods

The PRISMA Guidelines for conducting a systematic review and the checklist were used to guide the methodology and write-up of this review.

1.3.1 Inclusion and Exclusion Criteria

The searches were conducted for studies that were published in English and in peer-reviewed journals. Filters on search engines were used to specify language. Studies with participants above the age of 18 were excluded; this was done firstly by filtering on the search engines. At later stages participant characteristics were searched through in each study to make sure the participants were all under the age of 18. Intervention, treatment, and animal studies were also excluded; this was done by reading titles, abstracts, and entire studies.

1.3.2 Data Sources

PsycINFO, PsycARTICLES, and MEDLINE were searched using headings related to aggression, Tourette syndrome, and children (Appendix I). All relevant articles published before December 2017 were included. Once duplicate citations were removed 752 articles remained (Figure 1.1).

Titles were screened to exclude articles that were not specific to TS and that were evaluating treatments or genetic studies. All articles related to psychopathology in TS were included. After this screening, 138 articles remained. All abstracts were then screened for topics relating to understanding aggression in TS. Of the 138 articles, 61 abstracts were found to be irrelevant to the question of understanding anger in TS, and 77 remained.

Forty articles were then included after a full-text screening. It became apparent that there was a subgroup of articles that sought to understand the impact of comorbidity, often specifically of ADHD, on psychopathology in TS. As such studies in which the impact of ADHD comorbidity or symptoms on anger symptomology could be separated from non-ADHD groups were kept. Finally, due to the change in symptom expression of tics through development, studies that included individuals above the age of 18 were excluded.

Fifteen articles were found to fulfil the set criteria of understanding the relationship between inattention/ hyperactivity and aggression, rage, or oppositional behaviour in children and young people with tic disorders.

1.3.3 Quality Assessment

To evaluate the quality of the articles, the Standard Quality Assessment Criteria (Kmet, Lee, & Cook, 2004) for quantitative studies was used (Appendix II). The Standard Quality Assessment is a flexible tool that can be used for a wide range of studies, including case-control studies or single group cross-sectional studies. It has also shown

high interrater agreement for quantitative studies, with by-item agreement ranging from 73% - 100%. The questionnaire assesses 14 criteria in which the assessor marks the degree to which the paper met each criterion (“yes”=2, “partial”=1, “no”=0). Items that were not applicable to the study are marked as N/A and were excluded from the final calculation.

A summary score was calculated out of the total possible scores of applicable criteria. The total was therefore the number of applicable criteria, multiplied by two. In this study, the three criteria relating to interventional studies were excluded. Therefore, the total number of criteria was eleven, and the maximum total score was 22.

The assessment was completed for all papers. The assessor then went back and completed all of the assessments again in a random order to reduce risk of bias. The two scores were averaged and used for the review.

1.3.4 Data Extraction

The following data was extracted for all studies and inserted into an excel sheet:

1. Publication: the journal of publication, year, language and country of publication, and authors involved in the study.
2. Design: the type of study (cross-sectional, case-control, etc); prospective vs retrospective data collection, recruitment location and methods.
3. Participant details: number of participants (in each group), age range and mean ages (*SD*) in each group, diagnostic procedures and choice of manual used: DSM-III (American Psychiatric Association, 1980), DSM-III-R (American Psychiatric

Association, 1987), DSM-IV (1994), DSM-IV-TR (2000) or ICD-10 (1992), and existence of psychiatric comorbidity in cases and control populations, matching factors if groups were matched, measures used in the data collection (overall scores and subscale scores).

4. Outcome measure: methods used to define post-analytic groupings, group means where applicable, mean comparison and *p-values* between groups, regression measures (predictor values), and correlation values, each where applicable.

1.3.5 Data Items

The majority of studies (11/15) split the participant groups based on TS phenotypes, that is:

1. TS without ADHD: this could be TS-ADHD, or in some studies was represented as TS-only, where all other psychiatric comorbidities were also controlled for, including OCD, ODD, etc.
2. TS with ADHD (TS+ADHD).
3. TS + any other comorbidity.

These groups were sometimes divided before data collection (in 8/15 studies), and at other times this was done as a post-hoc analysis (7/15 studies).

In these studies, a variety of measures were administered that included parent- and teacher- filled standardized measures. The main data items extracted were group means and standard deviations of subscales relating to aggression. The following measures were included:

- The Child Behaviour Checklist (CBCL) aggression subscale, delinquent subscale, and the externalizing score, which is equal to the sum of the aggression and delinquent subscales.
- The Conners Comprehensive Behaviour Rating Scale (CBRS) was also used and included the parent (P) and teacher (T) forms (Conners, Pitkanen, & Rzepa, 2011), with the outcome variable of “conduct disturbance” extracted.
- The Strengths and Difficulties Questionnaire (SDQ) was also used, with conduct problems extracted as a proxy for aggression.
- When other comorbidities that are predictive of anger problems were reported, such as ODD and CD, they were extracted and used as proxies for aggressive behaviour.

In the four remaining studies, cohorts were divided by the presence, absence, or quality of their aggressive behaviour. The method of dividing the groups was extracted. One study used a modified questionnaire based on the DSM-IV (1994) criteria for IED and resulted in a binary variable of participants who either have “explosive outbursts” or “no explosive outbursts”. The main outcome measure was the incidence of ADHD comorbidity in each group. The second used a combination of three measures to divide the sample into a “more aggressive” vs “less aggressive” group: teacher-completed IOWA (Inattention/Overactivity with Aggression) Conners Rating Scale, parent-completed Mothers’ Objective Method for Subgrouping (MOMS) subscale, and direct observations of non-physical aggression in the classroom, to divide the sample. The third used the existence of a Disruptive Behaviour Disorder (DBD), which includes ADHD, CD, or ODD, to divide the sample into two groups “with DBD” or “without DBD”. The

outcome measure in these two studies was the mean attention difficulties score on the CBCL between the groups, as well as their standard deviations. The last study divided the sample of participants, who all had TS and ODD, into two subgroups “ODD headstrong traits” and “ODD irritable traits”. They used a regression analysis to examine whether certain types of ODD predicted a comorbidity of ADHD. The outcome measure was the regression beta coefficient.

Finally, in studies that included unaffected control groups, the group means of the aggressive subscale measures, as well as their standard deviations, were extracted for the TS-ADHD and healthy control participants.

1.3.6 Summary Measures

There were three principal summary measures collected depending on the study design. The first was the difference in means of anger or attention measures between phenotype groups. *Probability-values* were also included where reported. The second measure was the difference in the incidence of a comorbidity of ADHD, ODD, and/or CD between phenotype groups. The last was beta coefficients or R-squared measures in instances where regression or correlation were applied.

1.3.7 Analysis of Results

In order to measure the magnitude of the difference between group means in individual studies, a Cohen’s *d* effect size (ES) was calculated. This was possible in 9/15 of the

studies. This is calculated using the following formula (where M^1 = mean of the case group and M^2 = mean of control group):

$$\text{Effect Size } (d) = (M^1 - M^2) / SD_{\text{pooled}}$$

Where possible, the ES was pooled between studies to measure the magnitude of impact across studies. This was only possible in studies that used the CBCL measure and reported the aggression and delinquency subscales separately for participant groups. Five studies ESs in the aggressive and delinquent subscales were pooled to compare TS+ADHD to TS-ADHD. Next, three studies ESs were pooled to compare the aggressive and delinquent subscales in the TS-ADHD to the unaffected control subgroups.

In order to pool effect sizes, each study was assigned a sample error (se) based on its sample size and individual ES. An individual study weight was then calculated using the se. The following formula was used to calculate se and w (where n_1 was the sample size of the case group, and n_2 was the sample size of the control group):

$$se = \sqrt{\frac{n_1 + n_2}{n_1 n_2} + \frac{\overline{ES}_{sm}}{2(n_1 + n_2)}} \quad w = \frac{1}{se^2}$$

The ESs were then pooled together using the following formula:

$$\overline{ES} = \frac{\sum (w \times ES)}{\sum w}$$

Cohen (1992) stated that an effect size of 0.2 is considered small, 0.5 is medium, and 0.8 is considered large.

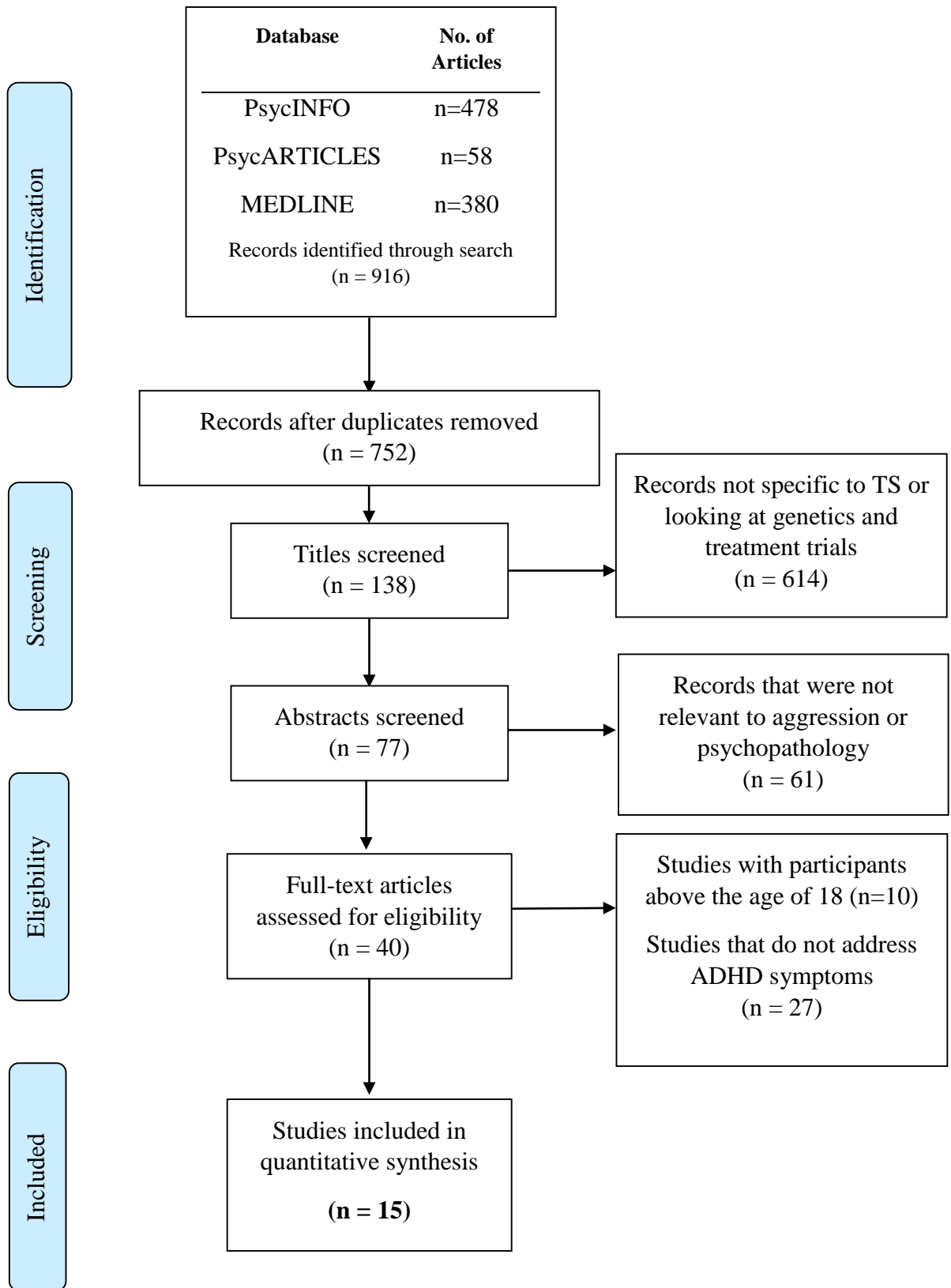


Figure 1.1 Visual Representation of the Search Process

1.4 Results

The electronic searches yielded 752 abstracts, with 77 abstracts selected for full review. After a full-text review of the 77 articles, 37 were excluded because they either did not answer the specific question of the impact of ADHD on anger in TS, or because they included participants above the age of 18. Fifteen articles remained that met the eligibility criteria for the systematic review.

The quality assessment (Appendix II; Kmet et al., 2004) was used to inform the data analysis. Each study was given a Red-Amber-Green rating, for poor, moderate, and good respectively (Table 1.1). Scores of 80% or higher were considered “good”, scores between 60-79% were considered “moderate”, and 59% and lower were considered “poor”. Six studies were considered good, five moderate, and four poor.

Stephens and Sandor’s study (1999) was excluded from the data analysis after the quality assessment as insufficient data was reported.. All 14 remaining studies were included in the data analysis.

1.4.1 Study Design




Of the 15 studies that met eligibility criteria for the review, eight studies were case control studies. Four of the eight case-control studies matched the groups by age, and other factors including gender, SES, and IQ, while the remaining four did not report matching the case and control groups. Seven studies were single-group cross-sectional studies, where cohorts were split into diagnostic groups after recruitment.






Of the all the studies, eleven studies collected prospective data while four studies analysed data from existing databases in the following countries: two multi-site international databases, one at an outpatient clinic for TS in Israel, and the last from University of Gottingen in Germany.





1.4.2 Diagnostic Criteria




The studies used a variety of diagnostic procedures (Table 1.1), predominantly consistent with the most up to date DSM at the time of data collection. Four studies used the criteria in DSM-III-R (1987) for the diagnosis of TD, CMT, CVT, TTD, and other comorbidities. One study used the best-estimate diagnostic procedure (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982) between two experienced clinicians. Ten studies used the criteria in *DSM-IV* (1994). In one of these, the DSM-IV was used for the comorbid disorders while the DSM-III-R was used for the tic diagnoses. One of these also used ICD-10 criteria to confirm the diagnosis of TD (World Health Organization, 1992). Finally, one study used DSM-IV-TR (2000) for all diagnoses.

Table 1.1 Study Characteristics

Study	Standard Quality Assessment Criteria	Study Design	Cases (n)	Control (n)	Age-range all; mean (SD) of each group	Source of recruitment	Matching factors	Diagnosis of TS	Relevant Measures	Prospective vs Retrospective	Outcome variables compared
Budman, Bruun, Park, Lesser, & Olson, 2000	68% 	Matched Case Control	TS + explosive outbursts (37)	TS - explosive outbursts (31)	6-16 years old; experimental group 11.9(2.8); control group 11.0(2.9)	Interdisciplinary specialty program, tertiary care centre	Age, sex, socioeconomic status (SES), Tanner stage, and medications	DSM-IV	IED criteria (modified), CY-BOCS, CBRS-P	Prospective	Comorbidity of ADHD
Carter et al., 2000	91% 	Case Control	TS - ADHD (16) TS + ADHD (33)	Unaffected control (23)	8-14 years old; TS+ADHD 11.10(1.56); TS-ADHD 10.40(1.14); control 10.80(1.77)	Control: newspaper and schools; TS: the Yale Child Study Center Tic Disorder Clinic	-	Best-estimate diagnostic procedure (J. F. Leckman et al., 1982)	CBCL, YGTSS, CY-BOCS	Prospective	CBCL: aggressive and delinquent subscales
De Groot, Janus, & Bornstein, 1995	77% 	Single-group cross-sectional	TS (92)	-	7-18 years old; 12.4(2.6)	General mailing to the Ohio Tourette syndrome Association	-	DSM-III-R	Tourette's syndrome List (TSSL), CBRS-P	Prospective	R-square: predictors for CBRS-P conduct disturbance subscale

Ghanizadeh & Mosallaei, 2009	55% 	Single-group cross-sectional	TS (35)	-	6-16 years old; 11.8 (3.1)	Child and Adolescent Psychiatric Clinic, Iran	-	DSM-IV	YGTS, CBCL, diagnosis of disruptive behaviour disorders	Prospective	CBCL: attention problems subscale
Hoekstra et al., 2004	95% 	Single group cross-sectional	TS-ADHD (25)	TS + ADHDina (15) TS + ADHDimp (18)	5-16 years old; ADHDimp 10.78 (2.6), ADHDina 11.40 (2.3), TS-ADHD 11.20 (3.8)	Association of patients with TS, and Child and Adolescent Psychiatry Center (Netherlands)	-	DSM-IV	CBCL, diagnosis of ADHD + subtype	Prospective	CBCL: aggressive and delinquent subscales
Lebowitz et al., 2012	59% 	Two studies; cross-sectional study	TS (143) CMT (10) CVT (1) TD/ NOS (5)	-	6-15 years old; study1 10.18(1.8); study2 11.2(1.7)	Multi-site across the USA	-	DSM-IV	Diagnostic Interview Schedule-DSM-IV; CBRS-P;	Retrospective	β: predictors of externalising disorder (ODD and/or CD)
Nolan, Sverd, Gadow, Sprafkin, & Ezor, 1996	82% 	Single group cross-sectional	TS + ADHD (47)	-	6-12 years old; 8.91(1.82)	Referrals to Child Psychiatry Outpatient Service in NYC.	-	DSM-III-R	YGTS, CBCL, IOWA, MOMS	Prospective	CBCL: hyperactive subscale
Pollak et al., 2009	59% 	Matched case control	TS-ADHD (38) TS+ADHD (142) ADHD-TS (121)	Unaffected control (48)	5-18 years old; TS-ADHD 10.0(2.9), TS+ADHD 10.7(2.7), ADHD-TS 10.4(2.7), control 10.2(3.2)	TS: TS Clinic, Shaare Zedek, Israel; control: ads & children of hospital staff	Sex, age, IQ, ADHD severity	DSM-IV	CBCL (Hebrew version), Y-BOCS, YGTS	Retrospective	CBCL externalizing= aggressive + delinquent subscales

Rizzo et al., 2007	77% 	Case control	TS-only (20) ADHD-only (20) TS+ADHD (20)	Unaffected control (20)	6-16 years old; TS-only 9.6 years (2.5); ADHD-only 9.23 (2.5); TS+ADHD 10.07 years (2.55)	Outpatient Child Neuropsychiatry and Pediatrics, University of Catania, Italy. Control: general pediatricians	-	DSM-IV	CBCL	Prospective	CBCL: aggressive and delinquent subscales
Roessner, Becker, Banaschewski, Freeman, et al., 2007	82% 	Single group cross-sectional	TS-ADHD-Com (1,282) TS-ADHD+Com (681) TS+ADHD-Com (1,425) TS+ADHD+Com (1,672)	-	5-17 years old; split by age group 5-7; 8-10; 10-13; 14-17	TS International Consortium (TIC) Database; 81 sites from 27 countries	-	DSM-III-R (TS) DSM-IV (comorbid disorders)	Comorbidity	Retrospective	Comorbidity: CD/ODD
Roessner, Becker, Banaschewski, & Rothenberger, 2007	82% 	Matched case control	TS-only (12) TS+ADHD (82) ADHD-only (129)	Unaffected control (144)	Range not stated, classified as 'children'; TS-only 11.1(2.6), TS+ADHD 10.7 (2.3), ADHD-only 10.5(2.5), control 10.4(2.4)	Outpatient Child and Adolescent Psychiatry, University of Gottingen; control: general outpatient clinic	Age and gender	DSM-IV-TR ICD-10 criteria for confirmation.	CBCL	Retrospective	CBCL: aggressive and delinquent subscales
Stephens & Sandor, 1999	45% 	Case control	TS-only (10) TS+ADHD (14) TS+ADHD+OCD (9)	Unaffected control (6)	6-14 years old; TS-only 9.8(2.0), TS+ADHD 10.6(2.2), TS+ADHD+OCD 11.44(1.5), control 9.0(1.8)	TS clinic, Toronto Western Hospital	-	DSM-III-R	CY-BOCS, CBCL, CBRS – P & T	Prospective	CBRS-P&T: antisocial, conduct subscales, CBCL aggressive behaviour

Sukhodolsky et al., 2003	95% 	Matched case control	TS-only (42) ADHD-only (52) TS+ADHD (52)	Unaffected control (61)	7-18 years old; TS-only 10.79(1.94); TS+ADHD 11.11 (2.08); ADHD-only 11.79(2.80); Controls 10.76 (2.31)	TS: TD Clinic and local TS Association ADHD: Yale outpatient clinic Control: telemarketing list	Age, gender, and socioeconomic status	DSM-IV	CBCL, YGTSS, CY-BOCS	Prospective	CBCL: aggressive and delinquent subscales, CTR conduct subscale
Tabori Kraft et al., 2012	77% 	Longitudinal three time-point case control	CTD (57) TS (26) CMT (31)	Unaffected control (5,027)	Longitudinal 3-phase study. Age at time 1: 9-11, time 2: 1 year later, time 3: 13-15	Birth cohort at Aarhus University Hospital, Denmark	-	Time 1: SDQ Time 2: DAWBA and DSM-IV to assign type of tic disorder	DAWBA, SDQ	Prospective	SDQ: conduct difficulties subscale
Thériault et al., 2014	68% 	Cross sectional single cohort	TS (129) CT (6)	-	5-17 years old; 10.3(2.6)	Tourette clinic of Sainte-Justine Hospital, Montreal	-	DSM-IV	CBRS-P, YGTSS, CY-BOCS, number of ODD symptoms	Prospective	Comorbidity: OCD, ADHD

Diagnoses: ADHDimp: ADHD of the hyperactive/impulsive or combined type; ADHDina: ADHD of the inattentive type; CMT: Chronic Motor Tics; CVT: Chronic Vocal Tics TD/NOS: Tic Disorder Not Otherwise Specified; Com: psychiatric comorbidity that is not ADHD.

Measures: CBCL: Child Behavior Checklist; CBRS-P: Conners Behavior Rating Scales (Parent); CBRS-T: Conners Behavior Rating Scales (Teacher); CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; DAWBA: Development and Well-Being Assessment; IOWA: Inattention/Overactivity with Aggression) Conners Rating Scale; MOMS: Parent-completed Mothers' Objective Method for Subgrouping; SDQ: Strengths and Difficulties Questionnaire.

1.4.3 Results Breakdown

The results are reported in two sections below: in the first section (Section 1.4.4) we seek to understand the added impact of a diagnosis of ADHD, or ADHD symptoms of inattention and hyperactivity, on aggressive symptoms in TS. In this section ten studies are used to compare the “aggression” scores and aggressive-proxy measures in TS+ADHD and TS-ADHD (or TS-only) groups, looking at the difference in mean scores between the two groups. We also look at the difference in CD or ODD comorbidity between the two groups when reported.

In the second section (Section 1.4.5) we explore the inverse relationship. In four studies, samples were divided based on the quality or existence of aggression symptoms (or proxy-measures). We therefore looked at the outcome of attention variables, seeking whether children with aggressive symptoms are more likely to also have ADHD symptoms (inattention or hyperactivity/impulsivity).

Both these sections will address the aim of better understanding the association between ADHD and aggressive symptoms in TS.

1.4.4 The Impact of ADHD on Aggression in TS

Ten articles considered the impact of attention difficulties, or a comorbidity of ADHD, on aggressive symptoms in TS (Table 1.2). An effect size was calculated in seven studies, and were pooled in five studies where the same measures were used.

In five studies (Carter et al., 2000; Hoekstra et al., 2004; Rizzo et al., 2007; Roessner, Becker, Banaschewski, & Rothenberger, 2007; Sukhodolsky et al., 2003), the

CBCL aggressive and delinquent scales were used as a measure of aggression. CBCL aggressive subscales was shown to be significantly higher in the TS+ADHD group compared to the TS-only, or TS-ADHD groups on all occasions where *p-values* were reported. The CBCL aggressive subscale pooled effect size was found to be large ($d=1.247$).

Of note, Hoesktra (2004) had divided the TS+ADHD group into two subgroups: ADHD predominantly inattentive type (INA), and predominantly impulsive or combined type (IMP). These were two mutually exclusive groups and therefore we calculated two ESs. However, since they were from the same study, the control group (TS-ADHD) was the same.

The delinquency subscale of the CBCL was also used as a proxy for aggression due to the high overlap in aggression and delinquency in development. The CBCL delinquency subscale was shown to be higher in the TS+ADHD group than the TS-ADHD group in 4/5 of the studies that used the measure. The pooled effect size was found to be small-medium ($d=0.439$).

Pollak et al. (2009) combined the CBCL aggressive and delinquent scales to form an externalizing (EXT) measure. The TS+ADHD group showed higher scores for the EXT measure than the TS-ADHD group, with a medium effect size ($d=0.593$). It was reported to be significant.

Tabori Kraft et al., (2012) used the Strengths and Difficulties Questionnaire (SDQ) hyperactive subscale and categorically divided the sample into a hyperactive or not hyperactive phenotype (where hyperactive was a score >5 on the parent rated SDQ

hyperactivity scale). The TS+hyperactive group showed higher conduct problems (on the SDQ) than the TS-hyperactive group, with a large effect size ($d=1.431$).

De Groot et al., 1995 showed that a history of ADHD was found to predict conduct disturbance, as measured by the CBRS-P ($R\text{-square}=0.88$ $p<0.001$). Additionally, a diagnosis of ADHD was shown to be a significant predictor of CD and/or ODD ($B=1.18$ and Wald's $\chi^2=6.03$, $p=0.014$; Lebowitz et al., 2012).

When the incidence of CD/ODD was considered throughout development, it was shown that at all stages (between 5-17 years of age) the incidence of CD/ODD was higher in the TS group with the ADHD comorbidity. The difference in comorbidity was at least 25% in each age group, but significance was not reported (Roessner, Becker, Banaschewski, Freeman, et al., 2007).

These findings support the hypothesis that the presence of inattention/ hyperactive difficulties, or a comorbid diagnosis of ADHD, increases the likelihood of showing aggressive symptoms in children with TS.

Table 1.2 The Impact of ADHD Phenotype on Aggression in TS

NB: where it's been possible to calculate effect size, strength is given in parentheses; small (S), medium (M), large (L)

Study	Cases (n)	Controls (n)	Outcome variable	Results	p-value	Effect size <i>Cohen's d</i>
Carter et al., 2000	TS + ADHD (33)	TS-ADHD (16)	CBCL aggressive	66.58 (12.13) vs 53.50 (6.12)	P<0.01	1.361 (L)
			CBCL delinquent	61.21 (8.61) vs 52.93 (5.74)	P<0.01	1.132 (L)
De Groot et al., 1995	TS (92)	-	Conduct Disturbance	R=0.88 history of ADHD predicts conduct disturbance	P<0.001	
Hoekstra et al., 2004	TS+ADHDimp (18), TS+ADHDina (15)	TS-ADHD (25)	CBCL aggressive	17.78 (8.21) vs 13.93 (6.50) vs 8.54 (6.43)	P<0.001	Imp= 1.253 (L) Ina= 0.834 (L)
			CBCL delinquent	3.72 (3.54) vs 4.20 (4.48) vs 1.08 (1.14)	P=0.009	Imp= 1.004 (L) Ina= 0.954 (L)
Lebowitz et al., 2012	TS+ADHD (61) TS+ADHD+OCD (38)	TS-only (50)	Comorbidity of EXT (ODD and/or CD)	B=1.18, Wald's $\chi^2=6.03$ ADHD predicts Externalizing Disorder (ODD and/or CD)	P=0.014	-
Pollak et al., 2009	TS+ADHD (142)	TS-ADHD (38)	CBCL EXT*	58.3 (11.8) vs 51.3 (11.8)	-	0.593 (M)
			Main effect of TS (on EXT)	F(1,339)=19.4	P<0.001	-
			Main effect of ADHD (on EXT)	F(1,339)=38.60	P<0.001	-

Rizzo et al., 2007	TS+ADHD (20)	TS-only (20)	CBCL aggressive	62.88 (3.43) vs 55.94 (3.05)	-	2.138 (L)				
			CBCL delinquent	60.39 (2.23) vs 65.39 (2.53)	-	-2.097 (L)				
Roessner, Becker, Banaschewski, Freeman, et al., 2007	TS+ ADHD+ comorbidity	5-7 yrs (185)	TS – ADHD+ comorbidity	5-7 (65)	ODD/CD	42% vs 12%	-	-		
					Comorbidity					
					8-10 (582)	8-10 (195)	ODD/CD	38% vs 12%	-	-
					Comorbidity					
					10-13 (526)	10-13 (197)	ODD/CD	39% vs 13%	-	-
Comorbidity										
14-17 (379)	14-17 (224)	ODD/CD	37% vs 12%	-	-					
Comorbidity										
Roessner, Becker, Banaschewski, & Rothenberger, 2007	TS+ADHD (82)	TS-only (12)	CBCL aggressive	67.2 (11.2) vs 56.0 (6.5)	-	1.223 (L)				
			CBCL delinquent	63.2 (9.3) vs 54.6 (5.7)	-	1.115 (L)				
Sukhodolsky et al., 2003	TS+ADHD (52)	TS-only (42)	ODD comorbidity	34.0% vs 13.3%	-	-				
			CD comorbidity	4.0% vs 0.0%	-	-				
			CBCL aggressive	63.3 (11.4) vs 54.0 (5.6)	p<0.05	1.036 (L)				
			CBCL delinquent	59.0 (8.5) vs 52.1 (4.9)	p<0.05	0.995 (L)				
			CTR conduct	60.5 (15.6) vs 52.1 (13.1)	p>0.05	0.583 (M)				
Tabori Kraft et al., 2012	TS + hyperactivity (15)	TS – hyperactivity (42)	SDQ Conduct problems	3.13 (1.92) vs 0.86 (1.16)	-	1.431 (L)				

ADHDimp= ADHD impulsive type; ADHDina= ADHD inattentive type, *EXT= CBCL externalizing score=delinquent + aggressive behaviour scores

1.4.5 Greater Aggression and the Incidence of Attention Difficulties in TS

Four studies (Table 1.3) compared the incidence of attention difficulties in more versus less aggressive phenotype groups. Here we sought to test the hypothesis that children with TS and aggressive symptoms are likely to also have inattention/hyperactivity difficulties. Cohen's d ES's were calculated where possible (2/4 studies) however it was not possible to pool them because of the difference in measures employed.

Budman et al. (2000) used a modified version of the DSM-IV (1994) diagnostic criteria for IED to screen children at the time of recruitment for having explosive outbursts (EO) or not. Cases (TS + EO) were matched with controls (TS - EO). A comorbidity of ADHD was diagnosed in 95% of the sample with EO, and 65% of the sample without EO ($p < 0.01$).

Two studies (Ghanizadeh & Mosallaei, 2009; Nolan et al., 1996) reported attention problems by the CBCL attention subscale. The first found that attention problems were significantly higher in the TS+DBD group than the TS-DBD group ($p < 0.01$) with a large ES ($d = 1.480$). Here DBDs included a diagnosis of ADHD, CD, and/or ODD.

The second used a post-hoc analysis to split the sample into a more and less aggressive group, and found hyperactivity to be higher in the "more aggressive" group, with an insignificant p-value ($p = 0.170$) and a small-medium ES ($d = 0.407$). The sample was divided based on the following measures for each child; teacher-completed IOWA Conners Rating Scale, MOMS aggressive subscale, and direct observations of non-physical aggression in the classroom.

In Thériault's study (2014) ODD headstrong traits were found to significantly predict ADHD comorbidity ($\beta=0.29$ $p=0.001$), while ODD irritable traits did not predict ADHD ($\beta=0.05$ $p=0.649$).

Table 1.3 The Co-occurrence of ADHD and Aggression in TS

NB: where it's been possible to calculate effect size, strength is given in parentheses; small (S), medium (M), large (L)

Study	Cases (n)	Controls (n)	Outcome variable	Results	p-value	Effect size <i>Cohen's d</i>
Budman et al., 2000	TS + explosive outbursts (37)	TS - explosive outbursts (31)	ADHD comorbidity	95% vs 65%	P=0.002	-
Ghanizadeh & Mosallaei, 2009	TS + DBD (25)	TS - DBD (10)	CBCL attention problems	53.2 (8.8) vs 41.1 (7.5)	P=0.002	1.480 (L)
Nolan et al., 1996	TS more aggressive (22)	TS less aggressive (25)	CBCL hyperactive scale	11.82 (3.75) vs 10.36 (3.41)	P=0.170	0.407 (SM)
Thériault et al., 2014	ODD headstrong traits		Predicting ADHD comorbidity	$\beta=0.29$	P=0.001*	-
	ODD irritable traits			$\beta=0.05$	P=0.649**	

DBD=Disruptive behaviour disorders → includes ADHD** (n=24), ODD (10), CD (2); *Regression analysis: ODD headstrong traits significantly predict ADHD; **Regression analysis: ODD irritable traits do not significantly predict ADHD

1.5 Discussion

To our knowledge, this is the first systematic review looking at the association between aggression and ADHD symptoms in TS. The paper reviewed 14 studies that explored the relationship between ADHD symptoms and aggression in children with TS (Table 1.1).

The study outcomes were divided into two main categories:

- The first outcome showed the difference in aggression between groups with more or less inattention/hyperactivity (Table 1.2). Our findings confirmed that aggression in TS is significantly associated with ADHD comorbidity and symptom severity. Where studies used similar methodologies, a large pool effect size was found ($d=1.247$) between the mean aggression scores on the CBCL when comparing TS+ADHD groups to TS-ADHD groups. More details of this finding are shown in Section 1.5.1.
- The second section evaluated the difference in attention difficulties between groups of more or less aggression or conduct difficulties (Table 1.3). Three out of three studies showed higher attention or hyperactivity difficulties in groups with more aggressive symptoms, leading to confirmation of the hypothesis that inattention and hyperactivity or more severe in groups with more aggression in TS. However, in one of these studies the difference was not significant. Due to the variety of methodologies used, no pooled effect sizes were calculated. More details of these findings are described in Section 1.5.2.

1.5.1 What is the Impact of ADHD symptoms on Aggression in TS?

Several studies in the literature have pointed to higher levels of impulsive and aggressive behaviours in the population of children with ADHD comorbidity in TS. The extent of the difference is measured in this study using pooled effect sizes where possible. Our study confirmed that aggression in TS is significantly associated with a comorbidity of ADHD. We found a large pooled effect size ($d=1.247$) between the means of the CBCL aggression scale in the TS+ADHD group compared to TS-ADHD. There was also more aggression in participants with impulsive type of ADHD than with the inattentive type of ADHD. These findings are consistent with our hypothesis that aggression in TS may be linked to the nature of ADHD.

The CBCL scales for delinquency, also known as rule-breaking behaviour, and aggression, have a phenotypic correlation from 0.48 to 0.76; the co-occurrence is well documented, and all questions in the two scales point to the direction of “problem” behaviours (Appendix III). Therefore delinquency was used as a proxy for aggression in this study. However, many CD experts have suggested looking at aggressive CD and delinquent CD as two separate syndromes (Frick et al., 1993; Lahey, McBurnett, & Loeber, 2000). This, therefore, raises the question of whether the delinquency scale, and diagnoses of CD/ODD are valid proxies for aggression.

Additionally, since the CBCL measure has been created for all children with or without psychiatric conditions, one issue that may arise is that items on the scale may be difficult to disentangle from TS traits. For example, on delinquency scale, one item “swears or uses obscene language” may be inaccurate as swearing tics can be seen independent of aggression and the symptoms may be confused.

Taken from the studies, delinquency is found to be higher in the TS+ADHD group than the TS-ADHD, with the exception of one study (Rizzo et al., 2007). The pooled effect size was found to be small-medium ($d=0.439$). Therefore, although there is a difference between the two groups on the delinquency scale, the difference is smaller than the difference documented on the aggression scale.

Pollak et al. (2009) showed that, when combining CBCL aggression and delinquent scales to form an externalizing score, and completing an ANCOVA, main effects were revealed for both TS and ADHD independently, but not an interaction effect. ADHD had a greater main effect than TS ($F=38.60$ vs 19.4 respectively $p<0.001$).

Sukhodolsky et al. (2003) showed an insignificant difference between the TS+ADHD and TS-only group means when using the CBRS-T eight-item conduct subscale. Again, the proxy of using conduct difficulties to represent aggression may introduce a new element of variability and therefore the outcome should be considered within context.

The SDQ conduct problems scale showed higher means in a more-hyperactive group than a less-hyperactive group of children with TS (Tabori Kraft et al., 2012). The sample was split between more and less hyperactive group using a threshold on the SDQ hyperactivity subscale in a post-hoc analysis. However, in using the hyperactivity scale as a proxy for ADHD, we might expect that other aspects of ADHD were overlooked. For example, children with high inattention or impulsivity may have been categorized as non-hyperactive.

A history of ADHD was found to predict conduct disturbance (De Groot et al., 1995). Similarly, ADHD comorbidity predicted DBD (CD and/ or ODD) (Lebowitz et al., 2012). These findings are consistent with existing literature where CD has been found to be significantly linked to ADHD in the TS population (Robertson et al., 2015). Similarly, several studies have shown links between ADHD and DBDs (Carter et al., 2000; Pierre, Nolan, Gadow, Sverd, & Sprafkin, 1999; Sukhodolsky et al., 2003).

Throughout development, there appears to be a higher incidence of comorbidity of DBDs in the population of children with TS and ADHD, compared to TS without ADHD. The existence of other comorbidities was not controlled for in this population. Although the study was cross-sectional, the proportions were relatively consistent between 5-17 years of age; the proportion of CD/ODD in the ADHD group was between 37-42%, and between 12-13% in the non-ADHD group.

It therefore follows that all of the proxies used for aggression in this study were found to be higher in the TS+ADHD group than in the TS-ADHD. Therefore children with TS and inattention/hyperactivity difficulties are more likely to show increased aggression and conduct problems.

1.5.2 Are Attention Difficulties More Pertinent in Aggressive Phenotypes in TS?

The incidence of inattention/hyperactivity in more aggressive groups of TS showed mixed results. There was a variety of methodologies used in splitting samples into more and less aggressive. Given this, it was not possible to calculate a pooled effect size.

Attention difficulties (using the CBCL) were significantly higher in the group of TS+DBD than the group of TS-DBD (Ghanizadeh & Mosallaei, 2009). However, in this study, a comorbidity of DBD included CD, ODD, and/or ADHD, while in the rest of this review, DBDs only included CD and ODD. Therefore, when considering that the TS+DBD group included a proportion of children with TS+ADHD, it is not unusual that attention difficulties would be higher in that group. Because of this, it is difficult to disentangle the relationship between attention and anger in these two phenotype groups.

The mean score of the CBCL hyperactive scale was insignificantly lower in a “less aggressive” TS group. The sample was split between more and less aggressive as a post-hoc analysis, and the validity of the threshold was unclear. Similarly, using a hyperactive scale as a proxy for ADHD may exclude children who had high levels of inattention, and may have potentially met the criteria for ADHD – inattentive subtype.

Budman et al., (2000) showed that children with explosive outbursts in TS were significantly more likely to have a diagnosis of ADHD. This study therefore supports the hypothesis that ADHD and impulsive aggression are significantly linked in TS. That said, 65% of the sample of children with TS and without explosive outbursts still had a diagnosis of ADHD, which is higher than the population base-rate.

Finally, ODD headstrong traits were significantly predictive of ADHD comorbidity, while ODD irritable traits were not. This further validates that there are different types of aggression in TS and therefore some types may be accounted for by ADHD while others might not.

According to these studies there is an unclear relationship between having aggressive symptoms in TS and the likelihood of having attention or hyperactive difficulties. The difficulty with drawing conclusive results is mainly due to the variation in the methodologies and outcome measures used between the studies.

1.5.3 Limitations

The main limitation of this study is the inconsistent methodological designs between the studies. In study design, we explored articles in which groups of children with TS could be compared with children with and without ADHD. However, while some studies used a TS-ADHD group as a control, other studies used a TS-only group. This introduces a variety of confounding variables to control for, with more than half of clinically referred children with TS suffering from two or more psychiatric comorbidities (Hirschtritt et al., 2015). As such, although ADHD may have been excluded in cohorts, it is possible that the children had other diagnoses such as OCD, ODD, CD, among others, which are each independently considered contributing factors to anger in the literature.

Another difficulty with comparing the studies is the use of varying proxies as measures of anger. Anger itself is not classified as a delineated comorbidity because of the varying aetiologies and behaviours expressed. As such standardized measures have had to be used, such as the CBCL aggression scale to account for typical expressions of aggression in childhood and the CBCL delinquency scale was also used for symptoms that typically co-occur with anger in childhood.

Disruptive Behaviour Disorders (CD and ODD) were also used as a proxy for aggression. However, the studies used, among others, have shown links between ADHD and disruptive behaviours including CD and ODD, therefore potentially introducing bias to the population should there be a neurobiological link between the conditions (Carter et al., 2000; Haddad, Umoh, Bhatia, & Robertson, 2009; Pierre et al., 1999; R J Stephens & Sandor, 1999; Termine et al., 2006). Additionally, in CD in particular, many traits that are not typically considered “aggression” per se can account for a diagnosis, such as theft and truancy. In one study, DBD comorbidity included a comorbidity of ADHD which would, by its nature, result in an elevated attentional and hyperactivity difficulties.

1.5.4 Future Studies

An important aspect that is explored in the literature that was overlooked in this study was the relationship between tic severity and aggression. Studies have shown tic severity to be associated with increased SIB (Mathews et al., 2004), explosive outbursts (Chen et al., 2013), irritability symptoms (Cox & Cavanna, 2015), and a history of aggressive behaviours (Robertson et al., 2015). On the other hand, Robertson (2015) also showed that this difference in tic severity was not found between people with or without CD / ODD diagnoses. Additionally, Kano (2008) and Budman (2008) found no link between tic severity and aggressive symptoms. While the relationship remains unclear, this should be considered, or controlled for, in future studies.

Other factors possibly contributing to aggression TS that have been considered in the literature but need to be explored more thoroughly are elevated parental aggravation (Robinson, Bitsko, Schieve, & Visser, 2013), stress and bullying in the context of TS,

emotional dysregulation and processing in TS (Drury et al., 2012), the impact of sleep difficulties (Stephens et al., 2013), and impairments in executive functioning more broadly (Hovik et al., 2017).

Considering the heterogeneity of anger expression, future research should work to break down types of aggression and disentangle the risk factors and aetiology for each type of aggression in TS. For example, aggressive symptoms may represent broader difficulties with emotional processing. It can also indicate insufficient role modelling from parents of regulating emotions, or modelling using violence to manage aggression (in cases of domestic violence). On the other hand, it can be linked to a child's experience of being victimised in different contexts, including being bullied in schools. It can also stem from difficulties with impulsivity and non-intended uses of aggression to regulate hyperactivity. As psychological questionnaires rarely ask about why a behaviour is happening, and instead ask what is happening and how often, the aetiology can often be missed in quantitative studies. Future studies can consider using more semi-structured interviews to explore the causes of the aggression, and can include (or control for) risk factors in their analysis for overall aggression.

1.5.5 Conclusion

The findings show that a comorbidity of ADHD, and ADHD symptoms, in children with TS are highly associated with an increased aggressive symptoms and other behavioural difficulties, including delinquency. In multiple regression studies, ADHD predicts aggressive symptoms. Similarly, in ADHD, impulsive traits were more closely linked to aggression than inattentive traits. In ODD, it is headstrong traits, rather than irritable traits

that predict ADHD comorbidity. Therefore, it is important that clinicians consider the existence of ADHD comorbidity and symptoms in TS to be more aware of the risk factors for behaviours that challenge.

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Part II: Empirical Study

Time Processing and Adaptive Functioning in Children with Tourette Syndrome

2.1 Abstract

Aim: To investigate the relationship between time processing abilities and adaptive functioning, or the ability to meet the demands of everyday life, in Tourette syndrome (TS).

Method: This was a joint project in which forty-seven children aged 6 to 15 with TS were recruited. Each child completed a battery of cognitive assessments that included a test of intelligence, a time processing measure that included discrimination and reproduction tasks, assessments of sustained and switching attention, and an assessment of executive functioning. Their caregivers concurrently completed clinical questionnaires on adaptive functioning and Attention Deficit / Hyperactivity Disorder symptom severity. A measure of tic severity was obtained using a structured interview with the child and parents. Standardised measure scores were compared to normative populations using one-sample t-tests. The relationships between cognitive functions and adaptive functioning were explored using Pearson's correlations and linear regressions.

Results: Intellectual ability and executive functioning were intact while adaptive functioning was significantly impaired. On the time tasks, longer time intervals were associated with smaller reproduction error. Tic severity was associated with reproduction error in supra-second durations but not in sub-second trials. With the exception of verbal comprehension, all IQ domains as well as attention tasks predicted reproduction error in the sub- and supra- second ranges. Age predicted time reproduction in the supra-second range. Sub-second reproduction error predicted overall adaptive functioning.

Conclusion: Timing is an important cognitive function that is shown to have a close relationship with other cognitive functions, particularly working memory and attention.

Time skills for longer durations appear to develop at later stages than short (sub-second) durations. Sub-second (automatic) timing skills are essential to day-to-day functioning, particularly socialisation, and can predict an individual's level of independence.

2.2 Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder that affects approximately 1% of the international population (Robertson, Eapen, & Cavanna, 2009) and is characterised by chronic involuntary movements and sounds, known as tics. The Diagnostic Statistical Manual of Mental Disorders (DSM 5th ed.; American Psychiatric Association, 2013) characterises it by the presence of multiple motor and one or more vocal tics that have been present for at least one year. Although the impairment is not included in the diagnostic criteria, studies have shown TS to be associated with difficulties relating to behaviour, mood, cognition, and overall quality of life. A recent study, for example, showed that young people with TS seen in specialist clinical settings had substantial educational impairments including being more likely to fail all subjects in primary school and being less eligible for, and likely to complete, secondary school (Pérez-Vigil et al., 2018).

In this study we consider the cognitive abilities of children with TS and investigate the impact of intellectual abilities on overall functioning. Time processing, or the ability perceive and estimate time intervals and adjust one's behaviour to specific timeframes, is a cognitive task that develops in infancy (Allman & Mareschal, 2016) and has been shown to be impaired in several neurodevelopmental conditions and movement disorders including Attention Deficit/ Hyperactivity Disorder (ADHD; Noreika, Falter, & Rubia, 2013), Autism Spectrum Condition (ASC; Allman, DeLeon, & Wearden, 2011), dyscalculia (Moll, Göbel, Gooch, Landerl, & Snowling, 2014), Huntington's and Parkinson's Disease (Avanzino et al., 2016). One recent study investigated time processing in TS and showed higher accuracy in the processing of longer time intervals

in TS children with lower tic severity (Vicario et al., 2010). It was proposed that this was due to the existence of a compensatory tic inhibition capacity that corresponds with prefrontal cortex activation and increased precision in processing longer intervals.

Time deficits are shown to impact broader functioning, such as social cognition (Striano & Reid, 2006; Trevarthen & Daniel, 2005), understanding causality (Freeman, 2008), and daily time management (Wennberg, Janeslätt, Kjellberg, & Gustafsson, 2018). These domains are intuitively linked to adaptive functioning, or the ability to meet the demands of daily life. Therefore, the aim of this study is to investigate the impact of time processing skills on adaptive functioning.

2.2.1 Neurobiology of TS

Differences exist in the neurobiological structures of children with TS and these pathways have been linked to the pathways involved in attention, working memory, and time processing, among other cognitive abilities. This leads to the hypothesis that time deficits exist in TS. In TS impairments are particularly found in the pathways that connect the striatal to cortical structures. Impairments in the cortico-striatal-thalamo-cortical (CTSC) circuitry has provided a framework to understanding TS and co-occurring disorders (Harris & Singer, 2006; Leckman, Bloch, Smith, Larabi, & Hampson, 2010; Mazzone et al., 2010). Based on what is known of the physiologic properties of the basal ganglia (BG), recent models of movement disorders hypothesise they act as a selection centre, facilitating movements and vocalisations while inhibiting competing ones (Mink, 2003). Stereotyped movements can result from activation of a focal population of striatal neurons, particularly the putamen in the BG (Mink, 2001). Unwanted activation of the

striatal neurons can occur for a variety of reasons, including excessive cortical or thalamic input to the striatum, deficient intrastriatal inhibition, or unusual membrane excitability (Mink, 2003).

The organisation of striatal and basal ganglia output, elaborated by Albin (2006; Figure 2.2), are seen to have an inhibitory function on involuntary movements. In TS, a discrete set of striatal neurons becomes active inappropriately, leading to an increase in inhibition of neurons in the BG (GPI: Internal segment of the Globus Pallidus or SNr: Substantia Nigra Pars Reticulata). This leads to the disinhibition of the thalamocortical mechanisms that are involved in the inhibition of unwanted motor patterns (tics).

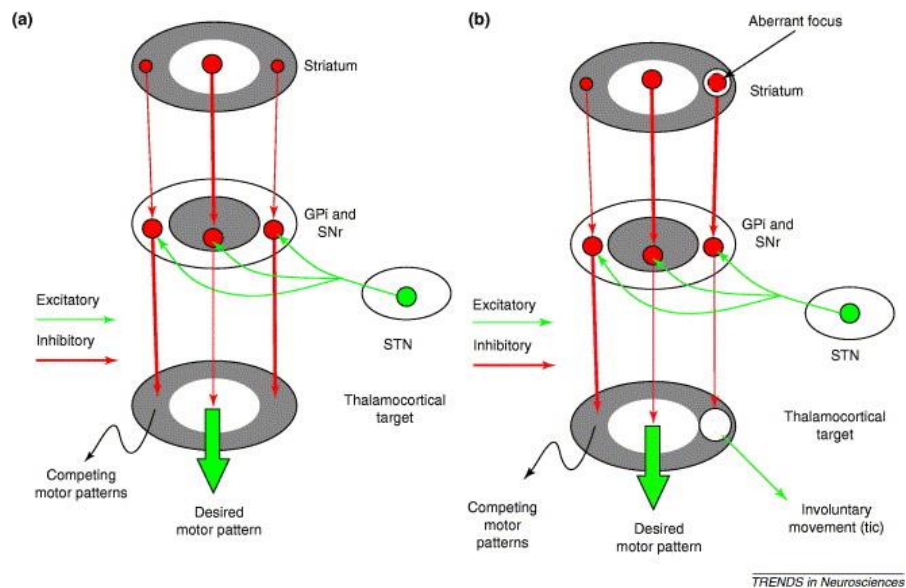


Figure 2.2 Visual Representation of Basal Ganglia Output Under Typical Conditions and in TS.

(a) Typical functional organisation of basal ganglia (BG) output. Line thickness depicts relative magnitude activity. Red representing inhibitory pathways and green representing excitatory pathways. Thalamocortical target shows ideal pattern of activating desired motor pattern and background of competing motor patterns. (b) Hypothetical functional organisation of BG in TS. Aberrant focus represents a discrete set of neurons in the striatum becoming active inappropriately, leading to the inhibition of structures in the BG. GPI (globus pallidus pars interna) and SNr (substantia nigra pars reticulata) are both structures in the BG; STN: subthalamic nucleus. Adapted from: Albin, 2006.

Many features of TS can be explained by abnormal BG output patterns, such as the erroneous inhibition of thoughts, behaviours, and movements (Smeets, Leentjens, Duits, Temel, & Ackermans, 2018). Mink (Mink, 2001) showed that abnormal activation of the premotor cortex or supplementary motor area (SMA) leads to complex tics and abnormal activation of the dorsolateral prefrontal cortex (DLPFC) produces attention deficits.

2.2.2 Neurobiology of Time Processing

Timing in the brain is an area of research that is under intensive investigation, and is increasingly becoming known as one of the brain's most important basic functions (Paton & Buonomano, 2018). There are multiple circuits within the brain that impact on an individual's ability to tell time and, depending on the length of time being processed can include an overlap in structures involved in TS such as the BG, SMA, and frontal cortex. These abilities have often been assessed by tasks that require three types of timing skills: the first is the production of a temporal pattern using a motor response (motor timing), the second is the perception or discrimination of time intervals (perceptual timing), and the third is the use of temporal foresight to consider future consequences of behaviour. In this study we focus on motor and perceptual timing abilities in TS.

The second neuroanatomical distinction has been made regarding the length of the timing intervals. There is evidence of the difference in processes involved with millisecond (sub-second) durations, and longer than one second (supra-second) durations (Lewis & Miall, 2003; Lewis & Miall, 2003; Rubia, 2006; Wiener, Turkeltaub, & Coslett,

2010). The processing of sub-second timing intervals (automatic timing) are crucial for motor control, and subcortical regions like the BG and cerebellum are significantly more involved in this interval duration (Noreika et al., 2013; Wiener et al., 2010). The cerebellum has long been hypothesised to be pertinent to timing, and especially making time predictions (Braitenberg, 1967, 2002; Coull, Cheng, & Meck, 2011). Wiener (2010) showed that the SMA and the right inferior frontal gyrus were the only two regions crucial to all timing durations. Specifically, it was shown that the left SMA was more involved in sub-second durations and right SMA in supra-second durations. Sub-second neural processes are shown to rely less on other cognitive functions like attention, working memory, and cognitive control functions, which are required for supra-second intervals (Noreika et al., 2013); this aligns with findings of high levels of right frontal cortex activation in longer interval durations for both perceptual and motor timing tasks (Baier et al., 2010; Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003).

The overlap in neurobiological pathways in time processing and the pathways of known impairment in neurodevelopmental conditions, including tic pathways, attention and working memory, leads to the hypothesis that time deficits exist in developmental conditions.

2.2.3 Time Processing in Developmental Disorders

The developmental processes involved in the formation of temporal processing ability is a growing area of neurobiological, psychological, and evolutionary research. Falter and Noreika (2011) postulate that abnormally developing cognitive functions have close and complex associations with timing, and that timing may play an important role in

developmental disorders. A review by Allman and Mareschal (2016) links the social parent-infant interactions in the first year of life with different types of temporal patterning that allows an infant to adjust expectations and behaviours to better suit the parent's tempo; this has been shown to be disrupted in autism. At a neurobiological level, these 'here & now' short-scale timing events are processed by cortico-striatal circuits (Allman & Meck, 2012). Disruptions to these circuits, such as in TS, are thought to create problems in sequencing components of action, thus producing stereotyped and repetitive thought and action, as well as impulsivity (Allman & Meck, 2012; Garner & Mason, 2002; Thelen, 1979). Stereotypies appear to be typical in infancy (Thelen, 1979) but can become problematic when extended into childhood, such as in developmental disorders (TS, ID, ASC).

In order to assess timing in developmental conditions, the most common approach has been the use of time discrimination and time reproduction tasks. In time discrimination tasks participants are asked to determine which of two interval lengths is longer in duration, while in time reproduction tasks, the participant is asked to produce an interval length by pressing on a key (usually a space bar) for the same length of time of a given interval.

2.2.3.1 Time Discrimination

Discrimination tasks tap into early perceptual timing skills and require limited motor ability. Vicario and colleagues, (2010) investigated the difference in time discrimination between a group of participants with pure-TS (with no other psychiatric comorbidity) and healthy controls, in sub-second and supra-second interval comparison tasks, and found

no significant difference between the groups. An early report (Goldstone & Lhamon, 1976) showed that durations of auditory stimuli could be accurately discriminated in TS, at a comparable level to healthy controls. Goudriaan et al. (2006) investigated discrimination in durations above one-second (2-20s) and found that adults with TS did not differ from healthy controls, and outperformed participants with pathological gambling and alcohol dependence. However, in this study time intervals were measured on a stopwatch therefore limiting the precision of the findings.

Although sparsely investigated in TS, it has been looked at in multiple other neurodevelopmental disorders. Noreika et al. (2013) reviewed twelve studies that used timing discrimination tasks in ADHD and concluded that interval discrimination is consistently lower in individuals with ADHD than in typically developing controls, both in the sub-second and supra-second interval ranges. One study (Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003) showed that children with diagnosed ADHD were significantly impaired in timing discrimination tasks, while community children with high levels of ADHD behaviours, but not meeting threshold for diagnosis, did not show impairment, thus suggesting that severity of symptoms may determine the level of impairment.

Time deficits are also shown to be related to other cognitive functions. Working memory measured in two studies (Toplak, Rucklidge, Hetherington, John, & Tannock, 2003; Toplak & Tannock, 2005) significantly predicted discrimination ability in ADHD groups, therefore suggesting that working memory ability is required for time comparisons. A recent study (Lee, 2018) supported these findings showing that children with higher working memory capacity performed better on time discrimination tasks, and

that, when controlling for working memory, the performance of children with ADHD was not worse than that of controls. Additionally, Rubia et al., (2007) showed that discrimination errors were positively correlated with premature responding on executive functions tasks, therefore indicating that premature responding might be inter-correlated with errors in timing, or potentially add noise to existing data.

Similar findings of impaired discrimination have been found in other neurodevelopmental conditions. In ASC, Allman et al., (2011) showed that individuals with autism experienced greater difficulty discriminating between longer durations (durations 3.5-5s), while Mostofsky et al. (2000) found no evidence of temporal discrimination difficulties, in supra-second durations, in young people with ASC. In dyscalculia (Cappelletti, Freeman, & Butterworth, 2011) time discrimination skills appeared to be spared, despite having impairments in numerosity.

2.2.3.2 Time Reproduction

Time reproduction tasks require a motor response from the participant in reproducing an observed interval, therefore has been discussed in the literature as both motor and perceptual timing task. These tasks rely more on motor skills, including hand-eye coordination, and holding temporal information in mind (working memory), especially those that are longer in durations than time discrimination tasks do (Dutke, 2005).

In participants pure-TS, Vicario et al., (2010) showed a significant positive correlation between tic severity and time reproduction error in supra-second intervals, meaning that the higher the level of severity, the higher the reproduction error of time

intervals. It was also shown that TS participants performed better than healthy controls on reproduction tasks in the supra-second range, with no significant difference in the sub-second range. Vicario et al., (2010) proposed that this could be explained by a compensatory phenomenon of tic suppression that corresponds with prefrontal cortex activation. The effect of dopamine D₂ receptor blocker pimozide on time reproduction was assessed in participants with TS (Vicario, Gulisano, Martino, & Rizzo, 2016) and showed that reproduction performance improved in supra-second intervals, observed by a reduction in performance variability after pimozide administration.

Noreika (2013) reviewed all 21 ADHD studies published between 1997 and 2012 that used time reproduction tasks to compare time processing in ADHD versus healthy controls. The most consistent findings show decreased reproduction accuracy and higher absolute discrepancy scores in ADHD patients relative to controls. Five studies also found significantly higher reproduction errors in the ADHD group only for the relatively longer intervals. Similarly, time reproduction was explored in Specific Learning Disorders (Moll et al., 2014) and it was found that mathematics disorder was associated with temporal reproduction deficits, especially in longer duration intervals. On the other hand, this was not found in reading disorders. The authors predict that this discrepancy is due to the deficits in attention in the reading disorder group.

In ASC there have been fewer studies, and more inconsistent findings, in the investigation of time reproduction skills. Two studies (Martin, Poirier, & Bowler, 2010; Szelag, Kowalska, Galkowski, & Pöppel, 2004) tested high-functioning participants ASC and compared their performance to healthy control groups using temporal reproduction paradigms. Both studies showed impairments in ASC time reproduction. On the other

hand, Wallace and Happé (2008) showed no significant group differences between ASC and control groups, with some evidence of more accurate performance in the ASC group.

2.2.4 Adaptive Functioning in TS

Adaptive functioning is defined as one's ability to apply cognitive abilities in order to meet common demands of everyday life. The most commonly used adaptive behaviour measure used in the literature is the Vineland Adaptive Behaviour Scale (VABS), which recently released its 3rd edition (Sparrow, Cicchetti, & Saulnier, 2016). The VABS is a care-giver reported measure that assesses adaptive behaviour by three required domains: communication, daily living skills, and socialisation.

Adaptive behaviour has sparsely been investigated in TS. Only one study that we are aware of reported the complete VABS to assess adaptive functioning (Sukhodolsky et al., 2003). A pure-TS group did not differ from the control group on the Communication and Socialisation domains. The pure-TS group also showed significantly better functioning than a TS+ADHD group in the socialisation domain. In the daily living domain, impairment was maintained even after controlling for ADHD, indicating that both the TS-only and TS+ADHD groups performed significantly lower than the unaffected control group.

Some studies only reported the results of the socialisation domain in the VABS. Similar to Sukhodolsky (2003), Carter (2000) showed that in the socialisation domain, impairments were only significant in the TS population with a comorbidity of ADHD and that socialisation was spared in the uncomplicated TS group. Gorman (2010), on the other

hand, showed that impairment in the socialisation domain was still maintained in TS after controlling for a lifetime diagnosis ADHD.

Studies have shown close associations between time processing and cognitive functions that are closely linked to the domains of adaptive behaviour. For example, social cognition (Striano & Reid, 2006; Trevarthen & Daniel, 2005), language processing (Tallal, Miller, & Fitch, 1995) and understanding of causality (Freeman, 2008) were found to be associated with time processing in development. These cognitive functions are intuitively related to adaptive outcomes, therefore raising the question about the impact of time processing skills on adaptive functioning.

The impact of timing deficits has recently been explored in ADHD. Mioni et al (2017) showed that time perception predicted prospective memory accuracy in ADHD, showing the broader consequences of timing deficits in the population. Prospective memory is essential in completing and managing daily tasks, a key part of adaptive functioning. Similarly, time-related interventions in children with ADHD resulted in increased time processing abilities, and parents rated significantly higher daily time management in their children than the parents of children in a control (non-intervention) group (Wennberg et al., 2018). Therefore, improvements to time processing may lead to improvements in daily living and meeting the demands of daily life.

2.2.5 Aims

Our objective in this study is to investigate whether time processing abilities predict adaptive functioning abilities in TS.

1. Our first hypothesis is that children with TS will show significant impairments in adaptive functioning as compared with standardised norms.
2. The second hypothesis, based on Vicario et al., (2010), is that tic severity will be correlated with time reproduction errors in the supra-second range.
3. Our third hypothesis, based on findings in ADHD studies (Lee, 2018; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003; Toplak & Tannock, 2005), is that working memory and attention will predict time processing ability in regression models, and that executive functioning may also be related (Rubia, 2007).
4. Finally, we hypothesised that time processing will predict adaptive functioning and that attention may mediate this relationship.

2.3 Method

2.3.1 Participants

Full ethical approval was received from the National Health Service Bloomsbury Research Ethics Committee (REC reference 220775; Appendix IV). Funding was obtained from Tourette Action (Appendix V) in addition to the research allowance provided by UCL.

Informed consent was obtained from all participants' parents prior to being included in the study. Children also provided informed assent before taking part in the study. Information sheets and consent / assent forms for parents/ children can be found in Appendix VI.

Based on existing unpublished adaptive functioning data in the clinic, we expected to find a medium-to-large effect size for the relationship between adaptive functioning and standardised norms. A two-tailed power analysis for correlational tests with this magnitude of effect ($r=0.4$) and with the alpha threshold set to .05, suggested that a sample size of 50 would be required to achieve 80% power.

Forty-seven children aged 6 to 15 were took part in the study. As such, given the recruitment difficulties and limited resources available for the research, the study is only slightly under-powered.

The inclusion criteria were children aged 6-16 at the point of recruitment who received their education in English. Exclusion criteria were having a cognitive assessment in the past year, a diagnosis of an Intellectual Disability (ID) and severe and enduring mental health conditions or acquired brain injury. Children were recruited through the Tourette syndrome Clinic and Psychological Medicine Team database of patients seen over the past 3 years at a London specialist children's hospital, where approximately 100 new patients with TS are seen per year. Participant characteristics are summarised in Table 2.4.

2.3.2 Procedure

This was a joint research project with another DCLinPsy trainee, LH. Individual contributions are detailed in Appendix VII. Initial contact was made with information sheets by post (Appendix VI) and a subsequent phone call by one of the researchers. A choice of an appointment at the clinic or a visit by the researcher to the family home were

offered in order to maximise recruitment. Fewer than half (18/47) of the participants were seen in the clinic. All of the measures described below were administered by one of the two trainees in a single session, which was 3.5-4 hours in length, including breaks. The battery was broken up into two blocks, approximately equal in length, and counterbalanced to be administered in alternating order, in order to reduce bias or fatigue effects. A few months after the assessment, a cognitive report detailing the child's cognitive profile, areas of strength and areas for development, as well as a child-report were sent out to families (Appendix VIII).

2.3.3 Measures

All of the measures listed below were administered to the 47 participants, while their parent(s) completed the parent/caregiver-report measures. Only measures that were relevant to this study are listed below.

2.3.3.1 Child Performance Measures

General Intellectual Ability: The Wechsler Intelligence Scale for Children (WISC-V; Wechsler, 2016) is a measure of intelligence suitable for children ages 6 to 16. The test generates a full-scale IQ (FSIQ) and five index scores under the following domains: Verbal Comprehension (VCI), Visual Spatial (VSI), Fluid Reasoning (FRI), Working Memory (WMI), and Processing Speed (PSI). The complete test, without the ancillary subtests, was administered.

Executive functioning: An abbreviated version of the Behavioural Assessment of the Dysexecutive syndrome in Children (BADS-C; Emslie, Wilson, Burden, Nimmo-Smith, & Wilson, 2003) was administered. Three subtests relating to the executive functioning domains of interest were selected: Zoo map tests (1 and 2) to assess scanning and planning abilities, and the Six-parts test to assess planning and organisation.

Attention: An abbreviated version of the Test of Everyday Attention in Children, Second Edition (TEA-Ch2; Manly et al., 2016) was administered. The Simple RT and Vigil tests assessed sustained attention and the Red, Blues, Bags and Shoes (RBBS) task assessed attentional switching.

Time processing: The experimental time processing measure created and administered by Vicario on a previous TS study (Vicario et al., 2010) was used. In order to standardise the size of the stimulus between the two laptops used in the study, subjects sat at the distance from the computer that was suggested by the TEA-Ch2 manual guidelines. Presentation order of the tasks (comparison, reproduction) and presentation order of the blocks (sub- and supra-second) within each task were counterbalanced between subjects.

Time comparison task: the task instructions were described to participants and a trial block was administered to ensure their understanding. Participants were required to determine whether a test stimulus (a black circle presented on the screen) had been presented for a time interval longer or shorter than a reference stimulus (the same black circle) shown just before. If the first (i.e. the reference) stimulus was longer they were asked to press “1” on the keyboard and if the second (i.e. test) stimulus was longer they pressed “2” using their right and left index finger. Two separate blocks were administered, one with sub-second stimuli and one with supra-second stimuli.

In the sub-second block, the length of the reference stimulus was 400ms and was presented immediately before the test stimulus on each task. There were six difference sub-second test stimuli: 310, 340, 370, 430, 470, and 500ms, each of these was presented 10 times amounting to 60 randomised trials. In the supra-second block, the length of the reference stimulus was 1400ms and was presented immediately before the test stimulus on each task. The test stimuli intervals were 1280, 1320, 1360, 1440, 1480, and 1520ms in length, also presented 10 times amounting to 60 randomised trials. Therefore, in both blocks, half of the test stimuli were longer than the reference stimulus, and half were shorter. The performance of each subject was taken as the number of correct trials on each block and interval, therefore giving a score out of 10 for each subject on each interval length.

Time Reproduction Task: the task instructions were described and a trial block was administered once or twice before beginning the task. Subjects were asked to keep their eye on a black cross centrally located on the screen that was shown for 500ms. A black circle (test stimulus) appeared immediately after in the same place as the cross and disappeared after a certain interval. Participants were asked to reproduce the interval by pressing the space bar on the key pad using the index finger of their dominant hand for the same amount of time. Two blocks were administered, a sub-second and supra-second interval block.

In the sub-second block there were five test stimuli intervals administered: 500, 600, 700, 800, and 900ms. Each was administered 10 times in a randomised order amounting to 50 trials. In the supra-second block, five test stimuli were administered, 10 times each in a random order: 1500, 1600, 1700, 1800, 1900ms. The reproduction error

was calculated as the difference in time between the reproduced interval and the reference interval (Equation 2.1). The Absolute Reproduction Error (ARE; Equation 2.2) was calculated as the average of the *absolute* reproduction error at each interval length for each individual, divided by the length of the reference interval and multiplied by 100.

Equation 2.1 Reproduction Error

$$\text{Reproduction Error} = \text{Produced Interval} - \text{Reference Interval}$$

Equation 2.2 Absolute Reproduction Error

$$\text{Absolute Reproduction Error} = \frac{M|\text{Reproduction Error}|}{\text{Reference Interval}} \times 100$$

M = individual mean for each interval length

2.3.3.2 Parent/ Caregiver-Rated Measures

While the researcher administered the child performance measures, parents/ caregivers sat in another room and completed the measures listed below.

Adaptive Functioning: The Vineland Adaptive Behaviour Scales, Third Edition (VABS-3; Sparrow et al., 2016) comprehensive parent form was completed by each parent. It is standardised from ages 0-90 years. This measure assesses three required domains for the relevant age of study participants: communication, daily living skills, and socialisation. A final Adaptive Behaviour Composite (ABC) score is also extracted. Higher scores indicate an increased level of independence in each domain.

Attention: The Swanson, Nolan, and Pelham (SNAP-IV; Swanson, 1995) 26-item is based off of DSM-5 (2013) criteria for ADHD and ODD. Three subset scores are

produced: inattention, hyperactivity/ impulsivity, and opposition/defiance. The higher the score the higher the level of difficulty in each subset. A combined score of inattention and hyperactivity/impulsivity was calculated to represent ADHD severity.

Tic Severity: The Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989) was administered at the end of the assessment with child and caregivers present. A global tic severity score was calculated based on the number, frequency, intensity, complexity, interference of tics, as well as the level of impairment from tics, in the past week.

2.3.4 Statistical Analysis Procedures

Quantitative analysis was conducted using SPSS (version 25.0). All missing data was recorded in SPSS and the default method was used: correlations were computed based on the number of pairs with non-missing data. In regression, if any variables were missing, the entire case was excluded from the analysis.

1. First-step analysis assessed whether group means for standardised cognitive and behavioural measures were lower for children with TS as compared with control means. In order to test the hypothesis that children with TS show impairments in adaptive functioning, as compared with intellectual abilities, one-sample t-tests and effect sizes (*Cohen's d*) were calculated with the means from the participants in the study and compared to available standardised test norms.
2. Secondly, the relationship between adaptive functioning and all clinical variables was assessed by correlation. Due to the high number of correlations we conducted a Bonferroni test to reduce the risk of type I error.

3. Thirdly, calculation of time descriptive characteristics looking at group means of correct comparison scores, and percentage of reproduction error in each block and interval was calculated. Means were computed for sub- and supra- second blocks on both tasks.
4. Fourthly, in order to test the second hypothesis that tic severity is correlated with time reproduction errors (as found by Vicario, [2010]), a correlational analysis was calculated between timing variables and tic severity. Where findings were significant, bivariate outliers were excluded using the residuals and a Tukey 1.5 * hinge spread analysis.
5. Next, to test the hypothesis that working memory and attention predict time processing ability, as theorised by ADHD studies (Lee, 2018; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003; Toplak & Tannock, 2005), correlational and regression analyses were conducted for time and cognitive ability (IQ, attention, and executive functioning).
6. Finally, to test the fourth hypothesis that time processing predicts adaptive functioning, and that the relationship is mediated by attention, a regression analysis was conducted between time and adaptive functioning, controlling for intellectual ability. Additionally, mediation of attention (SNAP-IV) was measured using the PROCESS macro on SPSS.

Table 2.4 Clinical Characteristics of Participants

NB: diagnoses were reported as per clinical records. They were not confirmed at assessment.

Sample Characteristics	<i>N (%) / Mean (SD; range)</i>
N	47
Gender (male)	35 (74.5%)
Age at assessment (years)	11.85 (2.11; 6-15)
Age at motor tics onset (years)	5.90 (2.19; 2.5-10.5)
Age at vocal tics onset (years)	6.12 (2.70; 1-12)
Tic severity YGTSS (/100)	50.68 (17.90; 17-91)
IQ	98.74 (14.81; 69-129)
Diagnosis of TS	47 (100%)
Diagnosis of ADHD	12 (25.5%)
Diagnosis of Anxiety Disorder	11 (23.4%)
Diagnosis of OCD	5 (10.6%)
Diagnosis of ODD/CD	1 (2.1%)

2.4 Results

2.4.1 Neuropsychological and Behavioural Profile of TS

There was a broad range of abilities shown across the neuropsychological profile of the participant population. The mean intellectual ability score (Full-Scale IQ) for the sample was in the average range, however the sample scores varied from 69-129 (Table 2.5). Negligible to small effect sizes were observed between mean scores of the TS group and the standardised norms on the WISC FSIQ, and the four domains (VCI, VSI, FRI, and WMI). Processing Speed was found to be significantly lower in the TS group ($p < 0.05$) with a small-to-medium effect size. The attention measure used (TEA-Ch2) was found to be unimpaired with the exception of the switching attention task (RBBS). Executive

functioning was spared on the two planning tasks, and significantly impaired on the 6-parts test which required organisation and time management. Adaptive functioning was significantly impaired in all three domains: communication, daily living skills, and socialisation. The greatest degree of impairment was found in the Daily Living Skills domain.

2.4.1.1 Adaptive Functioning

A Pearson's correlational analysis was completed to explore the relationship between adaptive functioning and other standardised and clinical measures (Table 2.6). It was found that the FSIQ was significantly positively correlated with the adaptive functioning composite score. The index score for working memory showed a strong association with adaptive behaviour. The severity of ADHD, as determined by a composite of the inattention and hyperactivity/impulsivity scores on the SNAP-IV, was significantly associated with adaptive functioning. One measure of sustained attention (Vigil) was also found to be associated, while the other two (for sustained attention and switching tasks) were not. Age, tic severity, and executive functioning measures were not found to be associated with adaptive functioning. After a Bonferroni test to correct for multiple comparisons, FSIQ, PSI, and ADHD severity were still found to be significant.

Table 2.5 Neuropsychological Measures for Clinical Sample Compared to Normative Mean

NB: strength of effect size is given in parentheses; small (S), medium (M), large (L)

Domain	Measure	Variable	N	Test population mean (SD)	Sample mean (SD)	Sample range	t	p	Effect size (Cohen's d)
Intellectual Ability	WISC-V	FSIQ	47	100 (15)	98.74 (14.81)	69-129	-.581	.564	0.084 (S)
		VCI	47	100 (15)	97.89 (13.50)	68-124	-1.069	.290	0.148 (S)
		VSI	47	100 (15)	98.43 (14.16)	69-132	-.762	.450	0.108 (S)
		FRI	47	100 (15)	100.96 (15.40)	72-134	.426	.672	0.063 (S)
		WMI	47	100 (15)	99.55 (18.11)	65-138	-.169	.866	0.027 (S)
		PSI	47	100 (15)	93.26 (16.93)	66-129	-2.731*	.009	0.421 (SM)
		Attention	TEA-Ch2	Vigil	44	10 (3)	9 (3.03)	4-15	-2.186*
Simple RT	44			10 (3)	9.93 (4.55)	1-19	-.099	.921	0.018 (S)
RBBS	43			10 (3)	7.86 (3.90)	1-15	-3.596**	.001	0.615 (M)
Executive Functioning	BADSC	Zoo Map 1	47	10 (3)	9.83 (3.50)	2-16	-.334	.740	0.052 (S)
		Zoo Map 2	47	10 (3)	9.72 (3.27)	1-14	-.579	.565	0.089 (S)
		Six Parts Test	47	10 (3)	7.38 (2.12)	3-12	-8.455**	.000	1.008 (L)
Adaptive Functioning	VABS-3	Communication	46	100 (15)	86.30 (17.47)	36-122	-5.315**	.000	0.841 (ML)
		Daily Living Skills	43	100 (15)	82.53 (17.82)	20-114	-6.427**	.000	1.060 (L)
		Socialisation	45	100 (15)	86.28 (21.22)	34-126	-4.335**	.000	0.747 (ML)
		ABC	43	100 (15)	84.09 (15.95)	48-109	-6.542**	.000	1.028 (L)

*p<.05, **p<.001

Table 2.6 Correlational Analysis Vineland Adaptive Behaviour Composite (ABC) and Clinical Variables

Variable	N	Pearson Correlation (R)	p-value
Participant Age	43	0.060	.702
Full-Scale IQ	43	0.495* [^]	.002
Working Memory Index	43	0.357*	.019
Processing Speed Index	43	0.436* [^]	.003
Tic Severity	43	-0.291	.058
ADHD severity (clinical)	43	-0.559** [^]	.000
EF planning: ZooMap1	43	0.212	.172
EF planning: ZooMap2	43	0.011	.945
EF organisation: 6-Parts	43	0.054	.729
Sustained attention: Vigil	40	0.376*	.017
Sustained attention: SimpleRT	40	0.174	.283
Switching attention: RBBS	40	0.158	.329

*p<.05, **p<.001; [^]passed Bonferroni correction p<0.05/12. EF=executive functioning (measure by BADS-C); ADHD severity measure is a measure of the SNAP-IV two subscales: inattention + hyperactivity/impulsivity scales

2.4.2 Timing Tasks

2.4.2.1 Time Discrimination

The mean number of correctly discriminated stimuli in each interval was calculated. Each participant could achieve a maximum of 10 correct responses in each interval task. Within subject interval, means and then group means were calculated. In the sub-second range (Figure 2.3) there is a pattern of increasing accuracy with increasing interval length. Intervals 370 and 430 are closest in duration to the reference stimulus, therefore

potentially most difficult to discriminate, followed by 340 and 470, and then 310 and 500. In the supra-second range (Figure 2.4) there is a similar pattern of increasing accuracy with increased duration of interval. There is also a contrast in accuracy of the three intervals that are shorter than the reference, where the mean of correct responses in three intervals shorter than the reference=3.98, and the three intervals that are longer than the reference, where the mean of correct responses in the three interval longer than the reference=6.73. In both tasks, it was the length of the stimulus that correlated with accuracy rather than the difficulty of the task.

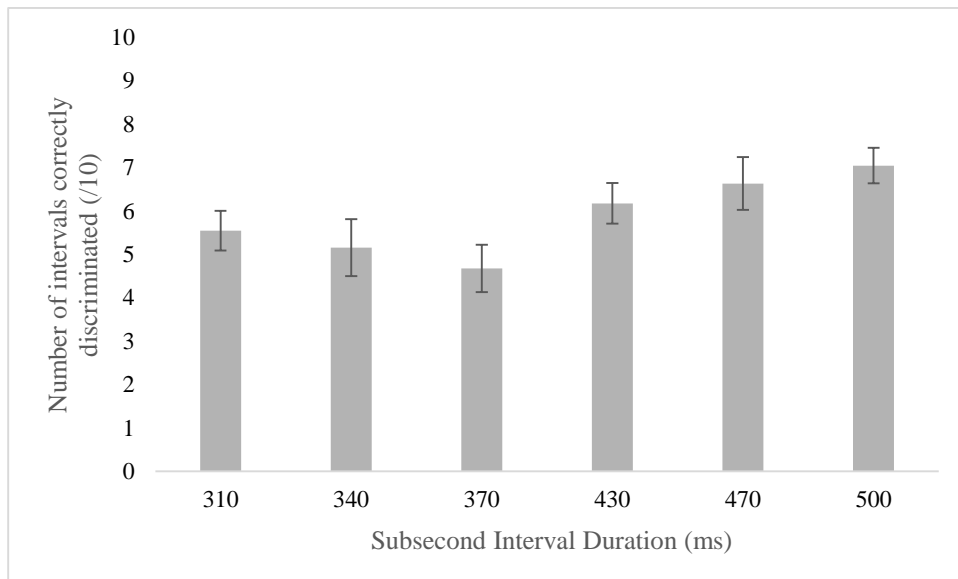


Figure 2.3 Average Number of Intervals Correctly Discriminated in the Sub-second Range

*Error bars represent 2*standard error; reference interval=400ms*

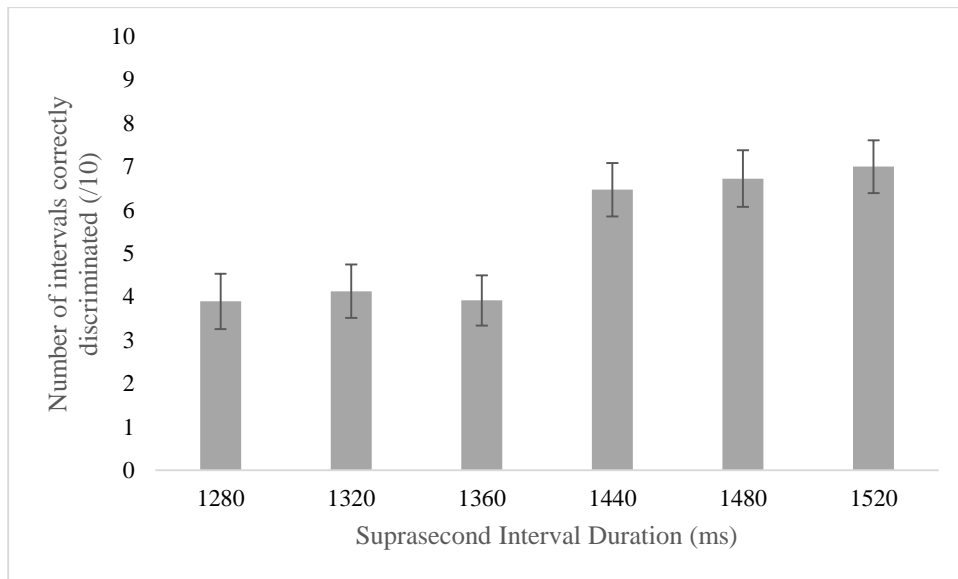


Figure 2.4 Average Number of Intervals Correctly Discriminated in the Supra-second Range

*Error bars represent 2*standard error; reference interval=1520ms*

2.4.2.2 Time Reproduction

The Absolute Reproduction Error (ARE) or the proportion of absolute error relative to the length of the interval shows a decreasing pattern with increasing duration of interval (Figure 2.5). This pattern is more apparent in the sub-second interval ranges (intervals 1-5), while the error appears to plateau in the supra-second range (intervals 6-10).

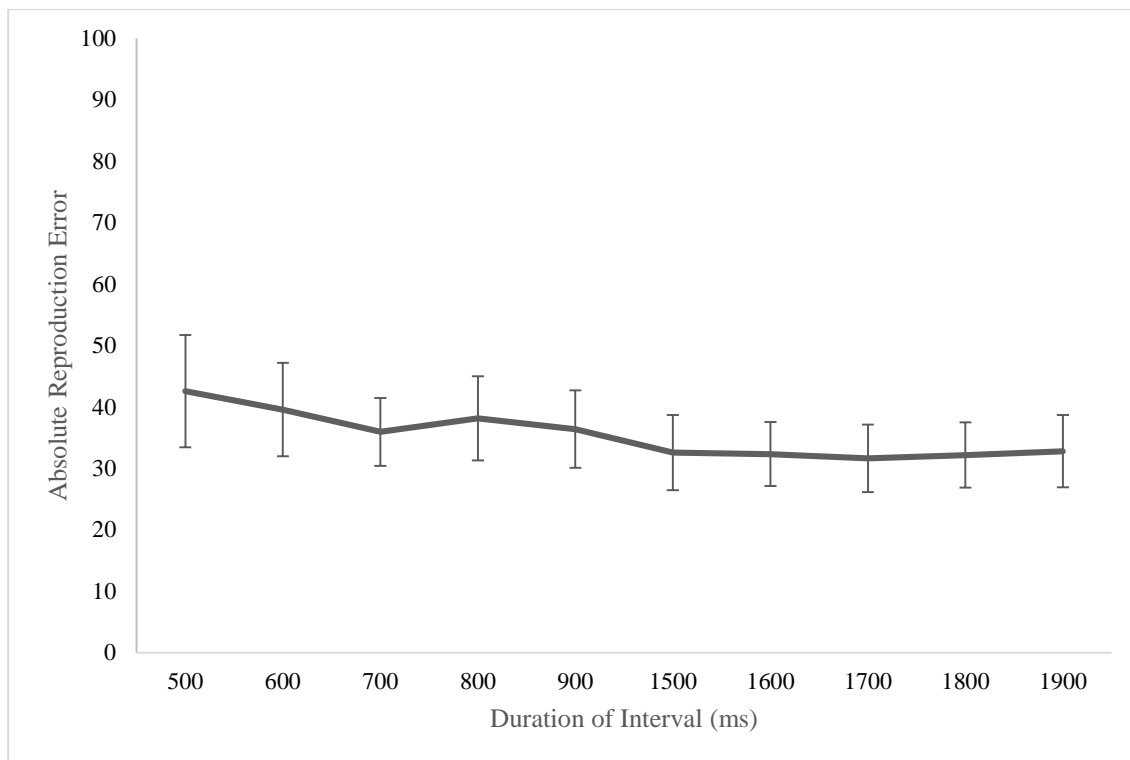


Figure 2.5 Absolute Reproduction Error (ARE) in the Sub- and Supra- second Ranges
*Error bars represent 2*standard error*

2.4.3 Tics and Timing

Mean sub- and supra-second scores were calculated for the discrimination and reproduction tasks. A correlation was performed on each group to examine the relationship between time skills and tic severity. A small positive correlation was found between tic severity and supra-second reproduction error ($r=0.301$, $p<0.05$), this was not evident in the sub-second range ($r=0.058$, $p>0.5$). Bivariate outliers were determined and excluded with the residuals and a Tukey 1.5 * hinge spread analysis. The result showed a significant moderately sized association between the time reproduction error in the supra-second range and tic severity ($r=0.573$, $p<0.001$, Figure 2.6).

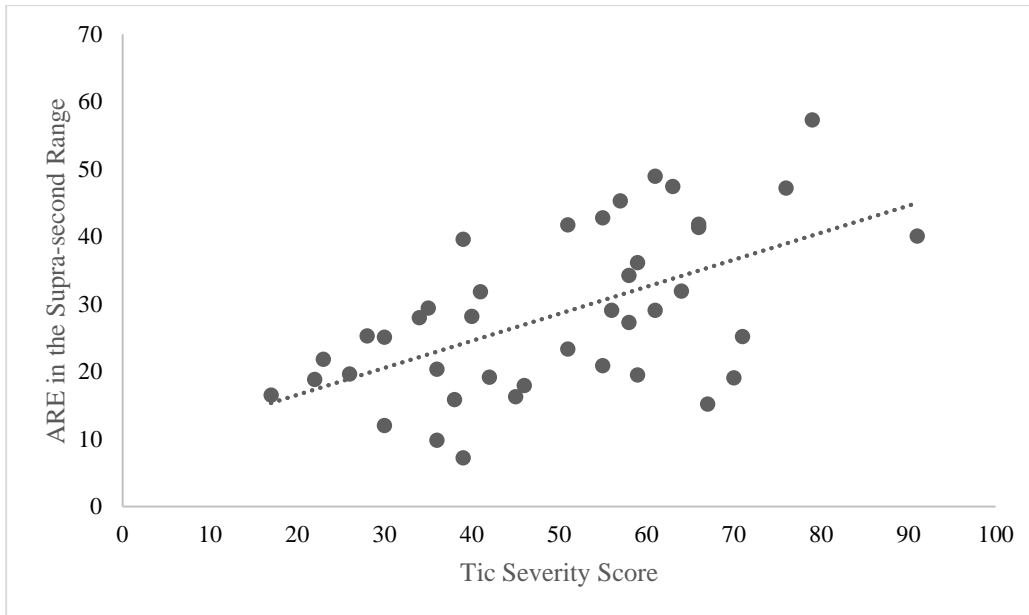


Figure 2.6 Tic Severity and Absolute Reproduction Error (ARE) in the Supra-second Range

On the discrimination tasks, a small negative correlation was found between tic severity and the number of correctly discriminated time intervals in the sub-second range (Figure 2.7; $r=-0.353$, $p<0.05$). Therefore, higher accuracy in discriminating tasks in the sub-second range was associated with lower levels of tic severity and impairment. This was not found in the supra-second range ($r=0.019$, $P<0.5$).

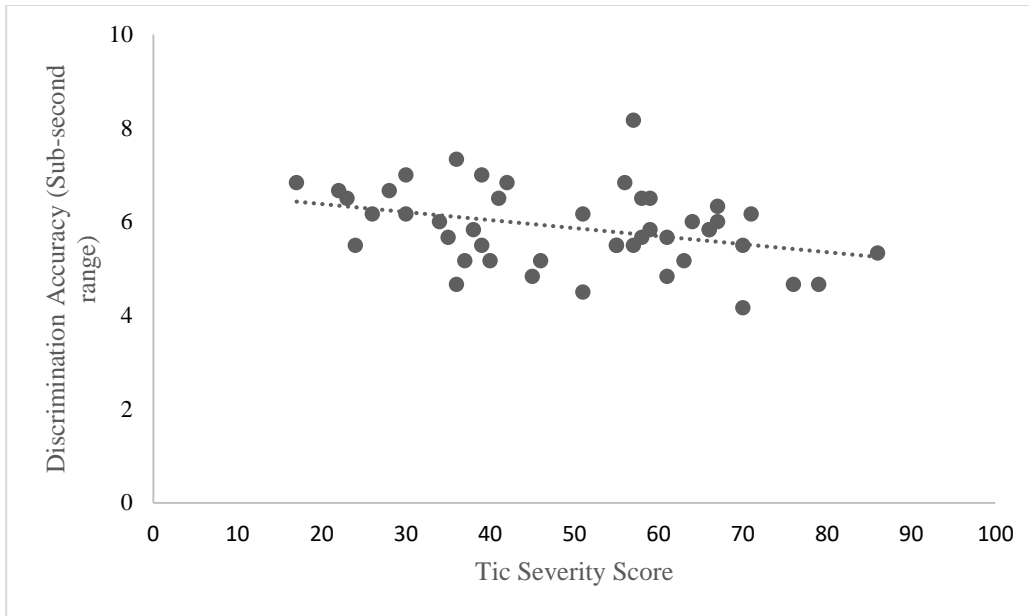


Figure 2.7 Tic Severity and Mean Discrimination Accuracy in the Sub-second Range

2.4.4 Cognition and Time

In order to explore the relationship between cognitive abilities and timing deficits, a correlation analysis as well as a multiple regression analysis were completed for each cognitive variable against each time variable.

On the time discrimination tasks, a small and significant correlation was found between discrimination accuracy in the sub-second range with fluid reasoning (FRI; $r=0.339$, $p<0.05$) and the sustained attention task, (Simple RT; $r=0.326$, $p<0.05$). Therefore, discrimination accuracy under one-second was associated with fluid reasoning and sustained attention. All other cognitive tasks were not correlated with sub-second discrimination accuracy. There were no significant correlations between cognitive abilities and discrimination accuracy in the supra-second range.

Absolute reproduction error was significantly associated with multiple domains measuring IQ and attention (Table 2.7). All measures of inattention were significantly

associated with sub-second reproduction error. However, the parent report clinical measure (SNAP-IV) and switching attention task were not significantly associated with supra-second reproduction error. Age and executive functioning were not associated with time reproduction error at either interval length.

Table 2.7 Pearson's Correlational analysis between cognitive and clinical variables and reproduction error in the sub- and supra-second domains

		Reproduction Error	Reproduction Error
		Sub-second	Supra-second
	Participant Age	-0.072	-0.273
IQ	FSIQ	-0.462**	-0.377**
	VCI	-0.242	-0.251
	VSI	-0.525**	-0.500**
	FRI	-0.383**	-0.393**
	WMI	-0.503**	-0.345*
	PSI	-0.399*	-0.208
Attention	ADHD SNAP	0.347*	0.210
	Vigil	-0.382*	-0.332*
	Simple RT	-0.334*	-0.439**
	RBBS	-0.306*	-0.125
Executive Function	ZM1	-0.105	0.241
	ZM2	-0.110	-0.130
	6-Parts	-0.110	-0.217

*p<.05, **p<.001; IQ=intellectual quotient measured using the WISC-V; ADHD SNAP=impulsivity subscale + inattention subscale on the 26 item SNAP-IV; SimpleRT, Vigil. RBBS=attention measures on the TEA-Ch2; Executive functioning=measured by the BADS-C subtests; ZM=zoo map test.

In order to complete a linear regression analysis between time reproduction error and cognitive variables, the following diagnostics were tested:

1. Using SPSS, it was found that the residual errors of the regression line were normally distributed. This was tested using a normal P-P Plot.
2. The data was found to meet criteria for homoscedasticity using a scatter plot of regression standardised predicted value and residual values. Both sub- and supra-second models showed approximately equal distribution of points around zero on the X and Y axes.
3. Collinearity of the predictor variables was assessed using Variance Inflation Factor (VIFs) scores. All VIFs were below 10, therefore suggesting that the variance of variables was not inflated by linear dependence on other variables. FSIQ had a high VIF (>20) score however this was to be expected because all the indices of FSIQ were included in the model.

The regression coefficient for each predictor variable is reported in Table 2.8. In both the sub- and supra- second range, working memory (WMI) difficulties predicted the extent of reproduction error. Visual Spatial skills (VSI) and the ability to switch attention (RBBS) significantly predicted reproduction error in the sub-second range. Age and fluid reasoning capacity (FRI) significantly impacted the extent of reproduction error in the supra-second range.

Table 2.8 The Impact of Cognition on Timing: Standardised Beta Coefficients from Linear Regression

Factor	Outcome Variables					
	Reproduction Error			Reproduction Error		
	Sub-second			Supra-second		
	B	SE B	β	B	SE B	β
Age	-0.107	0.115	-0.144	-0.250	0.116	-0.365*
IQ						
FSIQ	0.976	0.805	0.677	1.327	0.774	1.018
VCI	0.274	0.316	0.188	-0.081	0.304	-0.061
VSI	-0.980	0.386	-0.673*	-0.181	0.388	-0.130
FRI	-0.370	0.449	-0.269	-1.075	0.437	-0.865*
WMI	-0.649	0.261	-0.578*	-0.545	0.261	-0.532*
PSI	-0.100	0.281	-0.085	-0.406	0.271	-0.383
Attention						
ADHD SNAP	0.159	0.260	0.105	-0.250	-0.252	-0.182
Vigil	0.235	1.063	0.038	-0.260	1.052	-0.047
Simple RT	-0.155	0.732	-0.037	-0.605	0.706	-0.154
RBBS	-2.037	0.990	-0.376*	0.784	0.991	0.153
EF						
ZM1	-2.175	1.082	-0.387	0.912	1.053	0.178
ZM2	-0.638	0.942	-0.104	-0.355	0.905	-0.064
6-Parts	-2.518	1.562	-0.294	-1.677	1.500	-0.215

*p<.05, **p<.001; IQ=intellectual quotient measured using the WISC-V; ADHD SNAP=impulsivity subscale + inattention subscale on the 26 item SNAP-IV; SimpleRT, Vigil. RBBS=attention measures on the TEA-Ch2; EF= executive functioning as measured by the BADS-C subtests; ZM=zoo map test; B= unstandardized beta; SE B= the standard error for the unstandardized beta; β = the standardised beta.

2.4.5 Time and Adaptive Functioning

The impact of time on adaptive functioning was determined by a linear regression analysis. Based on the relationship between cognitive variables and adaptive functioning (Table 2.6), the variables of FSIQ and the SNAP ADHD measure were controlled for.

In the sub- and supra-second ranges, the models passed all assumptions required to run a linear regression. However, the model in the sub-second range showed signs of heteroscedasticity. This indicates that standard errors in the independent variables may be biased.

The impact of time reproduction ability on all adaptive functioning domains was measured using a linear regression analysis (Table 2.9). When controlling for other predictor variables, time reproduction error in the sub-second range significantly predicted socialization outcome. That is, the higher the error of sub-second reproduction, the poorer the outcome of socialisation. Although sub-second reproduction did not have a significant impact on the two other adaptive behaviour domains (communication and daily living skills), it did predict overall adaptive functioning. The supra-second reproduction error, on the other hand, did not significantly predict adaptive behaviour in any domains.

A regression analysis was also completed to investigate the hypothesis that attention difficulties mediate the impact of time reproduction in the sub-second range on socialisation (adaptive behaviour domain) using the PROCESS macro for SPSS. Results indicated that sub-second reproduction error was a significant predictor of ADHD as measured by SNAP-IV ($b=0.211$, $se=0.087$, $p<0.05$) and ADHD was a significant predictor of socialisation ($b=-0.790$, $se=0.187$, $p<0.001$). The direct effect of sub-second

reproduction error on socialisation was still found to be significant after mediation ($b=-0.444$, $se=0.113$, $p<0.001$). A bootstrap estimation approach of 5000 samples indicated that ADHD partially mediated the impact of sub-second reproduction error on socialisation ($b=-0.167$, $se=0.0821$, $95\% CI=-0.332, -0.012$).

Table 2.9 The Impact of Timing on Adaptive Functioning: Standardised Beta Coefficients from Linear Regression Models

Factor	Outcome variables											
	Adaptive Behaviour Composite			Communication			Daily Living Skills			Socialisation		
	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β
Reproduction Error (Sub-second)	-0.268	0.114	-0.353*	-0.189	0.142	-0.223	-0.247	0.138	-0.298	-0.490	0.144	-0.478*
Reproduction Error (Supra-second)	0.146	0.136	0.149	0.161	0.154	0.162	0.190	0.164	0.178	0.109	0.155	0.092
Full-Scale IQ	0.293	0.144	0.263*	0.425	0.173	0.354*	0.453	0.174	0.372*	0.014	0.179	0.010
ADHD SNAP	-0.506	-0.155	-0.406*	-0.426	0.192	-0.301*	-0.329	0.188	-0.241	-0.792	0.194	-0.469**

* $p < .05$, ** $p < .001$; B= unstandardized beta; SE B= the standard error for the unstandardized beta; β = the standardised beta.

2.5 Discussion

This paper explores time processing in children with TS. More specifically it investigates the relationship between timing, cognitive abilities, and adaptive functioning. Forty-seven children with TS and their parents or caregivers completed a battery of cognitive tasks and questionnaires covering intellectual ability, attention, executive function, time processing, tic severity, ADHD symptom severity, and adaptive functioning. The findings of this study will be discussed with reference to our hypotheses and existing literature on timing in neurodevelopmental conditions. The strengths and limitations will also be considered as well as recommendations for future research. Finally, conclusions on the study as a whole will be described.

2.5.1 Main Findings

The findings are listed below in line with the four original hypotheses:

1. Our first hypothesis was that children with TS would show significant impairments in adaptive functioning as compared with standardised norms. Our study confirmed this hypothesis as adaptive functioning was found to be a significant area of difficulty for the children we worked with.
2. The second hypothesis was that tic severity would be correlated with time reproduction errors. This was found to be true in the supra-second range, suggesting that more severe tics were associated with more reproduction errors at longer intervals.

3. Our third hypothesis was that working memory and attention would predict time processing ability in regression models, and that executive functioning may also be related. Our findings showed that working memory had a significant association (in a linear regression model) with time reproduction errors both in the sub-second and supra-second range. However, attention and executive functioning were not significantly associated in the regression model.
4. Finally, we hypothesised that time processing would predict adaptive functioning in a linear regression model and that attention would mediate this relationship. We found that time processing in the sub-second range predicted overall adaptive functioning, as well as socialisation, in the linear regression model, and that the ADHD measure (SNAP-IV) mediated the relationship between them. However, the direct effect of sub-second error on adaptive functioning was still significant after mediation.

2.5.2 Timing in TS

Analysis of time skills at a group level showed findings of note. The discrimination task in the sub- and supra- second ranges showed that participants were more likely to accurately discriminate two intervals if the given interval was longer in duration than the reference interval. This, therefore, showed a relationship of increasing accuracy with interval length in both time ranges. Vicario et al. (2010) showed a similar relationship of lower error percentages at longer interval durations, mainly shown on the supra-second task, both in the TS and the control groups. Therefore, participants were generally more

likely to predict that the test interval (which was always shown after the reference interval) was longer in duration.

Reproduction error was calculated as the absolute difference in time between the produced interval and the reference interval and divided by the length of the interval. The average absolute error was calculated for individuals and the group, at each interval. The main reason for using the absolute error was because our hypothesis revolved mainly around the degree of error rather than the degree of over or underestimation; existing literature did not point to the neuro-cognitive interpretations for patterns of under- or over-estimating.

Reproduction error showed a similar pattern of reduced error at longer intervals after adjusting for interval duration. This relationship was more apparent in the sub-second range, therefore showing that at shorter duration times, the error involved is a greater percentage of the interval duration that is displayed. The standard deviation also showed a pattern of decreasing at lower intervals, therefore indicating the variability of error was larger at shorter durations. Based on these findings we propose that the structures hypothesised to be involved in sub-second, or automatic timing, such as the BG, cerebellum, and left SMA (Noreika et al., 2013; Wiener et al., 2010) may be more greatly impacted in TS than the structures and neural processes involved in supra-second time reproduction, such as the right frontal cortex (Baier et al., 2010; Lawrence et al., 2003), and the neural processes of cognitive control (executive functioning), attention, and working memory (Noreika et al., 2013). This finding was somewhat consistent with the population neuropsychological profile (Table 2.6). Overall intellectual ability and working memory were found to be unimpaired in the group. Two out of three executive

functioning tasks were also unimpaired. The attention tasks, on the other hand, showed greater levels of impairments relative to standardised norms.

2.5.2.1 How is Timing Related to Tics?

Tic severity in our study shows a small association with discrimination errors in the sub-second range. Time discrimination involves into early perceptual timing skills, and sub-second intervals explore automatic timing abilities. This may indicate tics being associated with impairments of perceptual and automatic timing abilities. These findings were not found in other TS studies (Vicario et al., 2010). However, Rubia et al., (2003) found that severity of ADHD traits impacted on time discrimination ability.

Similar to Vicario et al. (2010) we found a moderate association between tic severity and reproduction error in the supra-second range after excluding bivariate outliers. Time reproduction is considered both a perceptual and motor timing task in the literature. Motor timing has been found to depend on co-activation of the BG, cerebellum as well as the SMA and DLPFC. Specifically, in supra-second duration processing, studies have found a relatively higher activation of the right SMA and DLPFC (Jantzen, Oullier, Marshall, Steinberg, & Kelso, 2007; Wiener et al., 2010). Magnetic resonance imaging (MRI) data from TS studies have shown the involvement of the DLPFC and SMA in tic generation (Bohlhalter et al., 2006; Fattapposta et al., 2005). Tic severity has also been found to be associated with DLPFC volume (Fredericksen et al., 2002; Peterson & Staib, 2001). These findings point to the likelihood that at higher levels of tic severity and consequently DLPFC changes result in greater impairments in supra-second and motor timing tasks. On the other hand, Vicario et al (2010) suggested that this pattern may reflect

a compensatory phenomenon in which tic suppression requires prefrontal cortex activation, resulting in enhanced performance in participants with high tic suppression capacity.

2.5.2.2 Cognitive Tasks and Timing

Cognitive functions have been shown to have close and complex associations with timing (Falter & Noreika, 2011). Supra-second interval processing may especially be influenced by attention and working memory (Mangels & Ivry, 2001; Noreika et al., 2013). Similarly, time discrimination tasks were predicted to be significantly impacted by working memory in ADHD (Lee, 2018; Toplak et al., 2003; Toplak & Tannock, 2005).

Working memory predicted reproduction error in our study, both in the sub- and supra- second ranges, such that better performance on the WISC-V working memory tasks resulted in significantly lower reproduction errors. Sustained attention was negatively correlated with both sub- and supra- second reproduction errors, however in a regression analysis did not predict reproduction error. Switching attention ability negatively predicted reproduction error in the sub-second range such that switching attention caused reductions in reproduction error in the sub-second range. This indicates that switching attention is an important part of automatic timing.

Allman and Mareschal (2016) highlight the difference in “here & now” timing to longer durations that require information to be stored in memory and retrieved. They state that during the first year of life (from approximately 6-12 months of age), perceptual and cognitive development is mainly constrained to events in the here-and-now. One example

of this is social parent-infant interactions that reveal different types of temporal patterns allowing infants to adjust their behaviour to match their parent's tempo.

Age has been shown to be associated with improved temporal sensitivity (Droit-Volet, 2008; Droit-Volet & Wearden, 2001; McCormack, Brown, Maylor, Darby, & Green, 1999; Zélanti & Droit-Volet, 2011). Zelanti & Droit-Volet (2011) explored short (under 1 second) intermediate (1.25-2.5 seconds) and long (greater than 3 seconds) time perception tasks with 5 year-olds, 9-year-olds, and adults (mean=22.75y, SD=3.52). It was found that improvements occurred earlier in life for durations under 1 s and later for longer durations. For example, for durations under 2.5s, 9-year-olds achieved a level of time sensitivity close to that observed in adults, however when the duration was longer, their sensitivity was low and was more similar to that of 5-year-olds. Furthermore, the age-related improvement in time sensitivity in the long durations was explained by the development of attention and executive functions.

Considering the age range of the participants in our study (7-16) one might expect that the shorter duration sensitivity will have already been developed while the longer duration sensitivity may have still been in the process of development and therefore be more significantly impacted by their age. This aligns with our data showing the age significantly and negatively predicted reproduction error in the supra-second range, and not in the sub-second range. Therefore, the trajectory of time development in TS is similar to that shown in the wider unaffected population.

2.5.2.3 Adaptive Functioning

Clinically, the team at the specialist TS clinic in London reported observing a tendency for children with TS to show a spared cognitive profile and impairments in adaptive functioning. This hypothesis was supported by our findings (Table 2.5) which showed all three domains of adaptive functioning as measured by the VABS-3 to be significantly impaired compared to standardised norms, with a large effect size on the composite score. In a correlational analysis of cognitive and clinical variables, adaptive functioning was associated with IQ, working memory, processing speed, sustained attention (Vigil), and negatively with ADHD severity (on the SNAP-IV). Tic severity was not associated with adaptive functioning, therefore potentially indicating that other clinical variables aside from the tics themselves, such as attention and working memory, contribute to these impairments in functioning. This is somewhat consistent with Sukhodolsky et al., (2003) who showed that TS+ADHD groups had significantly higher levels of adaptive impairments than the pure-TS group. However, the daily living domain impairments remained impaired even after controlling for ADHD. Daily Living Skills was the domain of the greatest impairment in our study. Gorman et al., (2010) showed that impairments in the socialisation domain were maintained after controlling for ADHD in a TS population. Based on our findings we propose that inattention, hyperactivity, and intellectual difficulties contribute to adaptive impairments in TS, and that other variables are likely to further contribute.

Timing deficits have been shown to impact functions that are closely linked to adaptive behaviour. For example, Mioni et al. (2016) showed that in children with ADHD, time perception predicted prospective memory accuracy. They also showed less efficient

clock checking strategies. The consequences of this to daily life include difficulties with automatising routines, understanding the concept of time and therefore attending appointments independently, sticking to time-related expectations, planning and completing longer-term projects, and using a calendar or watch (Barkley, 1997; Langberg, Becker, Epstein, Vaughn, & Girio-herrera, 2013; Wennberg et al., 2018). These difficulties are naturally link to broader aspects of life such as completing daily routines, maintaining relationships with friends and family, achieving independence in managing a schedule, homework, and school work more broadly (Wennberg et al., 2018).

Our findings are show that automatic timing deficits (in the sub-second range) predict adaptive behaviour outcome in TS. It is shown to have the most significant impact on the socialisation domain. This was still consistent after controlling for FSIQ and ADHD symptoms. ADHD was found to partially mediate the impact of sub-second error and socialisation; however, the direct impact of timing error was still found to be significant. Additionally, sub-second time reproduction error was significantly negatively correlated with all adaptive functioning domains ($p < .01$ in all domains). There was no correlational or predictive relationship between supra-second error and adaptive functioning. Therefore, impairments in sub-second (automatic) timing, which has been shown to be regulated by the BG and cerebellum, have a more significant impact on adaptive outcome than supra-second timing difficulties.

2.5.3 Limitations, Strengths, and Future Research

2.5.3.1 Limitations

One area of limitation in this study was around the sample of participants we worked with. A key limitation of the sample was not having a control group to which we could compare the performance of the participants. Using a control group would give a clearer picture of the performance of children with TS in our group, as the assessments in the study were completed as part of a three-to-four-hour assessment battery, while standardised means are not. Additionally, because the time measure was unstandardized, this meant that we could not report whether timing in TS is impaired compared to unaffected control groups. This is an area of the literature that is sparsely investigated, therefore having clarity on timing in TS compared with the wider population would be important to explore. Additionally, the children and young people we saw were of a wide age range (7-15 years old). This is a time of development of many cognitive functions, including timing skills and executive functions. Therefore, age is a variable that may have impacted the participants' performance, particularly on unstandardized measures.

As an experimental measure, the timing task introduced some limitations of its own. On the discrimination task, the finding that children tended to assume the test interval was longer than the reference interval may indicate that people tend to experience more recent durations as longer. This introduces a bias to the findings in the study. Another issue with the discrimination task to note is that, in one noticeable case, the child continued to push one button (selecting the test interval as longer than the reference). Because of this, it appeared that they accurately discriminated three intervals (longer than the reference) and scored zero on the intervals shorter than the reference. This introduces

the bias of appearing to improve in accuracy with increasing interval length. Since the discrimination task is binary, there is the possibility that children guessed answers to get the task done faster.

Being an experimental measure, it has not been standardised to all ages. Therefore, it is possible that the younger participants had more difficulty understanding and completing the task. The producer of the measure informed us that it was appropriate for the age range of the children we were working with, and let us know that he did not have difficulties with it in the past. We also ran several practice trials with participants before completing the task to make sure they understood it. However, with that in mind, one limitation of the study is limited evidence of how appropriate the timing measure was for the young participants.

Another limitation was around the data and data analysis. Because of the experimental nature of this study, there was a large number of hypotheses that aimed to better understand the relationship between multiple variables: time, adaptive functioning, and intellectual ability. However, there were consequently a large number of correlations done, which introduces the high risk of type I error throughout the study. Therefore, it will be important that these tests are repeated in future studies to validate our findings. With regards to the data, there was inconsistent reporting of comorbid diagnoses and medication use. The comorbid diagnoses were reported by families or found in the clinical notes, however there was no standardised portion of the assessment to confirm or reject an assigned diagnosis, and the ratio of diagnoses was lower in the sample than that of the reported comorbidity rates in the literature. The way that we have been able to redeem this was by measuring symptom severity using clinical questionnaires. Medication,

specifically D₂ receptor blocker pimoziide, is shown to reduce variability in performance of supra-second reproduction tasks in TS (Vicario et al., 2016). In ADHD, Methylphenidate is found to improve motor timing and time reproduction both in the sub- and supra- second ranges (Baldwin et al., 2004; Ben-Pazi, Shalev, Gross-Tsur, & Bergman, 2006; Rubia et al., 2003; Smith et al., 2013). Information on medication was not obtained in the study. The main reason for this was because rather than looking at impairments in time processing, we were looking at the impact of time on broader functioning. However, information on medication use, or controlling for use, might have given more insight into the differences in timing abilities within the group. It could also give more information about other symptom levels, and the extent to which symptoms are being managed or treated.

The length of the assessment was an important factor that was considered in the ethical approval process. On average the assessment lasted between 3.5 to 4 hours, including a short break. This was never done after-school to limit fatigue. However, some signs of fatigue or boredom were evident in the assessment procedures. The two computer assessments lasted approximately 45-50 minutes, which most children reported was boring. Therefore, we ran the risk that performance was not optimal due to the length of the assessment.

Because of limitations in time and resources, assessments were offered in the families' homes. Although each family was aware that we needed a quiet room, there were often distractions in the environment, such as pets, or parents popping in to offer food, as well as background noise. As such, there was an element of the environment not being as standardised as would typically be in a clinical setting.

2.5.3.2 Strengths

The greatest strength of this study was the sample size. Being a national specialist service, the clinic sees a large number of children with TS annually. To our knowledge, most studies that assess intellectual ability in TS have sample sizes of 10-20.

The second strength of the study was the standardisation across the two clinicians completing the assessment. Working closely together, we both made sure to similarly counterbalance the assessments and complete them all in one sitting. We regularly made contact between appointments to make sure we were using the same wording. Following the appointments, we did our scoring together to ensure consistency in our interpretation of the results.

2.5.3.3 Future Directions for Research

Adaptive functioning is an essential area of research in TS because it considers the day to day impact of an individual's difficulties. By measuring adaptive functioning one has a clear understanding of a person's ability to function in their environment without support, therefore leading to clear information on a person's needs. As such, it is imperative that more substantial research is conducted around the level of impairment in adaptive functioning in children with TS as this can lead to more representative assessments and targeted interventions to the individual's needs.

Secondly, considering the findings of this study, timing is an area that should be more thoroughly investigated in neurodevelopmental disorders. Given that automatic

timing has been shown to predict adaptive functioning highlights the level of importance of the cognitive ability in development. Accordingly, the treatment or development of programmes to improve timing abilities in children can have a significant positive outcome in one's ability to cope daily. This may especially impact socialisation with others. Therefore, an important future direction of research would involve time interventions to anticipate wider level day-to-day improvements.

2.5.4 Conclusion

Adaptive functioning is impaired in children with TS and is impacted by intellectual ability, sub-second (automatic) timing, and ADHD severity. Our findings suggest that automatic timing skills predicts socialisation, and can therefore predict an individual's level of independence day-to-day. Timing has a close relationship with other cognitive functions, including working memory and attention. Although attention mediates the relationship between sub-second time reproduction and adaptive functioning, timing maintains a direct and significant impact on adaptive functioning. We also found that timing skills at supra-second time intervals developed at a later stage than sub-second timing, and within our cohort, age had a more significant impact on the supra-second time tasks.

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Part III: Critical Appraisal

3.1 Introduction

This appraisal sets out to critically reflect on the process of doing this research. Firstly, general reflections on Tourette syndrome (TS) as a neurodevelopmental condition are discussed. The process of completing the project, from the ethical procedures to using clinical skills in the data collection process and working in a pair will be reflected on. Finally, the appraisal will close with thoughts for people considering doing this type of research and future directions for research in TS.

3.2 Understanding TS

Prior to the onset of this study I had no experience of working with young people with TS, however I had worked for some time with children with Autism Spectrum Condition (ASC) within a behavioural model. This is likely to have influenced my decision to pursue neurodevelopmental research, and has shaped my understanding of neurodevelopmental conditions. On the other hand, not having had the experience of working in TS prior to this project allowed me to observe the clinical practice and existing research with the lens of an outsider. Some key observations and considerations are discussed below.

3.2.1 Spectrum of Difficulties

An undeniable quality of working with children with TS is the variability in the symptoms and level of impairment in each individual's life. Cravedi et al., (2018) propose that TS phenotypical heterogeneity can be hierarchically clustered into at least three main groups; the first is TS with neurodevelopmental comorbidities (including ASC, ADHD, and

intellectual disabilities), the second is TS with no comorbidity (pure-TS), and the third is TS with higher intelligence, higher attentional impairment, school problems related to ADHD, and handwriting problems related to tics. Because of this variability, even within the clusters themselves, this raises the risk of averaging artefacts, where group level findings may not accurately represent the individuals. Therefore, in our study, average means may not represent the wider TS populations.

As shown in the literature review of this paper, impairment is often a consequence of the individual comorbidity rather than TS itself. This introduced our first ethical dilemma of deciding our exclusion criteria; choosing between working with pure-TS and working with children with comorbidity. The former allows one to better understand the impact of tics themselves, while the latter increases the external validity of the findings, as pure-TS has been shown to only represent approximately 10% of the TS population (Robertson, Cavanna, & Eapen, 2015). However, in the case of this research, we were exploring the impact of certain traits, such as the severity of inattention and severity of time processing impairments, on adaptive functioning. This led us to the decision to be less conservative on setting exclusion criteria. With that in mind, the likelihood of comorbid psychiatric conditions in our sample must be considered, particularly when comparing the neuropsychological and behavioural profile of participants to standardised norms.

It is found that the majority of children reaching clinical attention, from which our sample was recruited, have common comorbid conditions like ADHD, Obsessive Compulsive Disorder (OCD) and impulse control disorders (Cohen, Leckman, & Bloch, 2013). Working clinically with children with TS further highlighted the heterogeneity in

phenotypic profile in the population, therefore confirming our decision to recruit a population with existing comorbidities to better represent the general TS population and improve the external validity of the study.

3.2.2 Diagnostic Changes and Validity

In light of the high rates of comorbidity in TS, the accuracy in diagnostic rates of both TS as well as comorbid conditions must be considered. The literature review considered the impact of ADHD on aggressive symptoms mainly by exploring the binary profiles of TS-ADHD (or pure-TS) and TS+ADHD. The studies used several editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM); 3rd edition revised (American Psychiatric Association, 1987), 4th edition (1994), and 4th edition text revised (2000). However, there have been several alterations to the diagnostic criteria for ADHD between the editions. The term ADHD was introduced in the DSM-III-R (1987), with the elimination of Attention Deficit Disorder (ADD) without hyperactivity. In the DSM-IV (1994) the term was retained and three specific subtypes were introduced: predominantly inattentive, predominantly hyperactive-impulsive, and combined. Therefore, at this point the possibility of a diagnosis of a purely inattentive form was reintroduced (Barkley, 2006; Lange, Reichl, Lange, Tucha, & Tucha, 2010).

The validity and reliability of an ADHD as a diagnosis has been questioned in the past. Critics have described ADHD as a label for difficult, not ill, children, describing symptoms as simply being at the extreme end of the normal range (Furman, 2005). ADHD has also been found to be causally heterogeneous (Coghill & Seth, 2011) leading to the possibility that ADHD represents multifaceted difficulties in children. Another level of

criticism is regarding the method for collecting reports about levels of impairment; since these are not clarified in the criteria, some people gather information regarding impairments at school or at work by getting information from parents, while others gather information directly from school or work, which is more often the case in Europe (Taylor et al., 2004).

Accordingly, in our empirical study, there is value in using clinical measures, rather than diagnoses at face value, to determine severity of symptoms. On the other hand, using parent-report measures without confirmation of a second opinion depends on the honesty and understanding of each parent. It also introduces the risk of a response bias that may apply to all questionnaires, including the tic severity and adaptive functioning questionnaires. Parents who might be struggling to manage their child's difficulties may be more likely to over-estimate the level of severity on the questionnaires. This risk is further exacerbated because, as researchers, we were also part of the clinical team at the hospital; this might have led parents to using the questionnaires in order to flag their child's needs to the clinical team.

3.2.3 Epigenetics of Neurodevelopmental Disorders

The high rates of comorbidity of neuropsychiatric disorders has been an important area of reflection during my research. As such, an interest of mine has been the exploration in the overlap between the causality of these conditions, and the potential that they may be different expressions of similar underlying neurological processes.

A growing evidence base explores the impact of early life programming and epigenetic regulation as determinants for the predisposition to neurodevelopmental disorders. As such, at a molecular level, there may be factors that make children vulnerable to developing one or multiple neurodevelopmental disorder in their lifetime (Kundakovic & Jaric, 2017). The complex interplay between genetics, early experience, and later environment is thought to underlie the weak but consistent heritability of numerous neurodevelopmental disorders (Bale et al., 2010). The estrogenic pathways, for example, which is involved in cell death and birth in the developing nervous system, are thought to be implicated by epigenetic changes (McCarthy et al., 2009), resulting in lasting effects of developmental estradiol action. Estradiol evokes multiple mechanisms, and may contribute to the sex bias found in many neurodevelopmental disorders including TS, ASD, and ADHD (Bale et al., 2010). Because of these areas of overlap, the future of neurodevelopmental research may be restructured to consider causality of conditions in order to determine the best options for treatment, rather than the current-day models of determining outcome by behavioural symptomology.

3.3 Research Process

Conducting this research was a novel process for me, including the procedures of completing NHS ethics and collecting data. The process was facilitated with three experienced supervisors and a research partner with research experience. Multiple factors needed to be considered in the process to optimise the quality of our data and validity of our findings. Some of these thoughts are described below.

3.3.1 Selection Bias

As with many studies, there is the risk of bias in the sample of participants who were recruited to the study. During recruitment, the first form of contact was information sheets (parent and child versions) sent in the post, and then followed up with a phone call. There were some themes in the reasons people chose not to participate in the study; one theme was around the child's ability to manage sitting through a three-hour assessment. This could be due to the severity of tics, for example, that might be exacerbated in assessment settings. Many children reported anecdotally that having to sit still could be a trigger for tics, while others report feeling exhausted after spending several hours having to suppress them, such as at school. The other difficulty that could understandably inhibit engagement would be severity of inattention or hyperactivity. Parents of children with ADHD would therefore likely be more concerned about agreeing to engage in the study. On the other hand, another response that was reported by parents was that their child had been doing better than when they were when had been seen clinically, and they feared that doing the assessment might be a reminder of more difficult or distressing times. Therefore, there may have been a bias in that children who were managing better were more likely to opt-in to the study, while children who were recently having difficulties might have also opted-out.

3.3.2 The Overlap in Clinical and Research

Working clinically as well as in a research capacity within the same context provided some positive as well as more challenging opportunities. Overall, clinical skills in working

with children in a psychological context were essential to optimising the assessment environment. Being attuned to signs of fatigue and frustration was important to make sure that each child was performing at his or her best. When this was the case we made sure to introduce as many breaks as the participant needed in order to focus. Using positive praise throughout created a more supportive and encouraging environment for participants, which was especially important for children who had had negative experiences of schooling and assessments in the past.

Interpreting the data and sharing child and parent reports also required a level of clinical knowledge; it was important to provide information and highlight concerns without unnecessarily risking raising alarm bells, considering most participants were no longer open to the service. As such, being attuned to child and parent concerns was a significant portion of conducting the research. In one instance, I was concerned by the reports a parent was sharing around risks to the child's safety. In this case, I was able to discuss it in supervision and accordingly wrote to the participants GP with suggestions for a plan. As such, it was not possible or appropriate to separate clinical needs of participants from the research context. The fact that two Trainee Clinical Psychologists, who had had several years of experience working clinically, conducted the assessments was helpful in managing the clinical and psychological concerns introduced during the assessment and interpretation process.

Although we worked hard to maintain boundaries between our clinical and research work, in one instance, after seeing a participant for the research assessment, I began seeing him clinically for work around anxiety. Before beginning the work, he gave consent to do both with the same person. Although the work in theory was meant to be

independent, the findings of the assessment showed some difficulties with expressive language and confirmed prior concerns around inattention. The consequence of this was offering further clinical assessments around language and making a referral for an ADHD assessment. In some ways this can be framed as a positive experience for the client, as he and his parents gained a better understanding of his difficulties. On the other hand, the ethical dilemma that the work we had agreed to pursue at the start of therapy (anxiety work) was now mixed with other elements. Additionally, managing both at the same time also undoubtedly had an impact on the therapeutic relationship. As such, if the opportunity presented itself again in future, I would work to maintain more defined boundaries around working clinically with participants on a research project.

3.3.3 Choice of Measures

The two main measures used in this study were the Vineland Adaptive Behaviour Scales, 3rd Edition (VABS-3; Sparrow, Cicchetti, & Saulnier, 2016) and the time processing measure used by Vicario et al., (2010). The specific time measure was chosen in order to best replicate the main study done on timing in TS. However, the fact that the measure itself was unstandardised introduced the main limitation to this study, which was that it was not possible to determine whether time processing was impaired in our sample of participants with TS. Therefore, had it been feasible, a change that would have been made to this study would be the addition of a control group.

Parent-report measures can introduce some concerns about accuracy of the data. This is because some measures can be difficult to understand, particularly the VABS-3. LH and I were sure to be consistent in our verbal and written instructions on the VABS-3

however, when going through them at the end of assessments, the majority of questionnaires were incomplete. This is mainly because of the complex expectations on the questionnaire; in each section, the child's baseline ability begins with five consecutive scores of two, and each section can be stopped after five consecutive scores of zero. What often happened is that we were unable to determine the baseline score because the parent had not "back tracked" to answer preceding questions. In 14 cases, it was not possible to go through the questionnaire at the end of the assessment, mainly due to running out of time, and therefore phone calls were made to parents to get further information. In the end, four remained that were not possible to complete. Ideally, had there been the time, it would have been best to go through the entire questionnaires with parents to increase the likelihood of accurate completion of the questionnaires. However, this process would have likely added an hour or so to the assessment time.

3.4 Implications of Findings and Future Research

During my research I have become acutely aware of the difference in volume of literature between TS and other closely linked neurodevelopmental conditions like ASC, ADHD, and anxiety. Working in the specialist London TS clinic, I was also aware of the referrals coming in from around the country that reported that there were no professionals at local services that could support or treat children with TS. This was especially surprising because the majority of the evidence in the literature points to using behavioural treatments for tic suppression, which in theory could be done at any local Child and Adolescent Mental Health Service (CAMHS). The National Autistic Society reports that the prevalence of ASC in the UK is at approximately 1% (Brugha et al., 2012), which is

not dissimilar to the international prevalence rate of TS at 1% (Robertson, Eapen, & Cavanna, 2009). That said, there are more comprehensive policies in place to ensure that ASC diagnosis and treatment are accessible at all local services. I believe part of the way to support clinicians to feel more confident in assessing and intervening in TS is by using research that clinicians can turn to in when seeking to use evidence-based practice.

As such this project can have clinical implications, primarily by helping clinicians know what to keep an eye out for to better understand the aetiology of difficulties in TS. Based on the empirical findings, adaptive functioning should be a main focus of all TS assessments. Attention is also shown to be impaired and can have significant impacts both on challenging behaviour (namely aggression) and day-to-day independence.

Future research should further investigate timing as an important cognitive skill that can have far-reaching impacts on one's abilities. To our knowledge this has been the first study in TS that explores the impact of time processing, however this can be replicated in other conditions where time processing is found to be especially impaired. Another area of consideration is the use of time-related interventions to improve overall functioning. In ADHD, medication has been found to have a positive impact on time processing (Baldwin et al., 2004; Ben-Pazi, Shalev, Gross-Tsur, & Bergman, 2006; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003; Smith et al., 2013). The next step would be to explore whether these improvements in time predict broader improvements in functioning, particularly socialisation.

3.5 Conclusions

In the process of carrying out this research project, I have learned far more than I anticipated about TS, and working as a researcher more broadly. Multiple ethical and practical dilemmas that we encountered resulted in me deepening my understanding of the project and how best to manage.

Through collaboration with my three supervisors and research partner I learned a great deal about conducting and interpreting neuropsychological assessments. I also learned what questions to ask when designing a project, and trying to weigh up often opposing factors such as feasibility, statistical power, ethical considerations, and using hypothesis driven approaches. Overall, conducting this research has enlightened me to the general process of undertaking research as well as the value of using research in clinical practice and vice versa.

Adaptive functioning and timing in TS are an area of sparse research but presents itself as an opportunity to better understand the aetiology of the difficulties children with TS face as well as an opportunity to explore new pathways for intervention.

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Appendix I: Search Terms

Search Terms used in MEDLINE, later adapted to each database:

Anger:

Exp anger; exp aggression; aggression.tw, (aggressi* adj5 behav*).tw; (violen* adj5 behav*).tw; anger.tw; angry.tw; social behavior disorders; oppositional defia*.tw; exp conduct disorder OR exp child behavior disorders; (conduct adj1 (disorder* or problem*)).tw; (externali* adj3 (problem* or behave*)).tw; ((antisocial or anti-social) adj5 behav*).tw; intermittent explosive disorder.mp; exp disruptive, impulse control, and conduct disorders; (explosi* adj3 outburst*).tw; rage.mp; (temper adj3 tantrum*).tw, (disruptive adj2 behavio?r).tw, (episode* adj3 rage).mp

Tics:

Exp tic disorders; exp Tourette syndrome; exp tics; Tourette.mp; (tic or tics).mp

Children:

Exp infant; exp child; adolescent*; juvenile*; teen*; young; youth*

Appendix II: Quality Assessment

Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields.

Criteria	YES (2)	PARTIAL (1)	NO (0)	N/A
1 Question / objective sufficiently described?				
2 Study design evident and appropriate?				
3 Method of subject/comparison group selection or source of information/input variables described and appropriate?				
4 Subject (and comparison group, if applicable) characteristics sufficiently described?				
5 If interventional and random allocation was possible, was it described?				
6 If interventional and blinding of investigators was possible, was it reported?				
7 If interventional and blinding of subjects was possible, was it reported?				
8 Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?				
9 Sample size appropriate?				
10 Analytic methods described/justified and appropriate?				
11 Some estimate of variance is reported for the main results?				
12 Controlled for confounding?				
13 Results reported in sufficient detail?				
14 Conclusions supported by the results?				

Kmet, L.M., Lee, R.C., & Cook, L.S. (2004). *Standard quality assessment criteria for evaluating primary research papers from a variety of fields*. Alberta Heritage Foundation for Medical Research.

Appendix III: Child Behaviour Checklist Items

Item (item number) on the Child Behavior Checklist used to define rule-breaking (delinquent) and aggressive behaviour

Rule-Breaking Behavior (RB)	Aggressive Behavior (AGG)
Doesn't seem to feel guilty after misbehaving (26)	Argues a lot (3)
Hangs around with others who get in trouble (39)	Bragging, boasting (7)
Lying or cheating (43)	Cruelty, bullying, or meanness to others (16)
Prefers being with older kids (63)	Demands a lot of attention (19)
Runs away from home (67)	Destroys his/her own things (20)
Sets fires (72)	Destroys things belonging to his/her family or others (21)
Steals at home (81)	Disobedient at home (22)
Steals outside the home (82)	Disobedient at school (23)
Swears or uses obscene language (90)	Easily jealous (27)
Thinks about sex too much (96)	Gets teased a lot (37)
Truancy, skips school (101)	Physically attacks people (57)
Uses drugs for nonmedical purposes (105)	Screams a lot (68)
Vandalism (106)	Shows off or clowns (74)
	Stubborn, sullen or irritable (86)
	Sudden changes in mood or feelings (87)
	Talks to much (93)
	Teases a lot (94)
	Temper tantrums or hot temper (95)
	Threatens people (97)
	Unusually loud (104)

Bartels, M., Hudziak, J. J., Van den Oord, E. J. C. G., Van Beijsterveldt, C. E. M., Rietveld, M. J. H., & Boomsma, D. I. (2003). Co-occurrence of aggressive behavior and rule-breaking behavior at age 12: Multi-rater analyses. *Behavior Genetics*, 33(5), 607-621.

Appendix IV: HRA Ethical Approval

Dr Daniel Stark

Email: hra.approval@nhs.net

31 August 2017

Dear Dr Stark,

Letter of HRA Approval

Study title:	The Impact of executive functioning and time processing abilities on adaptive functioning in children with Tourette Syndrome
IRAS project ID:	220775
Protocol number:	17BB17
REC reference:	17/LO/1297
Sponsor	UCL Institute of Child Health

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

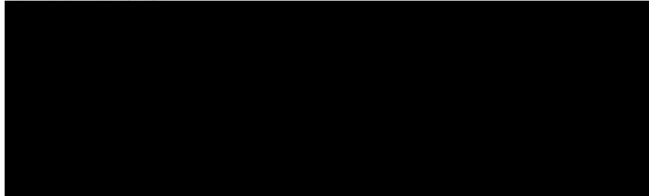
Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read *Appendix B* carefully, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

Appendix V: Tourette Action Funding Approval

Dr Tara Murphy



WC1N 3JH

08/03/17

Dear Dr Tara Murphy,

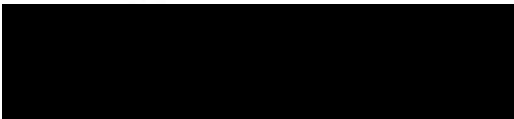
Very many thanks for your application to the Tourettes Action Grant Award scheme for 2016-2017.

I am delighted to inform you that your grant application was accepted for funding for the full amount you requested of **£1013**.

We will be in touch shortly with the Terms and Conditions of the grant award and the timeline for payment of funding etc

Please find attached feedback from two external peer reviewers.

Sincerely,



Dr Seonaid Anderson

Research Manager Tourettes Action

- supporting people with TS throughout their lives
- facilitating inclusion by raising accurate awareness of TS
- supporting research



Patrons:
 David Katz MBE
 Sir Jonathan Miller CBE
 Michael Ryan CBE
 Prof. Mary M Robertson MD,
 DSc(Eng), FRCP, FRCPsych, FRCPsych
 Dr Oliver Sacks CBE

Tourettes Action (UK) Association
 trading as Tourettes Action
 a voluntary limited by guarantee
 registered in England no. 4433463
 registered office as above
 registered charity no. 1043317



Appendix VI: Parent and Child Information Sheets and Consent /
Assent Forms

Patient & Carer Information Sheet

About the Project

Project title: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome

We work at *** We would like to invite you and your child to take part in a research study. Before you decide if you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please read through the following information carefully and discuss it with others if you wish. We would encourage you to ask us if there is anything that is not clear or if you would like more information. Take your time to decide whether or not you wish to take part. If you do decide to participate, this would involve completing paper and pen questionnaires about your child, and your child completing paper and pen and computerised game-like tasks. This could take place at your home, or at ***, depending on what you would prefer.

What is the purpose of the study?

This study is an educational project that is interested in the types of skills that make up adaptive functioning (the ability to complete everyday tasks such as using money, helping around the house and looking after themselves) in children with Tourette syndrome. We have identified executive functioning (or the ability to plan and problem-solve) and temporal processing (or the awareness of time information) as two skills that may support everyday functioning in children with Tourette syndrome. This is important, because if we know what skills contribute to everyday functioning, we can help towards the development of more effective and targeted treatments, that can improve the adaptive functioning in children with Tourette syndrome.

Why have my child and I been asked to help?

We are asking children, aged 7-15 years 11 months, who have been seen previously at or who have recently been referred to the clinic, if they are interested in participating.

Do I have to take part?

No. Taking part in this study is entirely voluntary. If you decide not to take part in this study, you do not have to give a reason and the standard of care your child receives will not be affected. If you do decide to take part, you can still withdraw at any time, without giving a reason, even if your child has started the testing session.

Testing sessions

To participate in the study it will be necessary for your child to complete a range of paper and pen and computerised game-like tasks, and for you to complete some questionnaires. This session will be conducted by one of our researchers, Lara Harris or Summer Fakhro, and can take place at your home, or at ***, based on what you would prefer, and will take no longer than 3 hours, including breaks.

Is there anything to be worried about if my child and I take part?

There are no specific risks from taking part in the study as your child's treatment will not be changed by participating the study in any way. If your child gets tired when we are doing the tasks and puzzles then they will be able to take breaks.

If anything about the session causes any distress, we would ask that you let us know so that we can offer support and think about what further help is needed.

Will taking part help my child?

There is no direct benefit of participation. We will, however, provide you with a report of your child's performance across a range of abilities once the testing session is complete. We will also give your child an easy-to-read report of his/ her strengths and weaknesses.

How will the information help people?

When the study has finished we will write to you to let you know what we found out. We hope that the findings from our study will improve people's understanding of Tourette syndrome and to help develop possible treatments.

Will my child's usual treatment be affected by taking part?

No. If your child is currently receiving treatment at *** Hospital, they would continue to be seen as a patient here throughout the study. Any school liaison work, or medication, would continue as normal and be unaffected by participation

Who will know that my child and I are taking part in the study?

All information that is collected about your child during the course of the study will be kept strictly confidential. We would keep all names, addresses and results from the assessments and questionnaires confidential. We will also keep all paperwork in a safe place, with names removed from any data. Any documentation with personal information (names, addresses etc) will be stored in a locked filing cabinet, only accessible by the research team. Should we write about the results of the study, no names will be used, and no information that would show it was your child would be shared. If you agree to participate, then we would write to your child's GP and the specialist who referred your child to the clinic to let them know your child is taking part in the study.

What will happen to the results of the study?

The results will not be known until all of the sessions are completed and we have analysed the data. We hope to have completed data analysis by the end of 2019. We would like to inform the rest of the Tourette's community about the anonymous results of the study. This may include professional publications and meetings as part of a doctoral university assignment, but neither you, nor your child would be recognisable from any written work. We will also write to you at the end of the study with a brief summary of what we found out.

Who has organised and approved the research?

An independent group of people, called a Research Ethics Committee, looks at all research in the NHS to protect your interests. This study has been reviewed and approved by the London Bloomsbury Research Ethics Committee. Their contact details are provided below. The research is being sponsored by UCL Institute of Child Health (ICH).

Who is funding the research?

Funding for the study has been provided from three sources. These are *** Hospital, University College London and Tourette Action, UK (the National Charity for Tourette syndrome).

What if something goes wrong?

This study is indemnified under the Clinical Negligence Scheme for NHS Trusts, which provides cover for negligent harm. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this via the Patient Advice and Liaison Service at *** (You can ring them on 020 7 or email them on.

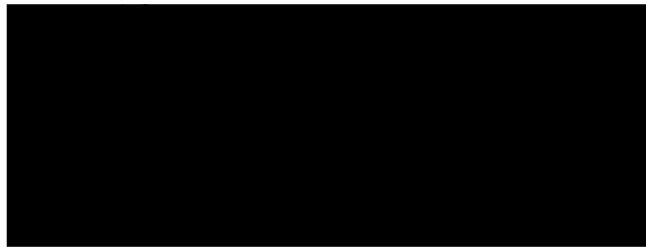
What do I do now?

Thank you for reading this information. If you and your child are interested in taking part in this study, please contact Lara Harris ([insert number] or Summer Fakhro ([insert number]) to hear more. If we do not hear from you, we will contact you by phone in one week to answer any questions you may have and to see if you are interested in taking part.

Who do I speak to if I have further questions or worries?

Contact: Lara Harris, Trainee Clinical Psychologist
Summer Fakhro, Trainee Clinical Psychologist

Address: TS Study



Email: lara.harris.15@ucl.ac.uk
S.fakhro.12@ucl.ac.uk

Tel: [Insert telephone numbers]

Supervised by: Dr Daniel Stark, Clinical Psychologist, [Insert telephone numbers]; Dr Tara Murphy, Consultant Clinical Psychologist, [Insert telephone numbers]; and Dr John King, Senior Lecturer and Clinical Psychologist, University College London [Insert telephone numbers]

[Insert contact details for Ethics Committee]



Information sheet for children and young people ages 7-9

Project title: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome

A study to see what thinking skills help you complete everyday tasks.

We work at *** Hospital. We are asking you and your parents/carers to take part in a project. This leaflet will tell you about the project. We hope you can read this with someone in your family. Please ask us if you have any questions. Take your time to think about whether or not you want to take part.



What is this project and why are we doing it?

We are interested in the thinking skills that help you to complete everyday tasks. We hope that finding out more about your thinking skills will help doctors and scientists develop better treatments for children with Tourette

syndrome.

Why have I been asked to take part?

We are asking all children who have visited *** Hospital for help with their Tourette syndrome to take part in the study.

Do I have to take part?

No, you do not have to take part. If you say no you do not have to tell us why and no one will be upset. You can stop the session even if you said yes at the beginning or if you have already started doing the puzzles.

Will taking part help me?

No, taking part will not help you directly. We will give you a brief description of your performance on the tasks, giving you an idea of some of your stronger and weaker areas. We hope that what we find out will help us and to design things that could help children with Tourette syndrome.

What will I be asked to do if I take part?



We would meet you and your parents or carers at your home or at ***. Then,

- Lara or Summer would spend about 3 hours with you doing puzzles and tasks, making them as fun as possible.
- You would be able to have short breaks if you feel tired or to stop anytime if you want to.
- We would also ask your parent/(s) or carer/(s) some questions.

Is there anything to be worried about if I take part?

When we do the games and puzzles you can take breaks if you get tired. We will make the meeting as fun as possible.

If you are upset about anything that happens during the study, please speak to your parent/(s) or carer/(s) about it. If you would like to speak to someone else, your parents know how to contact us and our address and phone number are at the end of this sheet.

Who will know I am taking part in the study?

We would keep your name, address and your results from the games and puzzles secret. We will write about the study but no names will be used. If you agreed then we would write to your doctor to let them know you are taking part.



What will happen to the results of the study?

We will write to you to let you and your parent/(s) / carer/(s) know what we found out.

Who do I speak to if I have a question?

You can speak to your parents. You can also contact Lara Harris or Summer Fakhro if you have any other questions.

Contact:

Lara Harris or **Summer Fakhro**,
Trainee Clinical Psychologists

Email:

lara.harris.15@ucl.ac.uk

s.fakhro.12@ucl.ac.uk

Tel: [Insert telephone numbers]



Supervised by: Dr Daniel Stark, Clinical Psychologist, [Insert telephone numbers]; Dr Tara Murphy, Consultant Clinical Psychologist, [Insert telephone numbers]; and Dr John King, Senior Lecturer and Clinical Psychologist, University College London [Insert telephone numbers]



Information sheet for children and young people ages 10-12

Project title: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome

A study to see what thinking skills help you complete everyday tasks.

We work at ***. We are asking you and your parents/carers to take part in a project. This leaflet will tell you about the project. We hope you can read about the project with someone in your family. Please ask us if you have any questions. Take your time to decide whether or not you want to take part.



What is this project and why are we doing it?

We are interested in the thinking skills that help you to complete everyday tasks. We think that thinking skills might help you and children with Tourette syndrome do things like getting ready for school and talking to friends. This is important, because if we know what things help you to do everyday things, we can help doctors and scientists develop better treatments.

Why have I been asked to take part?

We are asking all children who have visited *** for help with their Tourette syndrome to take part in the study.

Do I have to take part?

No, you do not have to take part. If you decide not to take part, you do not have to give a reason and no one will be upset. You can change your mind at any time. You can stop the session even if you said yes at the beginning or if you have already started completing the puzzles.

Will taking part help me?

Taking part will not help you directly. We will give you a brief description of your performance on the tasks, giving you an idea of some of your stronger and weaker areas. We also hope that what we find out will help us to work out things that could help children with Tourette syndrome.

What will I be asked to do if I take part?

Meeting



We would arrange to meet with you and your parents or carers at your home or at ***. At this meeting:

- Lara or Summer would spend about 3 hours with you doing puzzles and tasks, making them as fun as possible.
- You would be able to have short breaks if you feel tired or to stop anytime if you want to.
- We would also ask your parent/(s) or carer/(s) some questions.

Is there anything to be worried about if I take part?

When we do the games and puzzles you can take breaks if you get tired.

We will make the meeting as fun as possible. If you are upset by taking part in the study, please speak to your parents about it. If you would like to speak to someone else, your parents know how to contact us and our address and phone number are at the end of this sheet. Your treatment at *** will not be changed by taking part.

Who will know I am taking part in the study?

We would keep your name, address and your results from the games and puzzles secret. We will write about the study but no names will be used. If you agreed then we would write to your doctor to let them know you are taking part.



What will happen to the results of the study?

We will write to you to let you and your parent/(s) / carer/(s) know what we found out.

Who do I speak to if I have a question?

You can speak to your parents who also have information about this study. You can also contact Lara Harris or Summer Fakhro if you have any other questions.

Contact:

Lara Harris or **Summer Fakhro**, Trainee Clinical Psychologists

Email: lara.harris.15@ucl.ac.uk
s.fakhro.12@ucl.ac.uk

Tel: [Insert telephone numbers]



Supervised by: Dr Daniel Stark, Clinical Psychologist, [Insert telephone numbers]; Dr Tara Murphy, Consultant Clinical Psychologist, [Insert telephone numbers]; and Dr John King, Senior Lecturer and Clinical Psychologist, University College London [Insert telephone numbers]



Information sheet for children and young people ages 13-16

Project title: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome

What thinking skills help you complete everyday tasks?

We work at ^{***}. We are asking you and your parent/(s) or carer/(s) to take part in a project. This leaflet will tell you about the project. We hope you can read about the project with someone in your family. Please ask us if you have any questions. Take your time to decide whether or not you want to take part.

What is this project and why are we doing it?

This study is interested in the thinking skills that help you to complete everyday tasks. We think that the way children and young people think might help you and children with Tourette syndrome do things like getting ready for school and talk to friends. This is important, because if we know what things help you to do everyday things, we can help doctors and scientists develop better treatments.

Why have I been asked to take part?

We are asking all children who have visited ^{***} for help with their Tourette syndrome to take part in the study.

Do I have to take part?

No, you do not have to take part. If you decide not to take part in this study, you do not have to give a reason and no one will be upset. You can change your mind at any time. You can stop being in the study even if you said yes at the beginning or if you have already started completing the puzzles.

Will taking part help me?

Taking part will not help you directly. We will give you a brief description of your performance on the tasks, giving you an idea of some of your stronger and weaker areas. We hope that what we find out will help doctors and scientists develop treatments that could help children with Tourette syndrome.

What will I be asked to do if I take part?



Meeting

First we would arrange a meeting with you and your parents or carers at home or at ***. At this meeting:

- One of us would spend about 3 hours with you doing puzzles and asking you some questions.
- We will ask you to do a selection of different things and hope you will find them interesting.
- You would be able to have short breaks if you feel tired or to stop if you want to.
- We would also ask your parent/(s) or carer/(s) some questions.

Is there anything to be worried about if I take part?

When we do the games and puzzles you can take breaks if you get tired.

We will make the meeting as fun as possible. If you are upset by anything about taking part in the study, please speak to your parents about it. If you would like to speak to someone else, your parents know how to contact us and our address and phone number are at the end of this sheet. Your treatment at *** will not be changed by taking part.

Who will know I am taking part in the study?

We would keep your name, address and your results from the games and puzzles secret. We will write about the study but no names will be used. If you agreed then we would write to your doctor to let them know you are taking part.

What will happen to the results of the study?

The results will be available in December 2019. We will also write to you to let you and your parent/(s) / carer/(s) know what we found out.

Who do I speak to if I have further questions or worries?

Your parents also have information about this study. You can ask them questions. You can contact Lara Harris or Summer Fakhro if you have any other questions.

Contact: Lara Harris, Trainee Clinical Psychologist
Summer Fakhro, Trainee Clinical Psychologist
Email: lara.harris.15@ucl.ac.uk; s.fakhro.12@ucl.ac.uk
Tel: [Insert telephone numbers]

Supervised by: Dr Daniel Stark, Clinical Psychologist, *** [Insert telephone numbers]; Dr Tara Murphy, Consultant Clinical Psychologist, *** [Insert telephone numbers]; and Dr John King, Senior Lecturer and Clinical Psychologist, University College London [Insert telephone numbers]

Identification Number _____

CONSENT FORM FOR PARENT/(S) AND CARER/(S)

Title of Project: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome.

Names of Researchers: Lara Harris, Trainee Clinical Psychologist
Summer Fakhro, Trainee Clinical Psychologist
Dr Tara Murphy, Consultant Clinical Psychologist
Dr Daniel Stark, Clinical Psychologist
Dr John King, Senior Lecturer and Clinical Psychologist

Version and date of the participant information sheet that the parent/carer has read: _____

Please initial the box after each statement.

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.
2. I understand that my child's participation is voluntary and that I am free to withdraw at any time, without giving any reason, without medical care or legal rights being affected.
3. I understand that sections of my child's medical notes may be looked at by the researchers where it is relevant to my taking part in the study. I give permission for these individuals to have access to my child's records.
4. I agree to my child's GP being informed of their participation in the study.
5. I would like to receive a report of the study findings once the study is complete.
6. I agree to take part in the above study

Name of Child _____

_____ Name of Parent or Carer	_____ Date	_____ Signature
_____ Researcher	_____ Date	_____ Signature

Identification Number_____

PARTICIPANT ASSENT FORM: Children and young people ages 7-9

Title of Project: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome

Names of Researchers: Lara Harris, Trainee Clinical Psychologist
Summer Fakhro, Trainee Clinical Psychologist
Dr Tara Murphy, Consultant Clinical Psychologist
Dr Daniel Stark, Clinical Psychologist
Dr John King, Senior Lecturer and Clinical Psychologist

Please circle YES or NO

Do you understand the information I gave you? YES NO

Have you been able to ask me questions and have I answered your questions? YES NO

Would you like to take part? YES NO

Do you know that you can stop the session any time you like? YES NO

Name Date Signature

Researcher Date Signature

Identification Number_____

Identification Number _____

PARTICIPANT ASSENT FORM: Children and young people ages 13-16

Title of Project: The impact of executive functioning and temporal processing abilities on adaptive functioning in children with Tourette syndrome

Names of Researchers: Lara Harris, Trainee Clinical Psychologist
Summer Fakhro, Trainee Clinical Psychologist
Dr Tara Murphy, Consultant Clinical Psychologist
Dr Daniel Stark, Clinical Psychologist
Dr John King, Senior Lecturer and Clinical Psychologist

Please circle YES or NO

Have you understood the information you were given?	YES	NO
Have you been able to ask questions and had them answered?	YES	NO
Would you like to take part?	YES	NO
Do you understand that you can stop being involved in the study at any time you like?	YES	NO

Name

Date

Signature

Researcher

Date

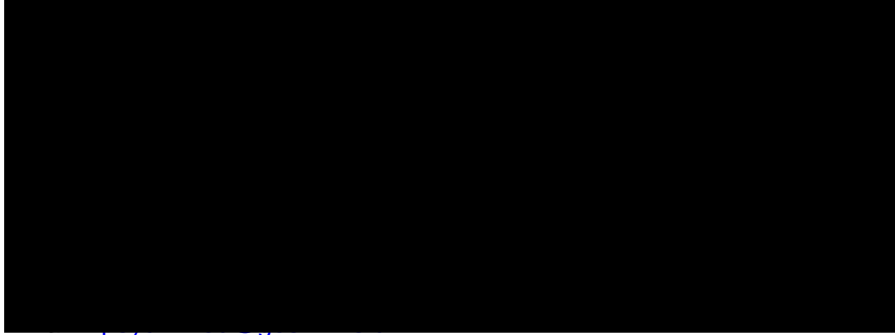
Signature

Appendix VII: Individual Trainee Contributions

This was a joint project with LH, Trainee Clinical Psychologist at University College London. After agreeing that we were both interested in working with children with Tourette syndrome (TS) and conducting a neuropsychological project looking at adaptive functioning in TS, we decided to explore different variables that might contribute to adaptive functioning outcome. With the support of our internal supervisor (Dr. John King) and external supervisors (Dr. Daniel Stark and Dr. Tara Murphy), we decided that LH and I would investigate executive functioning and time processing, respectively.

We worked jointly on preparing the funding application, the ethics application and cleaning out a database to choose participants who met our inclusion and exclusion criteria. We also attended all of our research meetings together and contributed to each other's work through discussions and sharing of ideas. Data for both studies were collected from the same participants in the same testing session. Approximately half of the assessments were carried out by LH (24/47) and the other half by me (23/47). Finally, the write-up for the projects was done completely independently of one another.

Appendix VIII: Parent and Child Cognitive Report Templates



Ref:
NHS No:

**RESEARCH ASSESSMENT
SUMMARY REPORT**

Name:	XXX XXX
Date of Birth:	-
Age at Assessment:	-
Date of Assessment	-

Cognitive Assessments

XXX participated in a cognitive assessment as part of our research to explore adaptive functioning (including socialisation, communication, and daily living skills) in children with Tourette syndrome. The assessment took place in a quiet room in (XXXX's home) / (***). XXX was cooperative and attended well throughout the assessment. The results from the assessment are presented at the end of this report.

Summary

Some of XXXX's areas of strength include:

Some areas that XXXX found more difficult:

Thank you to XXX and his/her family for their enormous contribution to this research into Tourette syndrome.

If you would like to discuss this report you can contact Daniel Stark until the end of March 2019 on.

Kind regards,

Summer Fakhro
Researcher &
Trainee Clinical Psychologist

Lara Harris
Researcher &
Trainee Clinical Psychologist

Dr Daniel Stark
Clinical Psychologist &
Paediatric Neuropsychologist

RESULTS OF COGNITIVE ASSESSMENTS

Note.

Standard scores have a Mean of 100 and a standard deviation of 15. A score of 100 corresponds to the performance of the average child of a given age on that scale. About two thirds of all children obtain scores between 85 and 115.

Scaled scores range from 1 - 19 with a score of 10 corresponding to the performance of the average child at a given age on that subtest. Scaled scores between 7 and 13 are said to fall within the average range.

T-scores range from 20-80 with a score of 50 corresponding to the performance of the average child at a given age on that subtest. T-scores between 40-60 are said to fall within the average range.

Percentile scores reflect the percentage of the population that would obtain lower or equivalent scaled scores.

General Intelligence

Wechsler Intelligence Scale for Children V – (WISC) UK

Scale	Standard Score	%ile	Range
Verbal Comprehension			
Visual Spatial			
Fluid Reasoning			
Working Memory			
Processing Speed			
Full Scale IQ (FSIQ)			

Attention

Test of Everyday Attention for Children – II

Index of attention	Subtest	Scaled Score	%ile	Range
Sustained attention	Vigil			
Sustained attention & Response inhibition	Simple RT			

Swanson, Nolan and Pelham - IV (SNAP- IV)

Domains	Parent Report Scores		
	Average	%ile	Range
Inattention			
Hyperactivity/ Impulsivity			
Total Scores			

Executive Function

Behavioural Assessment of the Dysexecutive syndrome in Children (BADS-C)

Subtest	Standard Score	%ile	Range
Key Search Test			
Zoo Map Test 1			
Zoo Map Test 2			

Behaviour Rating Inventory of Executive Function (BRIEF) –Parent Version

Scale/Index	T Score	%ile	Range
Inhibit			
Shift			
Emotional Control			
Initiate			
Working Memory			
Plan/Organize			
Organization of Materials			
Monitor			
Behavioral Regulation Index (BRI)			
Metacognition Index (MI)			
Global Executive Composite (GEC)			

Tic Severity

Yale Global Tic Severity Scale (YGTSS)

Domains	Parent Report Scores	
	Current Tics	Worst Ever
Total Phonic		
Total Motor		
Impairment Classification		

Behaviour

Vineland Adaptive Behaviour Scale - 3 (VABS)

Domains	Parent Report Scores		
	Standard Score	%ile	Classification
Communication			
Daily Living Skills			
Socialisation			
Motor Skills			

Jane Doe

This report explains my strengths and the things I find more difficult.

It gives tips on how I can help myself and how other people can help me.

Things I am good at:

Understanding what I am being asked to do

Reading and spelling words

Playing the flute

Solving problems

Drawing



Things I find hard:

Concentrating

Remembering lots of information and the order

Focusing on more than one thing at a time

It can take me a longer time to understand what I am supposed to do

Remembering all the things that I need for school



How other people can help me:

Sitting at the front of the class and away from windows or doors will help me to focus on my work

It is hard for me to do more than one thing at a time – please give me the information I need in writing as it will help me to learn better

When I need to focus really hard and concentrate for a long time on



How I can help myself:

If I do not understand what I am being taught, it is important to say this. It is ok to ask for extra help.

I should practice the skills I learn at school at home so I have a better chance at learning.

It's important to remind myself to keep practising and trying on things I am less confident with. The more times I try something the better I will be.

When studying I should re-read things several times and test myself to help me to learn



How I can help myself....

- **If I do not understand what I am been taught, it is important say this. It is ok to ask for extra help.**
- **I should practice the skills I learn at school at home so I have a better chance at learning.**
- **It's important to remind myself to keep practising and trying on things I am less confident with. The more times I repeat something the better I get**



Report Compiled by: (INSERT CLINICIAN)

Child's Name

Date: (INSERT DATE)



This report explains my strengths and some of the things I find difficult.

It gives me tips on how I can help myself and how other people can help me.



How other people can help me...

- Sitting at the front of the class and away from windows or doors will help me to focus on my work
- It is hard for me to do more than one thing at a time – please give me the information I need in writing as it will help me to learn better
- When I need to focus really hard and for a long time on my work, I would be better in a smaller and quiet room
- I find it hard to



My Strengths

- Understanding what I am being asked to do
- Reading and spelling words
- Playing the flute
- Working out problems in maths



Things I find difficult

- Concentrating
- Remembering lots of information and instructions
- Focusing on more than one thing at a time
- It can take me a longer time to understand what I am supposed to do
- Remembering all the things that I need for school