

**Investigating executive functioning abilities in**  
**Tourette Syndrome (TS) and effects on adaptive**  
**functioning**

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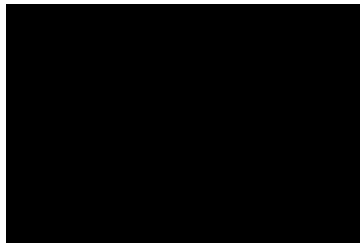
**University College London**

## **UCL Doctorate in Clinical Psychology**

### **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.

Signature:



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Date: 19-08-2018

## **Overview**

This thesis focuses on Executive Functioning abilities in children and young people with Tourette Syndrome (TS).

Part 1 comprises a literature review, using a systematic review method, to determine whether executive functioning impairments are present in individuals with TS. The review explores the extent to which EF impairments, if found, are exacerbated by comorbidity (e.g., with Attention-Deficit Hyperactivity Disorder, ADHD), mediated by the type of measure used, and if profiles of performance change across the developmental lifespan.

The empirical research paper in Part 2 examines distinct components of executive functioning, using experimental and ecologically valid behavioural measures in a group of 47 children with diagnoses of Tourette Syndrome. Of primary interest was to explore whether executive functioning is impaired in these children, and if executive functioning abilities impact on adaptive functioning. The work described was a joint project with my colleague, Summer Fakhro.

The critical appraisal (Part 3) offers some reflections about the research process, on working with young people with complex conditions in a research capacity, and outlines some recommendations for future research.

## **Impact Statement**

The clinical team at the Department of Child and Adolescent Mental Health, Great Ormond Street Hospital have observed a high prevalence of adaptive functioning problems in children with TS. These impairments impact a range of important domains including socialisation, daily living skills, communication and motor skills. Adaptive functioning deficits can be extremely debilitating, affecting children's abilities to navigate a wide-range of everyday tasks. Executive functioning abilities, that make inhibition, planning, initiation and organisation possible, appear intuitively to be likely to affect adaptive functioning. No studies to our knowledge have explored this association in TS, but a parent-report measure of executive functioning (BRIEF) contributed to most adaptive functioning domains in children with ASD (Happé, Booth, Charlton, & Hughes, 2006).

Investigating whether executive and adaptive functioning abilities are associated in children with TS is of clinical interest because by identifying factors that have the greatest impact on adaptive functioning, neurorehabilitation strategies can be applied to develop those skills and produce wide generalised treatment gains in adaptive functioning and quality of life in children with TS. Research into cognitive rehabilitation in children has increased processing speed, executive functioning and memory skills that extend to improvements in home and school settings (Butler, Copeland, Fairclough, Mulhern, Katz, Kazak, ... & Sahler, 2008; Kesler, Lacayo, & Jo, 2011; van't Hooft, Andersson, Bergman, Sejersen, Von Wendt, & Bartfai, 2005).

Executive functioning involves several separable, but likely interconnected components. There is some evidence to suggest that inhibition may be impaired in individuals with TS (Morand-Beaulieu, Grot, Lavoie, Leclerc, Luck, & Lavoie, 2017),

but executive functioning profiles in people with TS across other executive functioning domains is unclear. The systematic review undertaken here analyses the available evidence on executive functioning across the broad domains of fluency, set-shifting, planning and working memory across child and adult TS populations, allowing some insight into how executive functioning profiles may change as a function of development in TS. Dissemination of this research will be targeted at two broad groups: the TS community and clinicians and academics working with individuals with TS and other neurodevelopmental conditions.

*The TS community:* Some likely ways to communicate these findings to children with TS and their families will be using short, accessible articles to be published on relevant websites. An accessible article will be submitted to Tourette's Action (who have provided funding for this project) summarising our findings, for publication on their website. All participating families will also receive an easily digestible summary of our findings, encouraging them to share the key messages with their friends and relatives.

*Clinicians and academics working in TS:* These results will be disseminated to professional groups by maintaining contact with Tourette's Action, and by submitting abstracts to present our findings at the Tourette's Action Conference in September 2018 and the annual European Conference on Tourette Syndrome and Tic Disorders in June 2019. Papers arising from the project will be submitted to relevant peer-reviewed research journals. An effort will be made to select those research journals that are most likely to reach researchers, lecturers, and clinicians working in the field of TS.

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Thank you to my husband, Anthony, for your patience and unwavering support while I've been putting the thesis together, and especially for supporting me through the pregnancy. I promise to be more available for a while from now on!

I could not have wished for a better person than Summer to work jointly on this project with. From the outset, you have been collaborative, kind, thoughtful and encouraging and I've really valued our friendship throughout this process.

Thank you to my supervisors, John, Tara and Daniel, for the opportunity to be involved in this project. I have learned a great deal from your insight and experience, and the guidance you have given me through developing the project and reviewing drafts of the work. You have been a constant source of support for which I am very grateful.

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## Part 1: Literature review

### Executive functioning in children and adults with Tourette

### Syndrome (TS), is there more to it than just inhibition? A

### Systematic Review

#### 1.1. Abstract

**Aims:** A recent meta-analysis found that inhibition may be impaired in individuals with TS (e.g. Morand-Beaulieu et al., 2017). The aim of the current paper was to review the available evidence on other components of executive functioning (fluency, planning, set shifting, and working memory) in TS. A key aim was to compare executive functioning profiles across child and adult studies to explore if there are differences in patterns of impairment across development, and across uncomplicated and heterogeneous groups to explore the extent to which any EF deficits can be explained by comorbidity (e.g. with ADHD).

**Method:** PSYCinfo, EMBASE and MEDLINE were searched using terms related to TS and executive functioning. The search yielded 157 papers, of which 25 were eligible for detailed systematic review. Proportion of impairment as a function of EF component, measure, participant age range and heterogeneity of presentation, was explored using categorical analysis. Where available data allowed, effect sizes were computed and pooled across measures using similar methodologies.

**Results:** The review found evidence of deficient performance in phonological fluency, child planning, and adult set shifting (TMT performance) and working memory in individuals with TS. Semantic and figural fluency, complex figure organisation, adult tower and six elements planning, and child set shifting and working memory were generally preserved.

**Conclusion:** Executive functioning deficits in TS are not limited to inhibition, but are unlikely to reflect broad executive function deficits, given that TS groups did not show impairment on all types of executive tasks. Phonological fluency impairments were found fairly consistently across child and adult groups, and these deficits were in the

context of preserved semantic and figural fluency. Planning deficits were found in the child but not adult data, and set shifting and working memory deficits were found only in the adult groups. Impairments were found in uncomplicated as well as heterogeneous TS groups, suggesting that executive deficits may be associated with TS over and above the impact of additional comorbid presentations. These findings have implications for understanding of TS, as well as clinical assessment and treatment in that individuals with TS may show executive functioning difficulties, and that certain measures may be more sensitive than others in detecting these impairments in TS. Once identified, neurorehabilitation strategies can be applied to develop these skills, improving functioning and quality of life in children with TS.



## **1.2. Introduction**

### ***1.2.1. Tourette Syndrome***

Tourette Syndrome (TS) is a neurodevelopmental condition characterised by involuntary sudden, rapid, recurrent and non-rhythmic movements and/or vocalisations (tics). Clinically, a diagnosis of TS can be made when both multiple motor and one or more vocal tic have been present for more than a year (DSM-5, American Psychiatric Association, 2013). Tics may be simple (e.g. repetitive throat clearing, or involving a single muscle groups) or complex (phrases or patterns of vocalisations or distinct, coordinated movements involving several muscle groups) in nature. In TS, tics onset in childhood, are at their most frequent during late childhood (9-12 years), and then remit or subside into adulthood (Groth, Mol Debes, Rask, Lange, & Skov, 2017). Of children receiving a TS diagnosis as they progress through adolescence, around one quarter will become tic-free, a half will reduce to a minimal level, and less than one quarter will continue to have persistent tics (Singer, 2011). For this reason, prevalence of TS is higher in children than in adults. Tics commonly wax and wane throughout a person's life, fluctuating in terms of type, frequency and severity. Tourette Syndrome is a spectrum condition and varies across individuals from mild to severe. There are gender differences in TS prevalence, and TS is between three to four times more common in males than females (Robertson, 2011). This strong male bias in prevalence rates is apparent in both adult as well as child TS ) (Lichter & Finnegan, 2015), although there is some suggestion that adult female TS is under-represented in prevalence research, and that prevalence is significantly (three times) higher in females in adulthood than childhood (Burd, Kerbeshian, Wikenheiser, & Fisher, 1986; Larry, Jacob, Mark, & Wayne, 1986). There is variation in the prevalence

rates reported, but most reports converge on the estimation that around 0.4-1.4% of school age children meet diagnostic criteria for TS (Lombroso & Scahill, 2008; Robertson, 2011; Scahill, Williams, et al., 2006; Scharf, Miller, Mathews, & Ben-Shlomo, 2012). In terms of prevalence of TS in adulthood, the figure is likely to be between 0.3-0.5% (Leckman, Zhang, Vitale, Lahnin, Lynch, Bondi, ... & Peterson, 1998; Stern, Burza, & Robertson, 2005).

Tourette Syndrome is a highly heterogeneous condition, with shared genetic and neurobiological substrates leading to high rates of comorbidity with other disorders. The most common comorbidity with TS is Attention Deficit Hyperactivity Disorder (ADHD), although comorbidity with Obsessive Compulsive Disorder (OCD) is also common. A lifetime prevalence study of a group of 1374 people with TS found that the most common comorbid disorders were OCD (50.0%) and ADHD (54.3%), in line with high prevalence rates reported elsewhere (Denckla, 2006; Gorman, Thompson, Plessen, Robertson, Leckman, & Peterson, 2010). Historically, researchers have generally recognised that TS and OCD are genetically related, with genetic relations between TS and ADHD being less clear-cut (Robertson, 2011). However, there is other evidence to suggest that TS and ADHD may be genetically linked (O'Rourke, Scharf, Platko, Stewart, Illmann, Geller, ... & Pauls, 2011).

### ***1.2.2. Executive functioning components and measures***

Executive functioning is a term used to describe a set of abilities that govern goal-directed behaviour, inhibiting inappropriate behaviour, thinking before acting and adapting to novel situations. As such, these skills are crucial for the cognitive control of behaviour, and impairments can have substantial impact at several levels of a person's life and development.

Executive function is a complex, higher-order skill. Difficulties with the construct validity of EF have long been recognised, and there have been several efforts to fractionate executive functioning into specific executive skills: For example, flexibility, inhibition, problem-solving, planning, impulse control, concept formation, abstract thinking, creativity (Delis, Kaplan, & Kramer, 2001); attentional control, cognitive flexibility and goal setting (Anderson, 2001); shifting, updating and inhibition (Miyake, Friedman, Emerson, Witzki, Howerter, & Wager, 2000) and inhibition, interference control, working memory and cognitive flexibility, including fluency (Diamond, 2014).

There is evidence to suggest that separable executive abilities appear to enlist distinct areas of the frontal lobes (Stuss & Alexander, 2000). Findings of differences in impairment across subtypes of executive function after frontal lobe injury (Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999; Lehto, 1996; Stuss & Alexander, 2000), and evidence suggesting that different executive skills come online at different stages through development (Case, 1992; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Luciana & Nelson, 1998) further support the case for considering specific executive skills separately. However, distinguishing between different types of executive function is not clear-cut, and different types of executive skills are likely to employ some of the same unitary functions (Miyake et al., 2000). Indeed, many available measures of executive functioning can be seen to assess more than one skill. For example, the Trail Making Test (Reitan, 1985) is widely considered to be a test of set shifting, in requiring the sudden adaption to another rule, but is also likely to require inhibition of the previous rule. Most accounts suggest that executive functioning is comprised of multiple, separable systems that are inter-related and function together (Stuss & Alexander, 2000). Also, the relatively late development of

EF abilities over the life course presents additional challenges. Despite these methodological issues, there is compelling evidence supporting the fractionation of executive functioning.

### ***1.2.3. Executive functions during development***

Maturation of executive functioning is widely understood to occur relatively late in development. Studies have suggested that executive functions begin at around 12 months of age, with most executive skills appearing around the age of eight, and further developing through adolescence (Case, 1992; Klingberg et al., 1999; Luciana & Nelson, 1998). These developments appear to align with stages of frontal lobe maturation (Anderson, 2001) and processes of synaptic plasticity (Selemon, 2013).

Several studies suggest that discrete executive functions develop at different stages. One review found that inhibition is the first executive function to appear (Jurado & Rosselli, 2007). By 12 months of age, young children are able to inhibit some behaviours (Diamond & Goldman-Rakic, 1989; Luciana & Nelson, 1998). By three years of age, children are able to inhibit behaviours well, although this can still be problematic, leading to perseverative errors (Espy, 1997). By 9 years, children are able to inhibit and monitor their behaviour effectively (Anderson, 2001).

In terms of working memory acquisition, pre-schoolers are likely to have only one third of the short term memory (STM) span capacity of the average adult, and most STM development is thought to occur during the early years, with span increasing only by less than one digit span item between the ages of 13 and adulthood (Dempster, 1981). However, on working memory tasks, where extra processing demands are added to traditional span methodologies, performance improves quite dramatically

from the ages 7-14, with further performance gains observed up until 18 years of age (Alloway & Alloway, 2013; Siegel, 1994).

Some studies suggest that verbal fluency is the final executive function to appear (see for example a review by Jurado & Rosselli, 2007). A developmental ‘spurt’ is observed in fluency between three and five years of age (Espy, 1997) and improvements in fluency continue throughout early adolescence (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). In terms of set shifting, the ability to switch rapidly between two simple rules appears between ages 3 and 4, although these children may find switching between more complex rules too difficult (Espy, 1997). More complex set shifting is achieved between seven and nine years of age, and continues to mature through adolescence (Anderson, 2001).

Simple planning abilities are observed in children as young as four, but planning in advance is problematic for younger children (Welsh, Pennington, & Groisser, 1991). However these skills develop dramatically between seven and nine years of age with further, more gradual development continuing into adolescence (Welsh et al., 1991).

The research suggests simple acquisition of executive skills in young childhood, which develop in complexity through childhood and into adolescence, and that distinct EF components appear to follow slightly different courses. These hypothesised discrete developmental trajectories of specific executive functioning abilities need to be borne in mind throughout this review. Most child neuropsychology studies group children of various ages together to assess a cognitive domain, and this is likely to also be the case with articles in this area. This poses obvious difficulty for any thorough analysis of the developmental stages that individuals with TS acquire EF

skills. However, broad contrasts between children with TS and control groups, as well as adults with TS will be considered and interpreted from a developmental perspective in order to provide insight into whether individuals with TS show atypical development of EF, relative to typically-developing controls.

#### ***1.2.4. Executive functioning in Tourette Syndrome***

Inhibitory control is important in TS, and many of the impulsive behaviours seen in TS are considered to be due to inhibitory deficits. A comprehensive, recent meta-analysis explored inhibitory deficits in individuals with TS, finding small-medium effect sizes showing impaired inhibition in both children ( $d=0.30$ ) and adults ( $d=0.35$ ) with TS (Morand-Beaulieu et al., 2017). Of crucial interest is whether children and adults with TS show impairments in other components of executive functioning.

In children with TS, there is some evidence of impaired executive functioning on some experimental tests, including on the set shifting and visual recognition memory subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, 2017, Rasmussen, Soleimani, Carroll, & Hodlevskyy, 2009) and the Test of Variables of Attention (TOVA, Greenberg, 2007, Harris, Schuerholz, Singer, Reader, Brown, Cox, & Denckla, 1995). Other studies have indicated preserved evaluation of abstract concepts (Bornstein, 1990), good abilities in planning and response inhibition (Ozonoff & Jensen, 1999) and verbal fluency (Braun, Stoetter, Randolph, Hsiao, Vladar, Gernert, ... & Chase, 1993) in children with TS.

Several studies have suggested that neuropsychological deficits in children with TS may be mediated by presence of comorbid difficulties. One study found evidence of poor arithmetic skill in a sample of children with TS, a pattern that was

moderated by performance on cognitive measures of attention performance (Huckeba, Chapieski, Hiscock, & Glaze, 2008). Another study showed that children with TS achieved lower processing speed and perceptual reasoning scores than the general population, and their matched control group (Debes, Lange, Jessen, Hjalgrim, & Skov, 2011). The authors also found that children with comorbid ADHD and OCD were impaired on motor and speed tasks.

In the adult literature, there is some evidence of impairments in several components of executive functioning. For example, one study found evidence for executive functioning deficits when analysing response latencies on tests of verbal fluency and working memory that were not moderated by tic severity in adults with uncomplicated TS (Eddy, Rickards, & Cavanna, 2012). Another study found evidence of deficient attentional maintenance, shifting and flexibility, along with decision making, using the spatial recognition memory and intra-extra dimensional set shift subtests of the CANTAB (Cambridge Cognition, 2017, Watkins, Sahakian, Robertson, Veale, Rogers, Pickard, ... & Robbins, 2005). The authors also found that impairments in decision-making were more pronounced in the TS group than their OCD group, where neither group showed deficient planning abilities using the Tower of London test (Berg & Byrd, 2002).

In summary, deficits in inhibition in both child and adult TS groups are fairly well established, and are present even in uncomplicated TS samples. However, the picture is less clear in terms of other components of executive functioning. There is certainly some evidence to suggest EF difficulties in children, and especially adults with TS, but there may also be a strong impact of comorbidity, especially with ADHD, on these observations.

### ***1.2.5. Review aims***

Theoretical models of executive functioning, and the types of executive functioning measures typically used in Neuropsychological TS research were considered when deriving the final EF components to be targeted by this review. The inhibition component was excluded as a comprehensive meta-analysis already exists (Morand-Beaulieu et al., 2017). In order to select abilities across a broad spectrum of EF abilities, we used a generic EF component (planning), along with more specific abilities (fluency, working memory). Fluency was of interest as it is thought to be one of the last executive functions to develop (Jurado & Rosselli, 2007), and so could make for useful child and adult comparisons. Working memory was included as this skill is likely to be necessary for many tasks requiring abstract reasoning. Set shifting was selected to investigate flexibility of thought in people with TS.

The following types of measures were commonly employed in studies investigating these four components of executive functioning:

- Fluency (using phonological, semantic and figural fluency measures);
- Planning (organisational score of the Rey-Osterreith Complex Figure test (Osterreith, 1944), Tower tests (Berg & Byrd, 2002), six elements (Wilson, Alderman, Burgess, Emslie, Evans, 1996);
- Set shifting (the Wisconsin Card Sorting Test, WCST, Grant & Berg, 1948) and Trail-Making Task, TMT (Reitan, 1985); and
- Working Memory (e.g. the Digit Ordering Task Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991 and the self-ordered pointing memory test, Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2006; Petrides & Milner, 1982).



The fact that comorbidity is highly prevalent in TS is an important concern for researchers aiming to explore profiles of neuropsychological impairments in TS. Researchers have treated comorbidity in their samples in various ways: through considering participants with uncomplicated TS (i.e. where no comorbidity exists), and comorbid groups (e.g. TS plus ADHD; TS plus OCD etc.) separately, or by evaluating the contribution of any given comorbidity through statistical analysis. Consideration of co-morbidity will be factored into the current review.

Many studies in the TS literature have used relatively small sample sizes, increasing the possibility of Type II error. Through considering data from several sources, including pooling effect sizes wherever possible, this review aims to address the difficulties posed by small sample sizes.

There were three main aspects to the review: (i) a detailed systematic review of the relevant literature; (ii) a categorical analysis of the proportion of studies finding preserved and impaired scores in the TS groups, relative to controls, and (iii) computation of pooled effect sizes on measures that used similar methodologies / TS group characteristics, where available data allowed.

The current review aims to:

- (i) Systematically review the existing evidence to assess whether these wider components of EF are impacted in TS, or whether executive functioning impairments are specific to difficulties in inhibition (Morand-Beaulieu et al., 2017).
- (ii) Test if there are differences in profiles of executive functioning ability between children and adults, and if these differences are moderated by EF component.

- (iii) Explore if divergent findings within each component of executive functioning are due to the types of measure used.
- (iv) Assess if EF abilities differ as a function of different comorbidities, particularly ADHD. A key aim is to investigate the extent to which any EF impairments are inherent in TS, or if they are more likely to be attributed to (e.g.) comorbid ADHD.

## **1.3. Method**

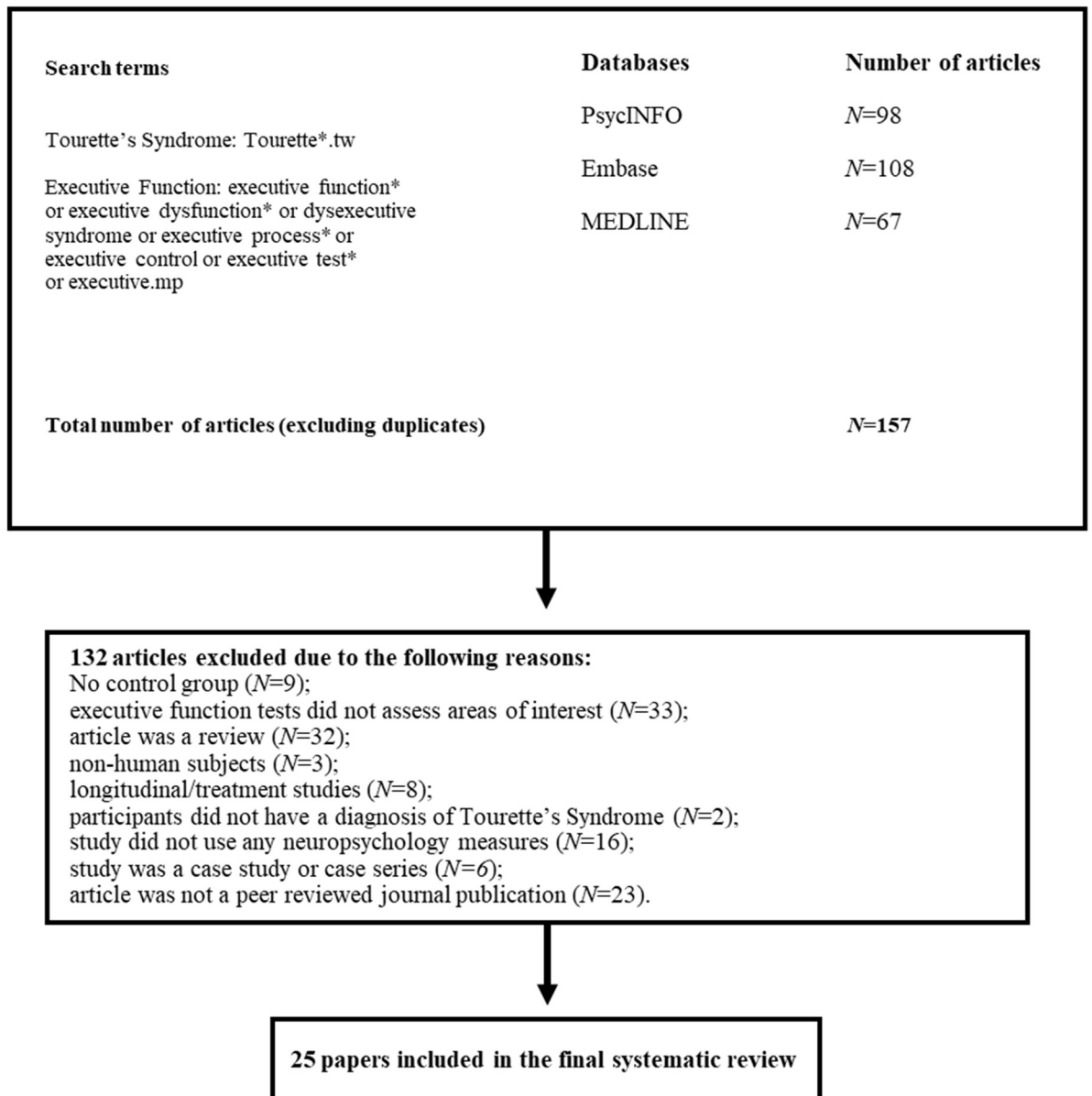
### ***1.3.1. Data sources and study inclusion***

A systematic literature review was conducted on 15th March 2018, using three electronic databases (PsycINFO, Embase and MEDLINE). Search terms related to Tourette Syndrome were additively combined with terms related to executive functioning. Appropriate constraints were applied (to ensure that articles related to human research and written in the English language). Once duplicate articles were removed, 157 articles remained. Due to the scarcity of research in this area, an inclusive approach to study selection was used, to maximise the sensitivity of the search. Articles were included provided they fulfilled the following criteria:

- (i) Participants had received a diagnosis of TS.
- (ii) The measures used assessed at least one of four components of executive functioning: fluency, planning, set shifting or working memory.
- (iii) The measures reported were objective neuropsychology assessments (i.e. not self-report).
- (iv) A typically-developing comparison group was included.
- (v) Studies were published in a peer reviewed journal.

The search process is summarised in Figure 1.1.

A data extraction tool was designed and used to identify the following information from each study: (i) the characteristics of study participants (age, TS diagnosis and comorbidity); (ii) a description of the study; (iii) the EF measures used; (iv) test statistics and means and standard deviations for calculating effect sizes and (v) a summary of key results.



*Figure 1.1. A visual representation of the search process.*

*N.B. All searches were limited to English language and humans; tw = searching title and abstract; mp = searching title, abstract, headings and keywords.*

### ***1.3.2. Study quality***

The Critical Appraisal Skills Programme (CASP, 2014) checklist for case control studies was used to assess study quality. The measure assesses the quality of study methodology and findings. The CASP is widely used and becoming one of the standard tools in the field, such that many readers are likely to be familiar with it, and also covers the key aspects that were important for the current review. The checklist is comprised of 11 items, and includes two qualitative items, giving a maximum quality score of nine. The CASP checklist is provided in Appendix A and the quality ratings for each of the studies reviewed are included in Table 1.2.

### ***1.3.3. Methodological issues in EF research***

Multiple tests have been developed to assess components of executive function (e.g. Tower tests – planning, Wisconsin Card Sorting Test – set shifting), and are used routinely in clinical practice. However, while these measures capture a specific process, they are also likely to draw on other processes. For example, Tower tests are used to assess planning ability, but these tasks are certain to also enlist a range of additional skills, including lower level perceptual abilities such as visual perception and higher order executive processes (e.g. working memory, inhibition). Although most tasks build in control for confounds in task development (e.g. the Tower of London has multiple levels of difficulty), it is possible that any impairment observed on these tasks could be due to difficulties in these additional areas. In fact, no task can be understood as targeting only one specific process.

Another difficulty is that studies and measures differ in the dependent measure reported, with some prioritising accuracy rates and others response latency. On some measures, results may be affected by a speed-accuracy trade-off, and so it is important

to consider both types of data when describing study findings where accuracy and response times are reported. Approaches to measuring EF remains a contentious issue and no “gold standard” for measure selection has been agreed (Kudlicka, Clare, & Hindle, 2011).

#### ***1.3.4. Data extraction and reporting***

##### ***1.3.4.1. Measures***

The review addressed a relatively broad question, investigating four separate components of executive functioning, and several different measures have been used across the studies to investigate each. Table 1.2 provides methodological information on the measures used to assess each EF type, and the number of instances where each measure was used across the sampled studies.

Fluency was the most homogeneous in terms of measure selection, with relatively similar methodologies used across letter, semantic and figural conditions. There was much wider variability in measures across the other EF components. For planning, the three Tower tests (Towers of London and Hanoi, and Stockings of Cambridge) follow a similar methodology. The other tasks, however, (the organisation score of the Rey-Osterrieth Complex Figure copy and the Six Elements test) have clear differences, the former a measure of how systematic a participant is in approaching a figure drawing, and the latter an ecological measure to determine how a participant can organise their time while following rules and needing to complete task demands.

The most frequently-used set shifting measure in the sampled studies was the WCST, and other rule-shift tasks using similar methods (Rule shift task, Attentional

set shifting, Task switch test and IED). Another frequently used task was the Trail Making Test, although the demands of this task are quite different (comparing completion time on matched tasks where the need for set shifting was manipulated). The Working Memory tasks used a range of methodologies, including N-back, digit-ordering, spatial and self-pointing memory measures.

Another important consideration was the dependent outcome measure reported. Even across studies using the same task, there may be differences in the dependent variables reported (e.g. on the Wisconsin Card Sorting Task, WCST, some authors report overall accuracy, whereas others report the proportion of perseverative errors made). Summaries of all types of outcome data were reported for the systematic review, in order to provide full descriptions of EF ability in each case, and to detect speed-accuracy trade-offs in performance. Studies are likely to report measures in accordance with standardised administration and scoring instructions for each task, but this will differ across tasks. For instance, some tasks will generate a primary outcome score (e.g. accuracy) with a secondary outcome of time. Accuracy rates were prioritised over latencies for the categorical analysis (proportion of studies reporting impairment) and effect size computations and pooling, as accuracy rates were reported more systematically across the studies, with the exception of one task that used response latency as the primary outcome (TMT).

#### ***1.3.4.2. Categorising measures for the systematic review and for effect size analysis.***

For the main systematic review analysis, data were grouped based on EF type (i.e. if a study assessed more than one component of EF, these data are entered separately, appearing in separate sections of the table). Data extracted from the 25 studies selected

led to 49 outcome data points (contrasts per measure between TS and control groups, table rows, Table 1.2). The findings were categorised by (i) EF component; and (ii) whether the study used child or adult participants.

Due to the small number of studies undertaken in this area, and the breadth of the executive functioning areas and measures involved, a formal meta-analysis was not possible. For analysis of effect sizes, measures that used similar methodologies were grouped together (see column labelled 'ES N' for information on measures that were categorised as sharing common task methodology). These totals were screened for whether the studies provided sufficient data to calculate effect sizes (means and standard deviation), and separated by age range (child/adult) and TS group (heterogeneous/uncomplicated). The number of groups on which the effect size calculations were based are provided in the Results section (Figure 1.3 explanatory notes).



*Table 1.1. Description of each of the measures used, and frequency of their occurrence across the selected studies.*

<b>EF component and measure</b>	<b>Reference(s)</b>	<b>Description</b>	<b><i>N</i></b>	<b><i>ES N</i></b>
<b><i>Fluency</i></b>				
Letter	Controlled Oral Association Test-FAS, COWAT, Delis, Kaplan, & Kramer, 2001	Participants are given 1 minute to produce as many unique words as possible starting with a given letter.	<b>11</b>	<b>11</b>
Semantic	Controlled Oral Association Test-Category, COWAT, Delis, Kaplan, & Kramer, 2001	Participants are given 1 minute to produce as many unique words as possible within a semantic category.	<b>7</b>	<b>7</b>
Figural	Ruff, Light, & Evans, 1987	Participants are given 1 minute to draw as many unique designs as possible by connecting at least two of the dots comprising a 5-dot matrix.	<b>2</b>	<b>2</b>
<b><i>Planning</i></b>				
Tower of London	Berg & Byrd, 2002	Participants are required to rearrange rings into a given target configuration whilst following a set of rules (e.g. move only one ring at a time).	<b>5</b>	
Tower of Hanoi	Simon, 1975	Participants are required to rearrange rings into a given target configuration whilst following a set of rules (e.g. move only one ring at a time).	<b>1</b>	<b>7</b>
Stockings of Cambridge	CANTAB, Cambridge Cognition, 2017	Participants are required to rearrange rings into a given target configuration whilst following a set of rules (e.g. move only one ring at a time).	<b>1</b>	
Rey-Osterrieth Complex Figure (RCFT) copy organisation	Osterrieth, 1944	Participants are required to reproduce an intricate image. There are copy and recall conditions, and the copy organisation score provides information on how the participant plans the task.	<b>3</b>	<b>3</b>
Six Elements	Wilson, Alderman, Burgess, Emslie, & Evans, 1996	Participants are given three tasks (dictation, arithmetic, and picture naming), each of which is divided into two parts (A and B). They must attempt each of the six subtasks within a 10-minute test period and are not allowed to do two parts of the same task consecutively.	<b>3</b>	<b>3</b>
<b><i>Set shifting</i></b>				
Wisconsin Card Sorting Task (WCST)	Grant & Berg, 1948	Cards are presented to the participant, who is asked to match the cards, but not advised how to match. They are told whether a given match is right or wrong.	<b>9</b>	<b>13</b>

<b>EF component and measure</b>	<b>Reference(s)</b>	<b>Description</b>	<b><i>N</i></b>	<b><i>ES N</i></b>
Rule shift Task	Channon, Pratt, & Robertson, 2003	Simpler version of the WCST, which negates the need to work out the rule.	<b>1</b>	
Attentional set shifting	Downes, Roberts, Sahakian, Evenden, Morris, & Robbins, 1989	Participants are required to selectively attend to and set-shift between shape, colour or number dimensions, conducting both intra- and extra-dimensional shifts.	<b>1</b>	
Task Switch Test	Yaniv et al., 2017	Participants are asked to switch between classifying number stimuli by their magnitude and parity.	<b>1</b>	
Intra-Extra Dimensional set shift task (IED)	CANTAB, Cambridge Cognition, 2017	Participants see pairs of simple shapes and learn which one is correct by touch. They are told whether choices are right or wrong and after six correct responses, the rules change. These shifts are intra-dimensional (related to shapes) and extra-dimensional (related to lines).	<b>1</b>	
Trail making task	Reitan, 1985	Participants connect a sequence of 25 consecutive targets as quickly as possible. In part A, the targets are numbers, and in part B the subject alternates between numbers and letters. Errors are corrected.	<b>4</b>	<b>4</b>
Object Alternation Test	Chang, McCracken, & Piacentini, 2007; Freedman, 1990	Participants are asked to guess which one of two cups was hiding an object. The object alternates position after each correct response. The test continues until 25 correct guesses are achieved.	<b>1</b>	<b>1</b>
<b><i>Working Memory</i></b>				
N-back	Kirchner, 1958	Participants see a sequence of stimuli, and indicate when the current stimulus matches the one from <i>n</i> steps earlier in the sequence. The load factor <i>n</i> is adjusted to manipulate difficulty.	<b>3</b>	<b>4</b>
Running Memory Task	Ozonoff & Strayer, 2001; Redick et al., 2012	N-back task using shapes.	<b>1</b>	
Digit-ordering Task-A	Cooper et al., 1991	Participants are given items of increasing length (3 to 8 digits) and are asked to repeat these digits in ascending order.	<b>3</b>	<b>3</b>
Spatial Memory Task	Ozonoff & Strayer, 2001	Participants were shown shapes at different spatial locations to memorize. After a delay, one of the shapes was re-presented and participants were required to report the location of that shape during the sequence.	<b>1</b>	<b>2</b>
Spatial Working Memory	CANTAB, Cambridge Cognition, 2017	Participants were required to find hidden tokens, searching boxes by touching them in sequence. Participants are asked to avoid (i) touching	<b>1</b>	

<b>EF component and measure</b>	<b>Reference(s)</b>	<b>Description</b>	<i>N</i>	<i>ES N</i>
		a box that has already contained a token and (ii) returning to touch a box that has been found to be empty in that trial.		
Box Search Task	Ozonoff & Strayer, 2001	Participants were required to search for “treasures” by selecting one of the six colored boxes. They were asked to search each box, but not to return to a box already searched.	<b>1</b>	<b>1</b>
Self-Ordered Pointing Task (SOP)	Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2006; Petrides & Milner, 1982	Participants are shown abstract designs, with varying numbers of designs in each set, and asked to select the designs and locations they were shown in each sequence.	<b>2</b>	<b>2</b>

#### ***1.3.4.3. Groups and co-morbidity***

The test groups across the sampled studies varied: there were 12 groups with uncomplicated TS (8 child N=147; 4 adult, N=92), 12 with heterogeneous TS (6 child, N=119; 6 adult, N=156), 4 with TS+ADHD (4 child, N=59), and 2 with TS+OCD (1 child, N=6; 1 adult, N=14). There was also one group with TS+(probable) ADHD (child, N=25) and another with TS heterogeneous but excluding OCD (child, N=15).

#### ***1.3.5. Statistics and effect sizes***

The primary outcome used in the review was whether performance by the test groups (participants with TS) differed significantly from that of matched controls. Provided statistical differences reflected lower scores in the TS than the control groups, significant differences were taken as evidence of TS deficit. For each study, statistics indicating the significance of differences between the TS group and control group were extracted from each article and reported in Table 1.2. Where possible, standardised effect sizes (Cohen's  $d$ ) were also calculated and provided in Table 1.2. Of a possible 49 findings (separated by study and EF component), effect sizes could be computed in 36 cases. Cohen's  $d$  was calculated using the difference between the test group and control group mean scores, divided by the pooled standard deviation for the two groups (i.e. Effect size ( $d$ ) =  $(M_{TS} - M_C) / SD_{pooled}$ , where TS = TS group and C = Control group).

## **1.4. Results**

### ***1.4.1. Corpus of studies***

The systematic literature search led to the inclusion of 25 articles for review.

Descriptions of these selected articles are summarised in Table 1.2.

### ***1.4.2. Study quality***

Study quality scores for each article are provided in Table 1.2. Generally, the studies were rated as being of extremely high standard: The mean score was 8 (SD=0.63) of a maximum quality score of 9. Where minor problems with study quality occurred, they were due to small sample sizes and uncertainty about the generalisability of the findings.

*Table 1.2. Summary of studies included in the systematic review*

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
1. (Channon et al., 2003)	8	TS-heterogeneous (29) of which TS-uncomplicated (14); TS+ADHD (9); TS+OCD (6)	21	Child (9-18)	Child participants with TS, TS and OCD, TS and ADHD, and controls were compared on performance on executive functioning, memory and learning tasks.	Fluency	Letter fluency ('S')	TS: $d=-0.539$ (M) TS+ADHD: $d=-1.148$ (L) TS+OCD: $d=-1.064$ (L) $p=.044$	Analysis of letter fluency performance across the four groups revealed a significant effect of group, though this result was not significant when using the authors' strict significance criterion (.05/3=.0167) to correct for multiple comparisons. Effect sizes were higher for the TS+ADHD and TS+OCD and control comparisons, than for the uncomplicated TS group.
2. (Drury, Shah, Stern, Crawford, & Channon, 2017)	8	TS-uncomplicated (15); TS+ADHD-heterogeneous for OCD (13)	25	Child (8-11)	The study evaluated social cognition (sarcasm comprehension) and executive functioning in children and adolescents with uncomplicated TS and TS+ADHD, comparing their performance with that of a matched control group.	Fluency	Letter and semantic fluency (with switching component)	TS: $p=.225$ TS+ADHD: $p=.05$ Insufficient data to calculate effect sizes	The TS+ADHD generated fewer words on the fluency measures than controls. The uncomplicated TS group did not differ from fluency performance in the control group.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
3. (Schuerholz, Singer, & Denckla, 1998)	8	TS-uncomplicated (18); TS+ADHD (23)	36	Child (7-15)	Neuropsychological performance in participants with TS, ADHD, TS+ADHD and controls were compared, and gender differences in neuropsychological profiles were also explored.	Fluency	Letter and semantic fluency	Letter word fluency: Male TS: $d=.029$ (S) Female TS: $d=-1.152$ (L) Gender data pooled: $p=.02$ Male TS+ADHD: $d=.206$ (S) Female TS+ADHD: $d=0.68$ (M) Gender data pooled: $p=.01$  Semantic word fluency: Male TS: $d=.416$ (S) Female TS: $d=0.333$ (S) Gender data pooled: NS Male TS+ADHD: $d=0.942$ (L) Female TS+ADHD: $d=0.166$ (S) Gender data pooled: NS	When data from both genders were pooled together, both TS groups generated significantly fewer words on the LWF test than controls. No group differences were found between the groups on SWF.
4. (Mahone, Koth, Cutting, Singer, & Denckla, 2001)	8	TS-uncomplicated (25)	28	Child (6-16)	Executive functioning was assessed in child participants with TS and ADHD, and compared to that of a matched control group.	Fluency	Letter, semantic and Ruff figural fluency	SWF: $d=0.0629$ (~), NS LWF: $d=-0.110$ (~), NS FF: $d=-0.204$ (S), NS	There were no differences in performance on any of the three fluency measures between children with uncomplicated TS and controls.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
5. (Schuerholz, Baumgardner, Singer, Reiss, & Denckla, 1996)	8	TS-uncomplicated (21); TS+ADHD (19); TS+probable ADHD (25)	27	Child (6-14)	The study analysed neuropsychological data, along with psychosocial and psychoeducational data, across groups of child participants with (1) uncomplicated TS; (2) TS+ADHD and (3) TS+probable ADHD, and unaffected siblings.	Fluency	Letter and semantic fluency	Letter word fluency: TS: $p=.02$ TS+ADHD: $p=.01$ TS+ADHD traits: $p=.05$  Semantic word fluency: TS: NS TS+ADHD: NS TS+ADHD traits: NS Insufficient data to calculate effect sizes.	On letter word fluency, the uncomplicated TS group and the TS+probable ADHD group generated significantly fewer words than controls. There were no significant differences in semantic word fluency between the groups.
6. (Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005)	8	TS-heterogeneous (24)	47	Child (6-13)	Executive functioning across three groups of children (TS; ASD and controls) was compared using a comprehensive battery of tests.	Fluency	Letter and semantic fluency	Letter fluency: $d=-0.279$ (S), NS; Semantic fluency: $d=-0.318$ (S), NS	No significant differences between groups were observed on either the letter or category fluency measures.
7. (Müller et al., 2003)	7	TS+OCD (14)	14	Adult	A battery of neuropsychological tests of executive functioning, memory and attention to groups of adult participants with (1) TS+OCD and (2) OCD and (3) control participants. Results were compared across group and test conditions.	Fluency	Controlled Oral Word Association Task (COWAT) – letter fluency; Ruff Figural Fluency Test (RFFT)	COWAT no. of words, $d=-0.2$ (S), $p=.45$ RFFT unique designs $d=-0.248$ (S), $p=.51$ RFFT perseverations ratio $d=0.35$ (S), $p=.35$	TS and control performance did not differ significantly on the COWAT (phonological fluency component) and the figural fluency measure.
8. (Eddy et al., 2012)	9	TS-uncomplicated (29)	20	Adult	The study investigated executive functioning in a group of adults with uncomplicated TS, and compared performance to that of a matched control group.	Fluency	Phonological fluency (FAS, DKEFS)	$d=0.722$ (M), $p=0.007$	The TS group generated significantly fewer words on the FAS task than controls.



Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
9. (Watkins et al., 2005)	8	TS-heterogeneous (20)	20	Adult	Executive functioning (assessed using tasks of planning, fluency, set shifting and inhibition) was compared across three adult participant groups: (1) TS (2) OCD and (3) controls.	Fluency	Letter and semantic fluency	Letter fluency: NS. Category fluency: NS. Insufficient data to calculate effect size.	No differences existed between TS and control groups on either measure of fluency.
10. (Goudriaan et al., 2006)	8	TS-heterogeneous (46)	49	Adult	This study aimed to investigate neuropsychological abilities in a group of pathological gamblers, and included a TS group (as an impulse disorder control group) and a control group without such difficulties. Performance on a comprehensive neuropsychological battery, including tests of executive function, was compared across the groups.	Fluency	Controlled Oral Word Association Test (COWAT)	No. correct: $d=-0.099$ (-), NS Perseverations: $d=0.314$ (S), NS	No significant differences were found between adult participants with TS and controls on the fluency measures.
11. (Eddy & Cavanna, 2017)	8	TS-uncomplicated (27)	25	Adult	Neuropsychological performance of adults with TS was compared with that of controls using a comprehensive battery.	Fluency	Letter and semantic fluency	Letter fluency: $d=-0.223$ (S), NS; Semantic fluency: $d=-0.236$ (S), NS	No significant differences between groups were observed on either the letter nor category fluency measures.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
12. (Termine et al., 2016)	8	TS-uncomplicated (13); TS+ADHD (8)	66	Child (6-15)	The performance of four groups of unmedicated male child participants on a comprehensive neuropsychological assessment battery were compared: TS, TS+ADHD, ADHD and controls.	Planning	Tower of London (TOL)	<p>Planning skills TS: <math>d=-0.705</math> (M), NS TS+ADHD: <math>d=-1.452</math> (L), <math>p=.003</math></p> <p>Planning efficiency TS: <math>d=1.294</math> (L), <math>p&lt;.001</math> TS+ADHD <math>d=1.574</math> (L), <math>p&lt;.001</math></p> <p>Comprehension of rules TS: <math>d=1.146</math> (L), NS TS+ADHD: <math>d=1.240</math> (L), <math>p=.021</math></p> <p>Time to complete (initiation) TS: <math>d=0.543</math> (M), NS TS+ADHD: <math>d=0.384</math> (S), NS</p> <p>Time to complete (execution) TS: <math>d=0.814</math> (L), <math>p=.002</math> TS+ADHD: <math>d=1.104</math> (L), NS</p> <p>Time to complete (total) TS: <math>d=0.714</math> (M), <math>p=.022</math> TS+ADHD: <math>d=0.866</math> (L), NS</p>	When comparing performance by the TS groups (uncomplicated TS and TS+ADHD) and control performance on the Tower of London test, the TS+ADHD group showed significantly poorer performance on the planning skills, planning efficiency, comprehension of rules contrasts, relative to controls. The uncomplicated TS group achieved significantly poorer scores on planning efficiency, comprehension of rules and time to complete (on both execution and total time contrasts) than controls.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
13. (Schuerholz et al., 1996)	8	TS-uncomplicated (21); TS+ADHD (19); TS+probable ADHD (25)	27	Child (6-14)	The study analysed neuropsychological data, along with psychosocial and psychoeducational data, across groups of child participants with (1) uncomplicated TS; (2) TS+ADHD and (3) TS+probable ADHD, and unaffected siblings.	Planning	Rey-Osterreith Complex Figure Test organisation score (RCFT)	TS: $p=.01$ TS+ADHD: NS TS+ADHD traits: NS Insufficient data to calculate effect sizes.	The TS-only group had better Rey Copy Organization scores than controls (comparison $p = 0.01$ ).
14. (Verté et al., 2005)	8	TS-heterogeneous (24)	47	Child (6-13)	Executive functioning across three groups of children (TS; ASD and controls) was compared using a comprehensive battery of tests.	Planning	Tower of London	Total score: $d=-0.519$ (M), NS; Decision time: $d=-0.244$ (S), NS; Execution time: $d=0.305$ (S), NS	No significant differences between groups were observed on the ToL.
15. (Channon et al., 2003)	8	TS-heterogeneous (29) of which TS-uncomplicated (14); TS+ADHD (9); TS+OCD (6)	21	Child (9-18)	Child participants with TS, TS and OCD, TS and ADHD, and controls were compared on performance on executive functioning, memory and learning tasks.	Planning	Six elements test (BADs)	TS: $d=-0.620$ (M), NS TS+ADHD: $d=-1.549$ (L), $p=.010$ TS+OCD: $d=-0.738$ (M), NS	On the six elements task, only the TS+ADHD group scored significantly below the control group and no other group differences were significant.
16. (Ozonoff & Jensen, 1999)	8	TS-heterogeneous sample (14)	14	Child (8-17)	The study investigated executive functioning in children with ASD, TS, and ADHD, comparing performance to that of a matched control group.	Planning	Tower of Hanoi (TOH)	$d=-0.109$ (~), NS	The TS group did not differ significantly from controls on the Tower of Hanoi task.
17. (Schuerholz et al., 1998)	8	TS-uncomplicated (18); TS+ADHD (23)	36	Child (7-15)	Neuropsychological performance in participants with TS, ADHD, TS+ADHD and controls were compared, and gender differences in neuropsychological profiles were also explored.	Planning	Rey-Osterreith Complex Figure Test - organisation score (RCFT)	TS: NS TS+ADHD: NS Insufficient data to calculate effect sizes.	No significant differences in performance were found when comparing the TS groups with controls.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
18. (Chang et al., 2007)	7	TS-heterogeneous but excluding OCD (15)	15	Child (7-14)	Performance on a neuropsychological battery examining executive, attention, memory and visuomotor abilities was compared across three child participant groups: (1) OCD without TS; (2) TS heterogeneous for other conditions, but excluding OCD and (3) controls.	Planning	Rey-Osterreith Complex Figure Test - organisation score (RCFT)	RCFT organisation score: $d=0$ (~), NS.	No significant differences existed between TS and control performance on the organisation dimension of the Rey-Osterreith Complex Figure test.
19. (Rasmussen et al., 2009)	8	TS-uncomplicated (21)	23	Child (7-13)	Children with uncomplicated TS completed tests from the CANTAB (comprising measures of memory, executive function and attention), and performance was compared with that of a matched control group.	Planning	Stockings of Cambridge (SOC)	Initial thinking time, NS Subsequent thinking time, NS Problems solved, $p<.05$ . Insufficient data to calculate effect sizes.	Though there were no differences in either thinking time contrast, the TS group performed significantly poorer in terms of problems solved on the Stockings of Cambridge task.
20. (Lavoie, Thibault, Stip, & O'Connor, 2007)	8	TS-heterogeneous (18)	18	Adult	Groups of adult participants with TS and chronic tic disorder were tested on a neuropsychology battery comprising memory, executive function and motor dexterity measures. Their performance was compared with that of a control group.	Planning	Tower of London (TOL)	Correct items, $d=0$ (~), NS Initiation time, $d=-0.144$ (~), NS Execution time, $d=0.33$ (S), NS Violations, $d=0.086$ (~), NS	There were no significant differences in Tower of London performance between the TS group and controls.
21. (Goudriaan et al., 2006)	8	TS-heterogeneous (46)	49	Adult	This study aimed to investigate neuropsychological abilities in a group of pathological gamblers, and included a TS group (as an impulse disorder control group) and a control group without such difficulties. Performance on a comprehensive neuropsychological battery, including tests of executive function, was compared across the groups.	Planning	Tower of London	Correct score: $d=-0.120$ (~), NS	No significant differences were found in performance on the Tower of London task between the TS group and controls.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
22. (Watkins et al., 2005)	8	TS-heterogeneous (20)	20	Adult	Executive functioning (assessed using tasks of planning, fluency, set shifting and inhibition) was compared across three adult participant groups: (1) TS (2) OCD and (3) controls.	Planning	Tower of London (TOL)	NS. Insufficient data to calculate effect size.	Adult TS participants were not impaired in planning ability relative to controls.
23. (Channon, Sinclair, Waller, Healey, & Robertson, 2004)	8	TS-uncomplicated (15)	23	Adult	A group of participants with uncomplicated TS were compared with matched controls on performance on tests of social and non-social (executive functioning) cognition.	Planning	Six elements test (BADs)	$d=-0.144$ (~), NS	Adult TS participants were not impaired on a test of planning ability relative to controls.
24. (Channon, Crawford, Vakili, & Robertson, 2003)	8	TS-uncomplicated (21)	21	Adult	Performance on tasks of social cognition along with executive functioning was explored in adult participants with TS, and compared with matched controls.	Planning	Six elements test (BADs)	No. of tasks attempted, NS	Both groups performed at / near ceiling on this test, and so significance testing and effect size calculation was not conducted.
25. (Ozonoff & Jensen, 1999)	8	TS-heterogeneous sample (14)	14	Child (range not provided, M age 12.4)	The study investigated executive functioning in children with ASD, TS, and ADHD, comparing performance to that of a matched control group,	Set shifting	Wisconsin Card Sorting Test (WCST)	$d=0.211$ (S), NS	On the Wisconsin Card Sorting Test, neither the TS nor ADHD groups differed significantly from controls.
26. (Verté et al., 2005)	8	TS-heterogeneous (24)	47	Child (6-13)	Executive functioning across three groups of children (TS; ASD and controls) was compared using a comprehensive battery of tests.	Set shifting	Wisconsin Card-Sorting Task (WCST).	$d=0.299$ (S), NS	No significant differences between groups were observed on the WCST.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
27. (Channon et al., 2003)	8	TS-heterogeneous (29) of which TS-uncomplicated (14); TS+ADHD (9); TS+OCD (6)	21	Child (9-18)	Child participants with TS, TS and OCD, TS and ADHD, and controls were compared on performance on executive functioning, memory and learning tasks.	Set shifting	Rule shift test (a simpler task than WCST, no requirement to work out rule); Trail Making Task (TMT)	<p>Rule shift test:  TS: <math>d=-0.460</math> (S), NS  TS/ADHD: <math>d=-0.609</math> (M), NS  TS/OCD: <math>d=0.194</math> (~), NS</p> <p>TMT part A:  TS: <math>d=0.432</math> (S), NS  TS/ADHD: <math>d=0.285</math> (S), NS  TS/OCD: <math>d=1.188</math> (~), NS</p> <p>TMT part B:  TS: <math>d=0.387</math> (S), NS  TS/ADHD: <math>d=0.640</math> (M), NS  TS/OCD: <math>d=0.930</math> (L), NS</p>	No significant group differences emerged in any of the patient group and control contrasts for either of the measures used.
28. (Chang et al., 2007)	7	TS-heterogeneous but excluding OCD (15)	15	Child (7-14)	Performance on a neuropsychological battery examining executive, attention, memory and visuospatial abilities was compared across three child participant groups: (1) OCD without TS; (2) TS heterogeneous for other conditions, but excluding OCD and (3) controls.	Set shifting	Object Alternation Test (learning criterion achieved)	$d=1.409$ (L), $p=.09$	No significant differences existed between TS and control performance on the Object Alternation Test.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
29. (Rasmussen et al., 2009)	8	TS-uncomplicated (21)	23	Child (7-13)	Children with uncomplicated TS completed tests from the CANTAB (comprising measures of memory, executive function and attention), and performance was compared with that of a matched control group.	Set shifting	Intra-Extra Dimensional Set Shift Rule acquisition and attentional set shifting (IED)	Stages completed: NS Total errors, $p < .05$ Insufficient data to calculate effect sizes.	Children with TS scored significantly poorer in terms of IED total errors than controls, although the groups were fairly matched on number of stages completed.
30. (Yaniv et al., 2017)	9	TS - heterogeneous sample (19)	19	Adult	A battery comprising computerised and manual neuropsychological tests (including several executive functioning measures) were administered to a group of adults with TS, with performance compared to that of a matched control group.	Set shifting	Wisconsin Card Sorting Task (WCST); Task Switching Test (TST)	TST Mixing RT $d = 0.355$ (S), NS TST Switching RT $d = -0.163$ (~), NS TST mixing accuracy $d = -0.780$ (M), $p < .01$ TST total accuracy $d = -0.866$ (L), $p < .05$ TST switching accuracy $d = -0.711$ (M), $p < .05$ WCST perseverative error $d = 0.318$ (S), NS WCST total error $d = 0.686$ (M), NS	No differences were found between the TS and control group on the WCST, or the temporal measures of the TST. The TS group performed significantly poorer on all three accuracy contracts on the TST (mixing, total and switching), relative to controls.
31. (Müller et al., 2003)	7	TS+OCD (14)	14	Adult	A battery of neuropsychological tests of executive functioning, memory and attention to groups of adult participants with (1) TS+OCD and (2) OCD and (3) control participants. Results were compared across group and test conditions.	Set shifting	Wisconsin Card Sorting Task (WCST)	No. of categories $d = -0.395$ (S), $p = 0.31$ Perseverative errors $d = 0.161$ (~), $p = .67$	No differences were found between the TS and control group on the WCST.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
32. (Eddy & Cavanna, 2015)	9	TS - heterogeneous sample (20)	20	Adult	The study investigated spontaneous mentalising in TS, through an ambiguous animations task depicting social interactions between shapes. A battery measuring executive functioning, alexithymia and clinical symptoms were also administered to their samples of adults with TS and a comparison control group.	Set shifting	Trail making test (TMT)	$d=0.828$ (L), $p=.021$	The (heterogeneous) TS group showed significantly greater difficulty on the TMT than controls.
33. (Matsuda et al., 2012)	8	TS-heterogeneous sample (33)	18	Adult	The study explored the impact of TS-related obsessive-compulsive symptoms (aggression and symmetry) on neuropsychological performance as a function of age. The test battery comprised measures of attention and executive functioning. The sample included a group of adults with TS, subdivided into participants with presence or absence of aggression and symmetry, and a control comparison group.	Set shifting	Wisconsin Card Sorting Test (WCST)	TS+aggression OCS: total errors, perseverative errors, cognitive level response, all $p's < .001$ TS+symmetry OCS: all contrasts NS. Insufficient data to calculate effect sizes.	Poorer performance in the TS-related OCS group on the aggression dimension on set shifting. No differences were found in the TS+symmetry group contrasts.
34. (Lavoie et al., 2007)	8	TS-heterogeneous (18)	22	Adult	Groups of adult participants with TS and chronic tic disorder were tested on a neuropsychology battery comprising memory, executive function and motor dexterity measures. Their performance was compared with that of a control group.	Set shifting	Trail making test (TMT); Wisconsin Card Sorting Test (WCST)	Interference score: $d=.120$ , NS Categories completed: $d=.194$ , NS Perseverations: $d=.213$ , NS Errors: $d=.009$ , NS	No contrasts on either measure of set shifting (WCST or TMT) found significant differences between TS and control performance.
35. (Goudriaan et al., 2006)	8	TS-heterogeneous (46)	49	Adult	This study aimed to investigate neuropsychological abilities in a group of pathological gamblers, and included a TS group (as an impulse disorder control group) and a control group without such difficulties. Performance on a comprehensive neuropsychology battery was compared across the groups.	Set shifting	Wisconsin Card Sorting Task (WCST)	Perseverations: $d=0.276$ (S), NS No. of correct categories: $d=-0.328$ (S), NS	No significant differences were found between TS and control performance on the WCST.



Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
36. (Watkins et al., 2005)	8	TS-heterogeneous (20)	20	Adult	Executive functioning (assessed using tasks of planning, fluency, set shifting and inhibition) was compared across three adult participant groups: (1) TS (2) OCD and (3) controls.	Set shifting	Attentional set shifting task	$p < .05$ . Insufficient data to calculate effect size.	Compared to controls, adult TS patients were impaired in set shifting.
37. (Channon et al., 2004)	8	TS-uncomplicated (15)	23	Adult	A group of participants with uncomplicated TS were compared with matched controls on performance on tests of social and non-social (executive functioning) cognition.	Set shifting	Wisconsin Card Sorting Test (WCST)	No. of categories: $d = -0.366$ (S), NS Perseverative errors: $d = 0.430$ (S), NS	Adult participants with TS did not differ from controls on a measure of set shifting.
38. (Channon et al., 2003)	8	TS-uncomplicated (21)	21	Adult	Performance on tasks of social cognition and executive functioning was explored in adult participants with TS, and compared with matched controls.	Set shifting	Wisconsin Card Sorting Test (WCST)	No. of categories: $d = -0.112$ (~), NS Perseverative error: $d = 0.175$ (~), NS	The TS group did not differ from controls in the number of correct categories achieved or in the number of perseverative errors committed on the WCST.
39. (Eddy & Cavanna, 2017)	8	TS-uncomplicated (27)	25	Adult	Neuropsychological performance of adults with TS was compared with that of controls using a comprehensive battery.	Set shifting	Wisconsin Card Sorting Test (WCST); Trail Making Test (TMT)	TMT: $d = 0.614$ (M), $p = .05$ ; WCST categories: $d = 0.0824$ (~), NS; WCST error: $d = 0.799$ (L), $p = .006$ ; WCST time: $d = 0.64$ (M), $p = .014$ .	There was evidence of poorer set shifting abilities in the TS group relative to controls across both measures of set shifting.
40. (Ozonoff & Strayer, 2001)	8	TS-heterogeneous (15)	15	Child (8-19)	Working Memory performance was investigated in a group of children with ASD, and contrasted to matched control groups of children with TS and typically-developing children. The authors used three computerised WM tasks.	Working Memory	Running Memory Task; Spatial Memory Task; Box Search Task	Group contrasts on all three measures = NS. Insufficient data to calculate effect size.	No significant group differences were detected on any of the three WM measures, indicating intact WM in TS and ASD.
41. (Verté et al., 2005)	8	TS-heterogeneous (24)	47	Child (6-13)	Executive functioning across three groups of children (TS; ASD and controls) was compared using a comprehensive battery of tests.	Working Memory	Self-ordered pointing task (SOP)	$d = -0.317$ (S), NS	No significant differences between groups were observed on either the letter nor category fluency measures.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
42. (Crawford, Channon, & Robertson, 2005)	8	TS-uncomplicated (20)	20	Child/adolescents (11-18)	Adolescents with uncomplicated TS were assessed on behavioural inhibition, working memory and reward learning, and performance was compared with a group of matched controls.	Working Memory	N back	Accuracy: 0-back $d=-.204$ (S), NS 1-back: $d=0.259$ (S), NS 2-back: $d=0.349$ (S), NS  Latency: 0-back: $d=-0.210$ (S), NS 1-back: $d=-0.339$ (S), NS 2-back: $d=-0.406$ (S), NS	The TS group did not differ significantly from the control group on the working memory measures.
43. (Rasmussen et al., 2009)	8	TS-uncomplicated (21)	23	Child (7-13)	Children with uncomplicated TS completed tests from the CANTAB (comprising measures of memory, executive function and attention), and performance was compared with that of a matched control group.	Working Memory	CANTAB: Spatial Working Memory (SWM)	Errors: $p<.05$ Strategy: NS. Insufficient data to calculate effect sizes.	Children with TS produced significantly shorter spatial spans than controls, although there were no differences in strategy use on this task.
44. (Jeter et al., 2015)	8	TS-heterogeneous sample-low severity (20); TS-heterogeneous sample-moderate severity (19)	29	Child (10-16)	The performance of children with TS+low tic severity, TS+moderate severity and matched controls on a series of oculomotor tasks, including working memory, response generation, and response inhibition, was analysed.	Working Memory	N-back (1 - 0 back)	WM load (1-back - 0-back), $p<.001$  WM load (error rate), $p=0.25$ . Insufficient data to calculate effect sizes.	When the data from the TS participants with low and moderate tic severity were combined, this group showed a greater detrimental effect of increased working memory load than controls, both in terms of latency and accuracy.

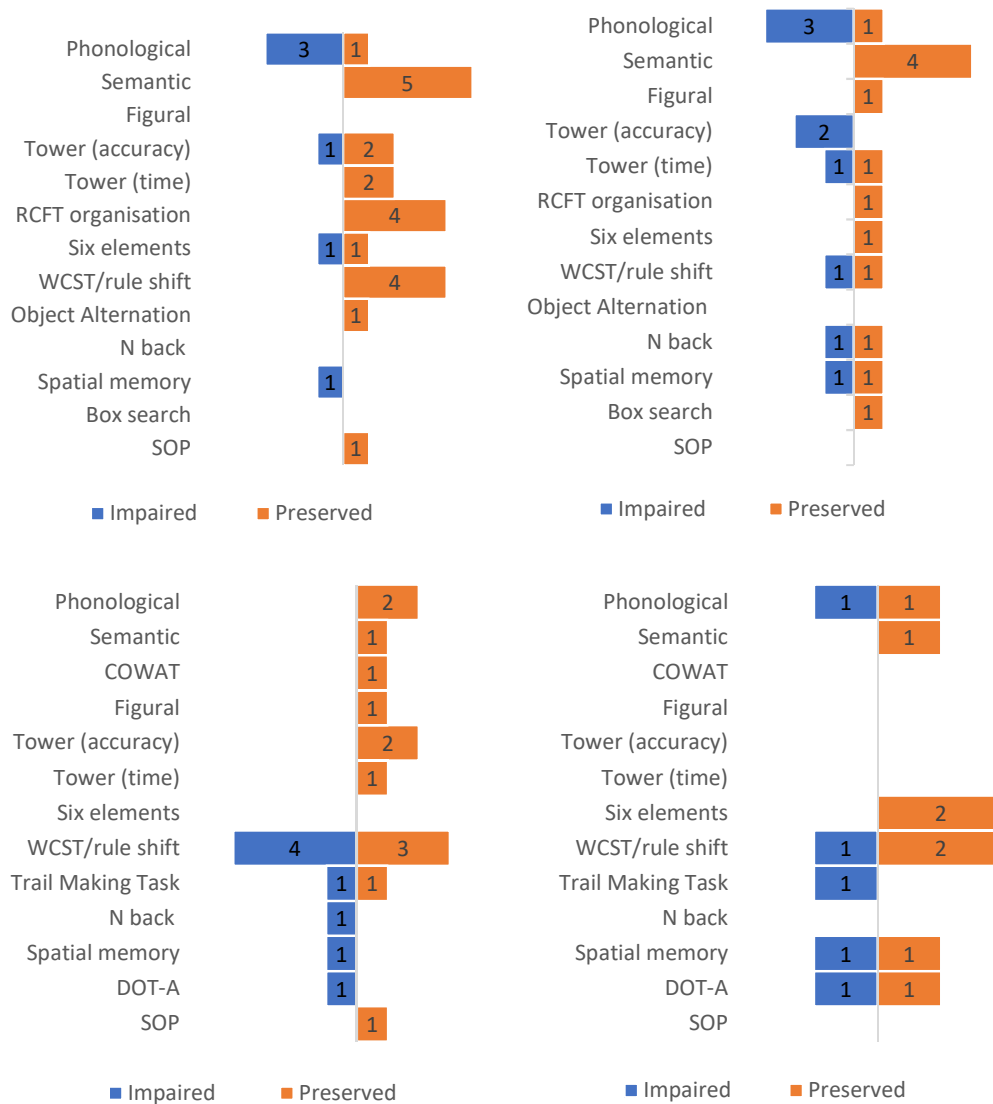
Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
45. (Müller et al., 2003)	7	TS+OCD (14)	14	Adult	A battery of neuropsychological tests of executive functioning, memory and attention to groups of adult participants with (1) TS+OCD and (2) OCD and (3) control participants. Results were compared across group and test conditions.	Working Memory	Computerised Battery for the Assessment of Attention deficits, CBAA (working memory subtest, a 2-back paradigm)	RT $d=0.408$ (S), $p=.28$ Errors $d=0.044$ (S), $p=.90$ Omissions $d=1.060$ (L), $p<.01$	Analysis of TS and control performance on the working memory test found no differences in RT or overall error rate, although the TS group did make significantly more omission errors than controls.
46. (Eddy & Cavanna, 2015)	9	TS - heterogeneous sample (20)	20	Adult	The study investigated spontaneous mentalising in TS, through an ambiguous animations task depicting social interactions between shapes. A battery measuring executive functioning, alexithymia and clinical symptoms were also administered to their samples of adults with TS and a comparison control group.	Working Memory	Digit ordering task (DOT-A)	$d=-0.578$ (M), $p=.038$	This heterogeneous TS group showed a significant impairment on the digit ordering task compared to control performance.
47. (Eddy et al., 2012)	9	TS-uncomplicated (29)	20	Adult	The study investigated executive functioning in a group of adults with uncomplicated TS, and compared performance to that of a matched control group.	Working Memory	Digit ordering task (DOT-A)	$d=0.539$ (M), $p=.043$	The TS group produced slightly shorter spans on the DOT-A task.
48. (Goudriaan et al., 2006)	8	TS-heterogeneous (46)	49	Adult	This study aimed to investigate neuropsychological abilities in a group of pathological gamblers, and included a TS group (as an impulse disorder control group) and a control group without such difficulties. Performance on a neuropsychological battery was compared across the groups.	Working Memory	Self-Ordered Pointing task (SOP)	Beta errors: $d=-0.21$ (S), NS Beta time: $d=-0.242$ (S), NS	There were no differences in performance on a self-ordered pointing task between adults with TS and controls.

Study	Quality rating	TS group (N)	Control (N)	Age Range	Study description	Executive function	Measures	Significance values (comparing TS and control group) and Cohen's <i>d</i> effect sizes.	Main findings
49. (Eddy & Cavanna, 2017)	8	TS-uncomplicated (27)	25	Adult	Neuropsychological performance of adults with TS was compared with that of controls using a comprehensive battery.	Working Memory	Digit-ordering task-adapted	$d=-0.121$ (S), NS	No significant differences between groups were observed on either the letter nor category fluency measures. <sup>1</sup>

<sup>1</sup> <sup>1</sup> *N.B. Indicators of strength of effect size given in parentheses (negligible (~), small (S); medium (M) and large (L)). All results refer to test group vs. control group contrasts, quality ratings (CASP), effect sizes and statistical differences reflect reduced TS performance, unless otherwise stated.*

The 25 studies included a total of 586 participants with TS, and 649 controls. These totals comprised 342 child participants: 133 children with uncomplicated TS, 59 with TS+ADHD, 6 with TS+OCD, 119 with heterogeneous presentations, and 380 child controls. Of the 244 adults with TS: 92 with uncomplicated TS, 14 with TS+OCD, and 138 with heterogeneous presentations, and 269 adult controls. The median sample size was 20 for adults with TS, 15 for children with TS and 20 for adult controls and 24 for child controls.

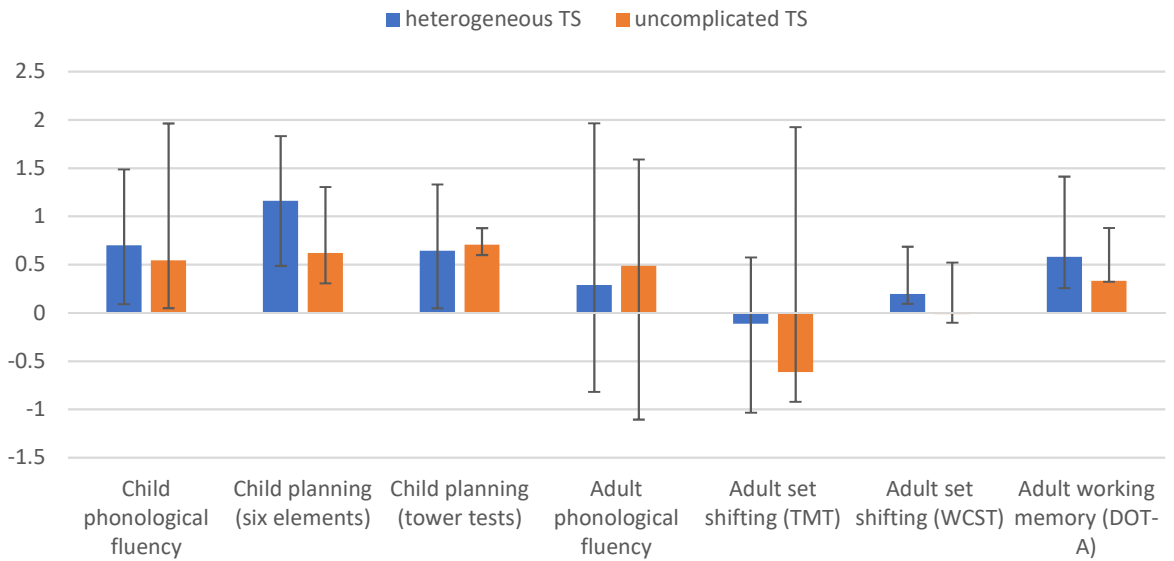
Figure 1.2 depicts the number of studies finding preserved and impaired abilities in the TS groups sampled, across child and adult, and heterogeneous and uncomplicated TS groups, where ‘preserved’ indicates no significant differences between the TS and control performance, or significantly elevated performance by the TS group, and ‘impaired’ reflects significantly poorer performance (lower accuracy rates or slower response latencies) in the TS group relative to controls.



*Figure 1.2. Number of studies showing preserved and impaired TS performance (compared to control performance) across TS group and age range. Top left panel: Child TS (heterogeneous); top right panel: Child TS (uncomplicated); bottom left panel: Adult TS (heterogeneous); bottom right panel (uncomplicated).*

Figure 1.3 represents the pooled effect sizes for each EF task type, based on available data, and stratified by age range and presence of heterogeneity.

Throughout the results section, individual findings are referred to using their study code (as provided in Table 1.2).



*Figure 1.3. Pooled effect sizes (contrasting TS with control performance) and 95% confidence intervals across heterogeneous and uncomplicated TS, and child (left panel) and adult (right panel) groups.*

<sup>2</sup>

### 1.4.3. Fluency

#### Child data

Figure 1.2 (upper panels) shows evidence of deficient phonological fluency in both groups with heterogeneous TS (in these cases, TS with confirmed and probable ADHD, 1, 2, 3, 5) as well as in participants with uncomplicated TS (1, 3, 4, 5). Strikingly, there was no evidence for impairments in semantic fluency across heterogeneous and uncomplicated TS groups, where all groups sampled showed that TS performance did not differ from control performance (3, 4, 5, 6). Similarly, there

<sup>2</sup> Number of groups on which these analyses were based were: Child phonological fluency, six elements and tower tasks: (heterogeneous N=3; 2; 3 and uncomplicated N=1, 1, 1, respectively). Adult phonological fluency, TMT, WCST and DOT-A: (heterogeneous N=1; 2; 3; 1 and uncomplicated N=2, 1, 2, 2 respectively). Negative TMT effect sizes reflect slower responding in TS

was no evidence for a figural fluency deficit in TS, though this result could have been affected by small sample size (only one study was sampled, 4).

Figure 1.3 (left panel) shows pooled effect sizes for measures with similar methodologies, where means and standard deviations were reported, across heterogeneous and uncomplicated TS groups. For the phonological fluency data, the pooled effect sizes were 0.70 for heterogeneous TS, and 0.54 for uncomplicated TS, indicating medium-large and medium effect sizes, respectively. No other fluency effect size contrasts were possible.

#### *Adult data*

There was some evidence of a phonological fluency deficit in the adult data, where one of the two studies sampled showed significantly poorer TS performance in the uncomplicated TS data (impairment was found in 8, but not 11), although no deficits were reported in the studies involving heterogeneous groups (both studies sampled (7,9) showed preserved performance, Figure 1.2 lower panels). As in the child data, no evidence of impairment was found on semantic (9, 11) or figural fluency (7). One study (10) indicated a deficit in a combined measure of phonological and semantic fluency, although this could be due to preserved semantic fluency effectively obscuring any problematic phonological fluency performance.

When phonological fluency effect sizes were pooled for the adult data, a small effect size was returned for the heterogeneous TS groups (.29) and a small-medium effect size for the uncomplicated TS groups (.49). No other effect size contrasts were possible.



### *Fluency summary*

In terms of the number of studies showing preserved and impaired fluency there was evidence of impaired phonological fluency across child and adult groups. This result was replicated in uncomplicated TS as well as heterogeneous TS child participants. This pattern was observed much more consistently in the child data, though there were few examples of fluency assessment in the adult studies sampled, which may influence this finding. For the effect size calculations, effects were of medium-large magnitudes in the child data, and small-medium sizes in the adult data. There was strong evidence to suggest that semantic fluency was preserved in TS, and this was the case unanimously across both child and adult studies. Similarly, no figural fluency deficits were indicated in the child or adult data, although this finding was based on few studies.

#### **1.4.4. Planning**

##### *Child data*

There was some evidence of deficient planning in the uncomplicated TS data on the Tower tasks, both in terms of accuracy (2/2 studies sampled, 12, 19) and time (12 studies sampled). Interestingly though, only one (12) study (of three) showed impaired performance in heterogeneous TS groups: there was some indication of deficient accuracy (1/3 studies sampled) but not time (0/1 studies sampled). These data were comprised of a TS+ADHD group (who showed impaired accuracy, 12) with no evidence of planning impairment in the more broadly heterogeneous TS groups (accuracy: 0/2 studies sampled, 14, 16). All TS groups achieved preserved scores on the RCFT (organisation score, all five groups sampled across three studies: 13, 17, 18).

In terms of the Six Parts test, only the TS+ADHD data showed problematic performance (1/1 of groups sampled, 15), with no evidence of a deficit on this measure in uncomplicated TS (0/1, 15) or TS+ADHD (0/1, 15).

When computing the pooled effect sizes for planning across two measures (six elements and tower tests), large and medium-large effect sizes were obtained for the heterogeneous groups (six elements: 1.16; tower tests: 0.64), reflecting a difference of over one standard deviation between heterogeneous TS and control performance on the six elements task. Medium-large effects on these measures were also found in uncomplicated TS groups (six elements: .62; tower tests: .71), though these effects were not statistically significant.

#### *Adult data*

Unfortunately, no adult studies looking at tower performance in uncomplicated TS, or TS plus specific comorbidities existed in our final sample. Of the three heterogeneous TS group studies included, none showed impairment on the tower measures on either accuracy (0/3, 20, 21, 22) or time (0/1, 20). No adult studies using the RCFT were included. The uncomplicated TS groups showed preserved performance on the six elements test (0/2, 23, 24), but this measure was not used in any other group in the selected papers. Effect size analysis for planning in the adult data was not possible due to insufficient studies and available data.

#### *Planning summary*

There was some suggestion of impaired planning in children with uncomplicated TS (evidenced on the tower tasks), and TS+ADHD on the tower and six elements measures. A large effect size was obtained in the heterogeneous data on the six

elements, which suggested that planning impairment was significantly moderated by comorbid ADHD on this task. No study reporting six elements performance in heterogeneous TS was reported in the adult data. Across the child studies, medium-large effect sizes, though not statistically significant, were obtained in heterogeneous TS tower performance, and on both planning tasks in the uncomplicated TS groups. There was no evidence for planning deficits in the adult data, but it should be noted that the groups and measures that produced planning deficits in the child data were not included as systematically in the selected adult studies.

#### ***1.4.5. Set shifting***

##### *Child data*

There was very little evidence of deficient set shifting in child TS: only one uncomplicated TS group (29) showed deficit on a rule shifting test (IED, where impairment was not found on a study using a simple version of the WCST: 27), and none of the eight studies reporting performance on other set shifting measures in other, heterogeneous TS groups indicated set shifting difficulty in child TS (25, 26, 27, 28). Of the rule shift tasks, only the IED task, (“CANTAB (Cognitive Assessment Software),” 2017) showed deficits in set shifting (29). No effect size computation was possible due to insufficient studies and available data.

##### *Adult data*

There was more evidence of set shifting problems in the adult population, though findings were mixed. In uncomplicated TS, one (39) of the three studies (37, 38) showed deficits on the WCST and another study using the TMT showed impaired

uncomplicated TS performance, relative to controls (39). Heterogeneous TS groups showed some deficits on rule shifting tasks (on 2 (33) of 5 groups sampled, impairment was not found in 34, 35, 36) and on TMT (1/2 studies sampled). One study (33) showed that set shifting problems (WCST) were attributable to comorbid OCS with TS (1/1). Another study (31) included in this analysis that used a TS+OCD group did not find a set shifting deficit, but participants were not grouped by OCS type as this was not a primary focus of the paper.

When effect sizes for the two set shifting task types (TMT and WCST-style tests) were pooled, only negligible effects were found in the heterogeneous TS data (TMT: -0.12; WCST: 0.19). An effect of medium-large magnitude was found in the uncomplicated TS TMT data (-0.61, indicating slower TMT performance), and no effect was obtained in WCST data from participants with uncomplicated TS (-0.01, Figure 1.3).

### *Set shifting summary*

Set shifting appeared unimpaired in child TS, although there were some signs of impairment in the adult studies reviewed. Some of the data suggested that some tests may be more sensitive to detecting set shifting deficits than others, with only the intra-extra dimensional (IED) and attentional set shifting tools producing deficits in the child and adult data, respectively. Impairment in TS populations may only become apparent under conditions of high task demands. One study showed that set shifting deficits were moderated by presence of Obsessive Compulsive Symptoms (aggression) rather than TS diagnosis, though this method was not adopted elsewhere in the selected studies. Effect sizes in the adult data were negligible in the heterogeneous TS groups

across both measures, and a medium-large effect on the TMT, but no effect on the WCST in the uncomplicated TS group data.

#### ***1.4.6. Working Memory***

##### *Child data*

There was little evidence of working memory difficulties in the child TS groups. Only two tasks showed significant under-performance compared with controls: Heterogeneous TS on N-back (1/2 studies sampled, in 44 but not 40) and uncomplicated TS on spatial span (1/2 studies sampled, in 43). None of the other studies, reporting a combination of working memory measures and TS groups, showed significant differences (40, 41, 42). No effect size analysis was possible due to insufficient studies and available data.

##### *Adult data*

There was proportionally more evidence of working memory deficits in the adult TS groups than observed in the child studies. In the adult research, the task used most frequently was the DOT-A, which showed some signs of impaired performance in the uncomplicated (1/2, in 47 but not 49) and heterogeneous (1/1, 46) TS groups. The heterogeneous TS group did not show a self-ordered pointing (SOP) deficit (0/1, 48), and mixed results were found in one study measuring N-back performance in TS+OCD (45), where participants were impaired in terms of omission errors, but not response latency or overall error.

In terms of the effect size analysis (Figure 1.3), there was some evidence of working memory impairment in the TS groups on the DOT-A task, where a medium-

large effect size was obtained in the heterogeneous TS data (.58), and a small-medium effect was found in uncomplicated TS (.33).

#### *Working Memory summary*

Across the studies sampled, adults with TS showed more signs of working memory impairment (where small-medium and medium-large effect sizes were obtained) than children with TS.

Only two tests elicited problematic performance in child TS (N-back and spatial span), and impairment was only seen in DOT A performance in the adult data.

#### ***1.4.7. Overall categorical analysis across heterogeneous and uncomplicated groups***

There was proportionally more impairment in the uncomplicated TS groups (9/22, 40%) than the heterogeneous TS groups (6/17, 22%) in the child data (Figure 1.2, upper panel), though this association was not significant when Chi Square tests were performed ( $X^2(1)=.128, p=.753$ ). For the adult studies, the proportion of outcomes indicating EF impairment in heterogeneous and uncomplicated TS groups was equivalent (8/21, 38% and 5/13, 38.4%, respectively, Figure 1.2, lower panel,  $X^2(1)=.000, p=1.00$ ).

### **1.5. Discussion**

The current paper involved a detailed systematic review (Table 1.2), from which a broad categorical analysis of four executive functions (fluency, planning, set shifting and working memory) in children and adults with heterogeneous and uncomplicated Tourette Syndrome (relative to control performance) was conducted (Figure 1.2).

While the focus of this review was on systematically reviewing the findings, techniques derived from meta-analysis were used where possible to provide pooled effect size data across tasks that employed similar methodologies and outcome data where possible, to increase sample sizes and maximise the utility of the review (Figure 1.3). The following four sections correspond to the aims stipulated in the introduction.

***1.5.1. Is there evidence of impairment in fluency, planning, set shifting or working memory in TS?***

Taken together, the results revealed several key findings: There was evidence for deficient phonological fluency in TS, and especially child TS, and this was in the context of unanimously preserved semantic and figural fluency. Strikingly, this profile applied across child and adult, and heterogeneous and uncomplicated TS populations. In planning, there was some evidence of impaired abilities in children with TS (i.e. in uncomplicated TS performance on the tower tests), and this was exacerbated by the presence of comorbid ADHD, suggesting a strong attentional component to planning performance in child TS. These results could be due to inconsistencies in methodologies in planning tasks applied in child and adult research: measures that produced planning deficits in the child data were not typically employed in the adult studies.

In set shifting, impairment was more consistently observed in the adult relative to the child data. Children with TS appeared unimpaired on all measures of set shifting compared to typically-developing controls. Similarly, adults with TS showed proportionally greater rates of impaired working memory performance than children, and this result could be due to developmental reasons or differences in the types of measures employed in child and adult research. Though STM is likely to be acquired

in infancy and early childhood (Dempster, 1981), working memory continues to develop throughout adolescence (Siegel, 1994). Working memory performance is therefore likely to be vulnerable to increases in task demands, and the tasks that showed TS deficits were complex in terms of load (N-back) and processing demands (spatial span and DOT-A).

Previous studies (Jackson, Parkinson, Jung, Ryan, Morgan, Hollis, & Jackson, 2011; Jackson, Parkinson, Manfredi, Millon, Hollis, & Jackson, 2013; Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006) have shown *strengths in* TS performance on executive functioning measures, a finding linked to the increased need to monitor and control behaviour in TS. Of the 49 sets of outcome data reviewed here, only one TS group (child, uncomplicated TS) on one measure (planning: Rey Copy Organisation score) showed significantly stronger performance in the TS group when contrasted with control performance (Schuerholz et al., 1996).

In terms of theoretical underpinning of the association between TS and executive functioning, most accounts converge on the idea that, in TS, there are disturbances in cortico-striatal-thalamic-cortical circuitry, that are responsible for connecting specific regions of the frontal cortex with subcortical structures (Leckman, Bloch, Smith, Larabi & Hampson, 2010; Singer & Harris, 2006). Frontal-striatal circuitry disruption can result in impaired executive functioning (e.g. and tasks involving planning, attention or decision making in particular: Tranel, Anderson & Benton, 1994; Robbins, 1996).

In summary, across the papers reviewed, there was evidence of impairment in phonological fluency, child planning, and adult set shifting (TMT performance) and working memory in TS. However, the findings were mixed, and several results indicated preserved executive functioning in TS (e.g. in semantic and figural fluency,



RCFT organisation, adult tower and six elements planning, and child set shifting and working memory).

***1.5.2. Are there different profiles of impairment across these EF components between children and adults?***

The only EF component that showed a similar profile across child and adult studies was fluency, where impairments in phonological, but not semantic or figural fluency were observed. Planning deficits were found in the child but not adult data, and set shifting and working memory deficits were found in the adult groups. This section will consider potential developmental explanations for these patterns of results. The possible contribution of inconsistencies in measure selection across child and adult studies is discussed in section 1.5.3.

All selected studies employed group methodologies, contrasting TS performance with that of age-matched controls. These approaches are designed to show whether children with TS show a developmental trajectory that is *atypical*, rather than the stage at which a given executive skill is acquired. Furthermore, the child TS studies pooled participants from wide age ranges together. These methodologies limit the extent to which a developmental approach could be adopted: Only broad interpretations about contrasts between child TS and control performance, and adult TS (where employed measures are similar) are possible, rather than a more precise indication of executive skill acquisition over development afforded by (e.g.) longitudinal methodologies.

Phonological fluency is understood to be acquired relatively late in development, with performance gains observed well into adolescence (Anderson et al., 2001). The finding that both child and adult TS groups showed impairment relative to

controls may suggest an atypical developmental trajectory where acquisition is slower in children, and this difference persists through adolescence. In adulthood, this could manifest in a more permanent impairment, as fluency development later though adulthood is thought to be limited.

Although all measures of executive function are likely to enlist additional cognitive and executive skills besides the skill they are designed to tap, tests of planning are perhaps among the most inclusive. Developmentally, simple planning is possible in children aged around four years, but the most significant gains in planning ability are seen between seven and nine years, with more limited progress towards adolescence (Welsh et al., 1991). Planning deficits were observed only in the child studies, which could indicate slower planning acquisition through childhood that resolves by adulthood. In adulthood it may also be that individuals are able to make use of cognitive strategies; whereby other well-developed cognitive and executive abilities may compensate for any specific executive impairments.

A similar pattern was observed across the set shifting and working memory studies, where proportionally more impairment was detected in adults than children. For instance, in terms of set shifting (in terms of WCST-style task performance), 1/6 studies showed impairment in the child TS data compared to 5/10 adult TS studies; and in working memory, 3/7 studies reported child TS impairment, compared to 5/8 adult TS groups. Developmentally, both abilities show similar trajectories: Simple set shifting is possible between ages three and four, and increasingly complex set shifting between ages seven and nine, and into adolescence (Anderson, 2001); STM develops in early childhood, and working memory abilities undergo rapid development between the ages 7-14, with some further improvement continuing up until 18 years of age (Siegel, 1994). Experimental tasks targeting both functions are often complex, with

difficulty being manipulated through task demands and memory load. One interpretation of the pattern of impaired adult but not child TS performance observed on these dimensions is that these complex skills are not yet fully acquired in the child TS and control groups, with difficulties only becoming apparent when these skills are fully acquired in adult (control) groups. It is also possible that tasks designed for adults afford greater opportunity to manipulate task difficulty, and many of the tasks where impairment was shown in adult groups were complex.

It is interesting to consider these child and adult contrasts in regard to the typical clinical course of TS, whereby symptoms are likely to diminish in adulthood. For instance, potential differences in tic severity in child and adult TS populations may be influencing these contrasts. Tic severity may on the one hand be greater in child participants than in adults, given the typical pattern, or alternatively, one might argue that those adults for whom symptoms still persist may be on the more severe end of the spectrum. In terms of causality, it may be that tics themselves interfere with neuropsychological performance, or that severity of tics may indicate an underlying neuropsychological vulnerability. Unfortunately, more detailed exploration of these ideas was not possible using the available data.

### ***1.5.3. Can divergent findings within EF component be explained by the type of measure used?***

The four executive functions considered in this review share broad developmental patterns where simple executive abilities are acquired relatively early, but more complex abilities continue to develop up until, and through adolescence. Given this, executive tasks with greater demands are likely to be more sensitive in detecting

impairments. As with most areas of neuropsychological research, various measures were employed across the selected studies, making comparisons and generalisation of findings difficult. Given the limited number of studies available, an inclusive approach was adopted, both for study inclusion and effect size analysis, where data from different tasks were combined provided they shared common methodologies (Table 1.1, final column, Figure 1.3).

The most consistent results were observed in fluency, where task methodologies were the most homogeneous of the EF dimensions investigated (Table 1.1). All 11 phonological fluency tasks followed the same instructions (name as many words beginning with a given letter in one minute), just as all seven semantic fluency tasks required naming of words belonging to a given category in one minute and the two figural fluency measures were the same tests (Ruff et al., 1987).

There was wide variation in task methodology across the remaining components. For planning, tasks could be broadly categorised into tower tasks (Towers of London / Hanoi, and Stockings of Cambridge), requiring ring-stacking while adhering to rules, the RCFT organisation copy score, which indicates how systematically a participant approaches the copy, and the six elements necessitating the completion of several tasks within a time limit, while adhering to a rule. These tasks are likely to recruit a range of functions, and each of the three sets of measures have different task demands. Crucially, the planning measures that produced deficits in the child data were not employed as often in the adult studies (only three adult studies used tower tasks, and only in heterogeneous TS populations).

In set shifting, the most frequently used task was the WCST (used in nine studies), and a further three tasks that followed a similar methodology (Task switch), a simpler version of the WCST (Rule switch task) and two more complex tasks,

involving both intra and extra-dimensional shifts (attentional set shifting and IED). Strikingly, these two latter tasks were the only rule-shifting tasks that revealed impairment in the child and adult TS data. This finding supports the idea that executive deficits in TS may only become apparent in conditions of high task demand. In contrast to the more complex rule shifting tasks, the TMT (part B) involves making the same shift repeatedly (alternating ascending letters and numbers). The TMT was employed exclusively in adult studies, and showed some statistically significant impairment. The primary outcome measure on this task is response latency, and latency data are likely to be more sensitive to variations in performance than accuracy rates.

There was a range of working memory measures reported in the reviewed studies, using N-back (N-back and running memory tasks), digit ordering (DOT-A), spatial tasks, box search and self-ordered pointing (SOP) methodologies (see Table 1.1 for task descriptions). Results were mixed across N-back, spatial, and SOP tasks in both child and adult data sets, though there was proportionately more impairment in the adult data. Evidence of impairment was observed across heterogeneous and uncomplicated TS adult groups on the DOT-A task, which at its greatest level of difficulty requires memorising eight-digit span lists and recalling them in ascending numerical order.

Across the three EF components where study measures were less consistent (planning, set shifting and working memory), some measures appeared more sensitive in detecting TS impairments than others. Equally, impairment was detected on one adult planning measure using latency outcome data, where planning tasks using accuracy scores did not show signs of deficit. Different planning tests were applied across child and adult studies; tower tests were effective in detecting impairment in children, but were applied less often in adult research. Although most

neuropsychological tests are limited to either child or adult application due to task design and available normative data, there is clear value in adapting or using child versions of tests that are frequently used in adult populations. Components of executive functioning are highly inter-related, and maturation of EF occurs relatively late over the developmental trajectory. Improved standardisation in use of measures in this area would enable clearer comparisons of EF abilities across child and adult groups, independent from effects resulting from the use of different measures (that may tap slightly different EF skills), offering greater insight into the impact of developmental changes in EF functioning in TS, in turn.

There was evidence across the set shifting studies that the more complex tasks (i.e. those involving intra and extra-dimensional shifts) detected impairments in individuals with TS relative to control performance where tasks requiring more straight-forward or repeated shifts did not. Similarly, the DOT-A task, which uses a hierarchy of increasing difficulty, showed impairment across heterogeneous and uncomplicated TS populations, and small-medium – medium effect sizes.

#### ***1.5.4. To what extent can any EF deficit identified be attributed to TS, rather than comorbidity?***

TS is a highly heterogeneous condition with several common comorbidities, the most prevalent being ADHD. Attention difficulties have well established implications for executive functioning, and so it was important to distinguish uncomplicated TS from TS with heterogeneity in the current review.

In terms of categorical analysis of outcomes showing impairment, there was proportionally more impairment in the uncomplicated TS groups than the

heterogeneous TS groups the child data, though this association was not significant (Figure 1.2, upper panel). However, heterogeneous child TS groups showed differences of greater magnitudes than uncomplicated TS groups, in pooled effect sizes contrasting TS and control performance: Child heterogeneous TS groups produced large (.7) and extremely large (1.15) effect sizes in phonological fluency and six elements performance, compared with medium (.54) and medium-large (.62) effect sizes in the uncomplicated TS data. These results might suggest that comorbidity, and heterogeneity with ADHD in particular, may exacerbate problematic fluency and planning performance in child TS. However, effect sizes were larger in the uncomplicated than heterogeneous TS groups for tower performance (.7 vs. .64).

For the adult studies, the proportion of outcomes indicating EF impairment in heterogeneous and uncomplicated TS groups was equivalent (Figure 1.2, lower panel), but again effect sizes were of a greater magnitude than in uncomplicated TS in working memory performance (DOT-A: .58 vs. .33) and set shifting (though effect sizes were negligible in both groups, WCST: .19 vs -0.01), suggesting a potential exacerbation of TS impairment when comorbidity is present. Interestingly, greater effect sizes were observed in the uncomplicated TS groups on phonological fluency (.59 vs. .29) and set shifting (TMT: .61 vs .12).

The reviewed findings show some signs of impaired EF performance in TS, even in the absence of comorbidity. Taken together, these data suggest that there may be executive functioning impairments intrinsic to TS, but that these deficits may be exaggerated by comorbid presentations such as ADHD in some areas of executive functioning (e.g. child six elements planning and adult phonological fluency and WCST performance).

### ***1.5.5. Limitations and future research***

The review was not without its limitations. Firstly, individual data were not available, and so it was impossible to investigate EF performance as a function of tic severity, exact age or use of medication. Also, computation of effect sizes was not always possible, meaning that the data presented are based on relatively small numbers of TS groups. There were inconsistencies in the measures used and outcome data reported, which hindered the extent to which firm conclusions could be made. Instead, this review represented an effort to present the study methods and findings in relatively full detail (Table 1.2), and presenting categorical (Figure 1.2) and effect size (Figure 1.3) data to provide a quantitative impression of the main findings, where the data in the selected studies allowed.

In terms of future research, the area would benefit substantially from improved consistency and standardisation of measure selection (i.e. adopting the same tasks, or at least adapted tasks following similar methodologies), which would enable stronger conclusions about group comparisons and improve generalisability of findings. The results emphasised the role of tool sensitivity, and suggested that tasks tapping more complex levels of each EF ability, and those employing analysis of response latencies were more likely to detect deficient performance. There is obvious value in adopting longitudinal methodologies in neuropsychological research into neurodevelopmental conditions, such as executive functioning in TS, though these studies are notoriously difficult and expensive to run.



### ***1.5.6. Summary and conclusions***

The current review found that impairments in executive functioning are not limited to inhibition in TS. On investigating the available studies of child and adult performance across four separate domains of executive functioning (fluency, planning, set shifting and working memory), deficits were found in phonological fluency, child planning, and adult set shifting (TMT performance) and working memory in TS. These findings were in the context of largely preserved semantic and figural fluency, RCFT organisation, adult tower and six elements planning, and child set shifting and working memory, pointing to discrete, component-specific EF deficits over general executive functioning impairment in TS. Executive functioning impairment was indicated in uncomplicated as well as heterogeneous TS groups, suggesting that there may be EF difficulties that are fundamental to TS. Unsurprisingly given the prevalence of comorbidity of TS with ADHD, there were instances where comorbidity further exacerbated EF difficulty. The results have implications for current understanding of neuropsychological performance in TS, and are informative from a neuropsychological rehabilitation perspective to target the most challenged aspects of function in children and adults.

### **1.6. References**

- Alloway, T. P., & Alloway, R. G. (2013). Working memory across the lifespan: A cross-sectional approach. *Journal of Cognitive Psychology, 25*(1), 84–93.  
<https://doi.org/10.1080/20445911.2012.748027>
- American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). *Diagnostic and Statistical Manual of*

*Mental Disorders 4th Edition TR.*, 280.

<https://doi.org/10.1176/appi.books.9780890425596.744053>

Anderson, V. (2001). *Developmental neuropsychology : a clinical approach. Brain damage, behaviour, and cognition.*

Anderson, V. a, Anderson, P., Northam, E., Jacobs, R., & Catroppa, C. (2001).

Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology*, 20(1), 385–406.

[https://doi.org/10.1207/S15326942DN2001\\_5](https://doi.org/10.1207/S15326942DN2001_5)

Ballhausen, N., Mahy, C. E. V., Hering, A., Voigt, B., Schnitzspahn, K. M., Lagner, P., ... Kliegel, M. (2017). Children's planning performance in the Zoo Map task (BADs-C): Is it driven by general cognitive ability, executive functioning, or prospection? *Applied Neuropsychology: Child*, 6(2), 138–144.

<https://doi.org/10.1080/21622965.2015.1124276>

Berg, W. K., & Byrd, D. L. (2002). The Tower of London Spatial Problem-Solving Task: Enhancing Clinical and Research Implementation. *Journal of Clinical and Experimental Neuropsychology (Neuropsychology, Development and Cognition: Section A)*, 24(5), 586–604.

<https://doi.org/10.1076/jcen.24.5.586.1006>

Bertens, D., Frankenmolen, N., Boelen, D. H. E., Kessels, R. P. C., & Fasotti, L.

(2015). Validity of an adapted scoring method for a Modified Six Elements Test in individuals with brain injury. *Archives of Clinical Neuropsychology*, 30(2),

122–129. <https://doi.org/10.1093/arclin/acu093>

Bloch, M. H., Sukhodolsky, D. G., Leckman, J. F., & Schultz, R. T. (2006). Fine-

motor skill deficits in childhood predict adulthood tic severity and global

psychosocial functioning in Tourette's syndrome. *Journal of Child Psychology*

*and Psychiatry and Allied Disciplines*, 47(6), 551–559.

<https://doi.org/10.1111/j.1469-7610.2005.01561.x>

Bornstein, R. A. (1990). Neuropsychological performance in children with Tourette's syndrome. *Psychiatry Res.*, 33(0165–1781 (Print)), 73–81.

Braun, A. R., Stoetter, B., Randolph, C., Hsiao, J. K., Vladar, K., Gernert, J., ...

Chase, T. N. (1993). The functional neuroanatomy of Tourette's syndrome: an FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. *Neuropsychopharmacology*, 9(4), 277–291.

<https://doi.org/10.1038/npp.1993.64>

Burd, L., Kerbeshian, J., Wikenheiser, M., & Fisher, W. (1986). Prevalence of Gilles de la Tourette's syndrome in North Dakota adults. *American Journal of Psychiatry*, 143(6), 787–788.

Burgess, P. & Shallice, T. (1997). *The Hayling and Brixton Tests. Test manual*. Bury St Edmunds, UK: Thames Valley Test Company.

Butler, R. W., Copeland, D. R., Fairclough, D. L., Mulhern, R. K., Katz, E. R.,

Kazak, A. E., ... Sahler, O. J. Z. (2008). A Multicenter, Randomized Clinical Trial of a Cognitive Remediation Program for Childhood Survivors of a Pediatric Malignancy. *Journal of Consulting and Clinical Psychology*, 76(3),

367–378. <https://doi.org/10.1037/0022-006X.76.3.367>

CANTAB (Cognitive Assessment Software). (2017), *Cambridge*.

Carter, A. S., O'Donnell, D. a., Schultz, R. T., Scahill, L., Leckman, J. F., & Pauls,

D. L. (2000). Social and Emotional Adjustment in Children Affected with Gilles de la Tourette's Syndrome: Associations with ADHD and Family Functioning.

*Journal of Child Psychology and Psychiatry*, 41(2), 215–223.

<https://doi.org/10.1111/1469-7610.00602>

- Case, R. (1992). The role of the frontal lobes in the regulation of cognitive development. *Brain and Cognition*, 20(1), 51–73. [https://doi.org/10.1016/0278-2626\(92\)90061-P](https://doi.org/10.1016/0278-2626(92)90061-P)
- CASP. (2014). , (2015). Critical Appraisal Skills Programme (CASP). [online].
- Chang, S. W., McCracken, J. T., & Piacentini, J. C. (2007). Neurocognitive correlates of child obsessive compulsive disorder and Tourette syndrome. *Journal of Clinical and Experimental Neuropsychology*, 29(7), 724–733. <https://doi.org/10.1080/13825580600966383>
- Channon, S., Crawford, S., Vakili, K., & Robertson, M. M. (2003). Real-life-type problem solving in Tourette syndrome. *Cognitive and Behavioral Neurology*, 16(1), 3–15. <https://doi.org/10.1097/00146965-200303000-00002>
- Channon, S., Pratt, P., & Robertson, M. M. (2003). Executive function, memory, and learning in Tourette's syndrome. *Neuropsychology*, 17(2), 247–254. <https://doi.org/10.1037/0894-4105.17.2.247>
- Channon, S., Sinclair, E., Waller, D., Healey, L., & Robertson, M. M. (2004). Social cognition in Tourette's syndrome: Intact theory of mind and impaired inhibitory functioning. *Journal of Autism and Developmental Disorders*, 34(6), 669–677. <https://doi.org/10.1007/s10803-004-5287-x>
- Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, 114 ( Pt 5, 2095–2122. <https://doi.org/10.1093/brain/114.5.2095>
- Crawford, S., Channon, S., & Robertson, M. M. (2005). Tourette's syndrome: performance on tests of behavioural inhibition, working memory and gambling. *Journal of Child Psychology and Psychiatry*, 46(12), 1327–1336.

<https://doi.org/10.1111/j.1469-7610.2005.01419.x>

Debes, N. M. M. M., Lange, T., Jessen, T. L., Hjalgrim, H., & Skov, L. (2011).

Performance on Wechsler intelligence scales in children with Tourette syndrome. *European Journal of Paediatric Neurology*, *15*(2), 146–154.

<https://doi.org/10.1016/j.ejpn.2010.07.007>

Delis, DC., Kaplan, E., Kramer, J. (2001). *Examiner's Manual for the Delis-Kaplan*

*Executive Function System. Child Neuropsychology* (Vol. 10).

<https://doi.org/10.1080/09297040490911140>

Delis, D., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan executive function system

(D-KEFS). *Canadian Journal of School Psychology*, *20*(1–2), 117–128.

<https://doi.org/10.1177/0829573506295469>

Dempster, F. N. (1981). Memory span: Sources of individual and developmental

differences. *Psychological Bulletin*, *89*(1), 63–100.

<https://doi.org/10.1037/0033-2909.89.1.63>

Denckla, M. B. (2006). Attention deficit hyperactivity disorder: the childhood co-

morbidity that most influences the disability burden in Tourette syndrome.

*Advances in Neurology*, *99*, 17–21. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/16536349>

Diamond, A. (2014). Executive Functions. *Annual Review of Clinical*

*Psychology*, *64*, 135–168. [https://doi.org/10.1146/annurev-psych-](https://doi.org/10.1146/annurev-psych-113011-143750)

113011-143750.Executive

Diamond, A., & Goldman-Rakic, P. S. (1989). Comparison of human infants and

rhesus monkeys on Piaget's AB task: evidence for dependence on dorsolateral prefrontal cortex. *Experimental Brain Research*, *74*(1), 24–40.

<https://doi.org/10.1007/BF00248277>

- Downes, JJ; Roberts, AC; Sahakian, BJ; Evenden, JL; Morris, RG & Robbins, T. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease. *Neuropsychologia*, 27, 1329–1343.
- Drury, H., Shah, S., Stern, J. S., Crawford, S., & Channon, S. (2017). Comprehension of direct and indirect sarcastic remarks in children and adolescents with Tourette syndrome. *Child Neuropsychology*, pp. 1–20.  
<https://doi.org/10.1080/09297049.2017.1284777>
- Dykens, E., Leckman, J., Riddle, M., Hardin, M., Schwartz, S., & Cohen, D. (1990). Intellectual, academic, and adaptive functioning of Tourette syndrome children with and without attention deficit disorder. *Journal of Abnormal Child Psychology*, 18(6), 607–615. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/2074343>
- Eddy, C. M., & Cavanna, A. E. (2015). Triangles, tricks and tics: Hyper-mentalizing in response to animated shapes in Tourette syndrome. *Cortex*, 71, 68–75.  
<https://doi.org/10.1016/j.cortex.2015.06.003>
- Eddy, C. M., & Cavanna, A. E. (2017). Set-Shifting Deficits: A Possible Neurocognitive Endophenotype for Tourette Syndrome Without ADHD. *Journal of Attention Disorders*, 21(10), 824–834.  
<https://doi.org/10.1177/1087054714545536>
- Eddy, C. M., Rickards, H. E., & Cavanna, A. E. (2012). Executive functions in uncomplicated Tourette syndrome. *Psychiatry Research*, 200(1), 46–48.  
<https://doi.org/10.1016/j.psychres.2012.05.023>
- Eddy, C. M., Rizzo, R., & Cavanna, A. E. (2009). Neuropsychological aspects of Tourette syndrome: A review. *Journal of Psychosomatic Research*.  
<https://doi.org/10.1016/j.jpsychores.2009.08.001>

- Emslie, H., Wilson, F. C., Burden, V., Nimmo-Smith, I., & Wilson, B. A. (2003). Behavioural Assessment of the Dysexecutive Syndrome (BADS). *Journal of Occupational Psychology, Employment and Disability*.  
<https://doi.org/10.1080/09602010802622730>
- Erenberg, G. (2005). The Relationship Between Tourette Syndrome, Attention Deficit Hyperactivity Disorder, and Stimulant Medication: A Critical Review. *Seminars in Pediatric Neurology*, 12(4), 217–221.  
<https://doi.org/10.1016/j.spen.2005.12.003>
- Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, 16(1), 143–149. <https://doi.org/10.3758/BF03203267>
- Espy, K. A. (1997). The Shape School: Assessing Executive Function in Preschool Children. *Developmental Neuropsychology*, 13(4), 495–499.  
<https://doi.org/10.1080/87565649709540690>
- Freedman, M. (1990). Object alternation and orbitofrontal system dysfunction in Alzheimer's and Parkinson's disease. *Brain and Cognition*, 14(2), 134–143.  
[https://doi.org/10.1016/0278-2626\(90\)90025-J](https://doi.org/10.1016/0278-2626(90)90025-J)
- Gilotty, L., Kenworthy, L., Wagner, A. E., Sirian, L., & Black, D. O. (2002). Adaptive Skills and Executive Function in Autism Spectrum Disorders. *Child Neuropsychology (Neuropsychology, Development and Cognition: Section C)*, 8(4), 241–248. <https://doi.org/10.1076/chin.8.4.241.13504>
- Gioia, G. a, Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Test Review: Behavior rating inventory of executive function. *Child Neuropsychology*, 6(3), 235–238. <https://doi.org/10.1076/chin.6.3.235.3152>
- Godefroy, O., Cabaret, M., Petit-Chenal, V., Pruvo, J. P., & Rousseaux, M. (1999).

- Control functions of the frontal lobes. Modularity of the central-supervisory system? *Cortex*, 35(1), 1–20. [https://doi.org/10.1016/S0010-9452\(08\)70782-2](https://doi.org/10.1016/S0010-9452(08)70782-2)
- Gorman, D. a, Thompson, N., Plessen, K. J., Robertson, M. M., Leckman, J. F., & Peterson, B. S. (2010). Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: controlled study. *The British Journal of Psychiatry : The Journal of Mental Science*, 197(1), 36–44. <https://doi.org/10.1192/bjp.bp.109.071050>
- Goudriaan, A. E., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2006). Neurocognitive functions in pathological gambling: A comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction*, 101(4), 534–547. <https://doi.org/10.1111/j.1360-0443.2006.01380.x>
- Grant, D. A., & Berg, E. (1948). A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. *Journal of Experimental Psychology*, 38(4), 404–411. <https://doi.org/10.1037/h0059831>
- Greenberg, L. M. (2007). The Test of Variables of Attention (Version 7.3) [Computer software]. Los Alamitos: The TOVA Company. (n.d.).
- Groth, C., Mol Debes, N., Rask, C. U., Lange, T., & Skov, L. (2017). Course of Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 56(4), 304–312. <https://doi.org/10.1016/j.jaac.2017.01.010>
- Happé, F., Booth, R., Charlton, R., & Hughes, C. (2006). Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: Examining profiles across domains and ages. *Brain and Cognition*, 61(1), 25–39. <https://doi.org/10.1016/j.bandc.2006.03.004>



- Harris, E.L., Schuerholz, L.J., Singer, H.S., Reader, M.J., Brown, J.E., Cox, C., et al. (n.d.). Executive function in children with Tourette syndrome and/or attention deficit hyperactivity disorder. *Journal of the International Neuropsychological Society*, 1(6), 511–.
- Huckeba, W., Chapieski, L., Hiscock, M., & Glaze, D. (2008). Arithmetic performance in children with Tourette syndrome: Relative contribution of cognitive and attentional factors. *Journal of Clinical and Experimental Neuropsychology*, 30(4), 410–420. <https://doi.org/10.1080/13803390701494970>
- Isquith, P. K., Crawford, J. S., Espy, K. A., & Gioia, G. A. (2005). Assessment of executive function in preschool-aged children. *Mental Retardation and Developmental Disabilities Research Reviews*.  
<https://doi.org/10.1002/mrdd.20075>
- Jackson, S. R., Parkinson, A., Jung, J., Ryan, S. E., Morgan, P. S., Hollis, C., & Jackson, G. M. (2011). Compensatory neural reorganization in Tourette syndrome. *Current Biology*, 21(7), 580–585.  
<https://doi.org/10.1016/j.cub.2011.02.047>
- Jackson, S. R., Parkinson, A., Manfredi, V., Millon, G., Hollis, C., & Jackson, G. M. (2013). Motor excitability is reduced prior to voluntary movements in children and adolescents with Tourette syndrome. *Journal of Neuropsychology*, 7(1), 29–44. <https://doi.org/10.1111/j.1748-6653.2012.02033.x>
- Jasmin, E., Couture, M., McKinley, P., Reid, G., Fombonne, E., & Gisel, E. (2009). Sensori-motor and daily living skills of preschool children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39(2), 231–241.  
<https://doi.org/10.1007/s10803-008-0617-z>
- Jeter, C. B., Patel, S. S., Morris, J. S., Chuang, A. Z., Butler, I. J., & Sereno, A. B.

- (2015). Oculomotor executive function abnormalities with increased tic severity in Tourette syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 56(2), 193–202. <https://doi.org/10.1111/jcpp.12298>
- Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology Review*.  
<https://doi.org/10.1007/s11065-007-9040-z>
- Kesler, S. R., Lacayo, N. J., & Jo, B. (2011). A pilot study of an online cognitive rehabilitation program for executive function skills in children with cancer-related brain injury. *Brain Injury*, 25(1), 101–112.  
<https://doi.org/10.3109/02699052.2010.536194>
- Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, 55(4), 352–358.  
<https://doi.org/10.1037/h0043688>
- Klingberg, T., Vaidya, C. J., Gabrieli, J. D. E., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. *NeuroReport*, 10(13), 2817–2821.  
<https://doi.org/10.1097/00001756-199909090-00022>
- Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders*.  
<https://doi.org/10.1002/mds.23868>
- Lambek, R., Tannock, R., Dalsgaard, S., Trillingsgaard, A., Damm, D., & Thomsen, P. H. (2010). Validating neuropsychological subtypes of ADHD: How do children with and without an executive function deficit differ? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 51(8), 895–904.  
<https://doi.org/10.1111/j.1469-7610.2010.02248.x>

- Langleben, D. D., Monterosso, J., Elman, I., Ash, B., Krikorian, G., & Austin, G. (2006). Effect of methylphenidate on Stroop Color-Word task performance in children with attention deficit hyperactivity disorder. *Psychiatry Research, 141*(3), 315–320. <https://doi.org/10.1016/j.psychres.2005.09.007>
- Larry, B., Jacob, K., Mark, W., & Wayne, F. (1986). A prevalence study of Gilles de la Tourette syndrome in North Dakota school-age children. *Journal of the American Academy of Child Psychiatry, 25*(4), 552–553. Retrieved from <http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=1987-28535-001&site=ehost-live&scope=site>
- Lavoie, M. E., Thibault, G., Stip, E., & O'Connor, K. P. (2007). Memory and executive functions in adults with Gilles de la Tourette syndrome and chronic tic disorder. *Cognitive Neuropsychiatry, 12*(2), 165–181. <https://doi.org/10.1080/13546800600826371>
- Leckman, J.F., Bloch, M.H., Smith, M.E., Larabi, D. & Hampson, M. (2010). Neurobiological substrates of Tourette's disorder. *J Child Adolesc Psychopharmacol* **20**:237–247.
- Leckman, J. F., Riddle, M. A., Hardin, M. T., Ort, S. I., Swarts, K. L., Stevenson, J., & Cohen, D. J. (1989). The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. *Journal of the American Academy of Child and Adolescent Psychiatry, 28*(4), 566–573. <https://doi.org/10.1097/00004583-198907000-00015>
- Leckman, J. F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., ... Peterson, B. S. (1998). Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics, 102*(1 Pt 1), 14–19. <https://doi.org/10.1542/peds.102.1.14>

- Lehto, J. (1996). Are Executive Function Tests Dependent on Working Memory Capacity? *The Quarterly Journal of Experimental Psychology*, *49A*(1), 29–50.  
<https://doi.org/10.1080/713755616>
- Lichter, D. G., & Finnegan, S. G. (2015). Influence of gender on Tourette syndrome beyond adolescence. *European Psychiatry*, *30*(2), 334–340.  
<https://doi.org/10.1016/j.eurpsy.2014.07.003>
- Lombroso, P. J., & Scahill, L. (2008). Tourette syndrome and obsessive-compulsive disorder. *Brain & Development*, *30*(4), 231–237.  
<https://doi.org/10.1016/j.braindev.2007.09.001>
- Luciana, M., & Nelson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia*, *36*(3), 273–293. [https://doi.org/10.1016/S0028-3932\(97\)00109-7](https://doi.org/10.1016/S0028-3932(97)00109-7)
- Macdonald, M., Lord, C., & Ulrich, D. (2013). The relationship of motor skills and adaptive behavior skills in young children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, *7*(11), 1383–1390.  
<https://doi.org/10.1016/j.rasd.2013.07.020>
- Mahone, E., Cirino, P., Cutting, L., Cerrone, P., Hagelthom, K., Hiemenz, J., et al. (2002). Validity of the Behavior Rating Inventory of Executive Function in children with ADHD and/or Tourette Syndrome. *Archives of Clinical Neuropsychology*, *17*, 643–66.
- Manly, T., Anderson, V., Crawford, J., George, M., Underbjerg, M. & Robertson, I. (2016). *The Test of Everyday Attention for Children-II (TEA-Ch-2)*. Bury St Edmunds, UK: Thames Valley Test Company.
- Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., & Robertson, I.

- H. (2001). The Differential Assessment of Children's Attention: The Test of Everyday Attention for Children (TEA-Ch), Normative Sample and ADHD Performance. *Journal of Child Psychology and Psychiatry*, 42(8), 1065–1081. <https://doi.org/10.1111/1469-7610.00806>
- Mahone, E., Koth, C. W., Cutting, L., Singer, H. S., & Denckla, M. B. (2001). Executive function in fluency and recall measures among children with Tourette syndrome or ADHD. *Journal of the International Neuropsychological Society*, 7(1), 102–111. <https://doi.org/10.1017/S1355617701711101>
- Matsuda, N., Kono, T., Nonaka, M., Shishikura, K., Konno, C., Kuwabara, H., ... Kano, Y. (2012). Impact of obsessive-compulsive symptoms in Tourette's syndrome on neuropsychological performance. *Psychiatry and Clinical Neurosciences*, 66(3), 195–202. <https://doi.org/10.1111/j.1440-1819.2012.02319.x>
- McKown, C., Allen, A., Russo-Ponsaran, N., & Johnson, J. (2013). Direct assessment of children's social-emotional comprehension. *Psychological Assessment*, 25, 1154–1166.
- McKown, C., Gumbiner, L. M., Russo, N. M., & Lipton, M. (2009). Social-emotional learning skill, self-regulation, and social competence in typically developing and clinic-referred children. *Journal of Clinical Child and Adolescent Psychology*, 38(6), 858–871. <https://doi.org/10.1080/15374410903258934>
- Mitchell, M., & Miller, L. S. (2008). Prediction of functional status in older adults: The ecological validity of four Delis-Kaplan Executive Function System tests. *Journal of Clinical and Experimental Neuropsychology*, 30(6), 683–690. <https://doi.org/10.1080/13803390701679893>

- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. <https://doi.org/10.1006/cogp.1999.0734>
- Moore, T. F., & Hollett, J. (2003). Giving voice to persons living with dementia: The researcher’s opportunities and challenges. *Nursing Science Quarterly*, *16*(2), 163–167. <https://doi.org/10.1177/0894318403251793251793>
- Morand-Beaulieu, S., Grot, S., Lavoie, J., Leclerc, J. B., Luck, D., & Lavoie, M. E. (2017). The puzzling question of inhibitory control in Tourette syndrome: A meta-analysis. *Neuroscience and Biobehavioral Reviews*. <https://doi.org/10.1016/j.neubiorev.2017.05.006>
- Mueller, S. C., Jackson, G. M., Dhalla, R., Datsopoulos, S., & Hollis, C. P. (2006). Enhanced cognitive control in young people with Tourette’s syndrome. *Current Biology*, *16*(6), 570–573. <https://doi.org/10.1016/j.cub.2006.01.064>
- Müller, S. V., Johannes, S., Wieringa, B., Weber, A., Müller-Vahl, K., Matzke, M., ... Münte, T. F. (2003). Disturbed monitoring and response inhibition in patients with Gilles de la Tourette syndrome and co-morbid obsessive compulsive disorder. *Behavioural Neurology*, *14*(1–2), 29–37. <https://doi.org/http://dx.doi.org/10.1155/2003/832906>
- O’Rourke, J. A., Scharf, J. M., Platko, J., Stewart, S. E., Illmann, C., Geller, D. A., ... Pauls, D. L. (2011). The familial association of Tourette’s disorder and ADHD: The impact of OCD symptoms. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, *156*(5), 553–560. <https://doi.org/10.1002/ajmg.b.31195>
- O’Keefe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., & Murphy, T. (2014).

Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: Attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, 20(5), 557–582.

<https://doi.org/10.1080/09297049.2013.832740>

Oosterman, J. M., Wijers, M., & Kessels, R. P. C. (2013). Planning or something else? Examining neuropsychological predictors of zoo map performance.

*Applied Neuropsychology*, 20(2), 103–109.

<https://doi.org/10.1080/09084282.2012.670150>

Osterrieth, P. A. (1944). Test of copying a complex figure; Contribution to the study of perception and memory. *Archives de Psychologie*, 30, 206–356.

Ozonoff, S., & Jensen, J. (1999). Specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism and Developmental Disorders*, 29(2), 171–177.

<https://doi.org/10.1023/A:1023052913110>

Ozonoff, S., & Strayer, D. L. (2001). Further Evidence of Intact Working Memory in Autism. *Journal of Autism and Developmental Disorders*, 31(3), 257–263.

<https://doi.org/10.1023/A:1010794902139>

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal- lobe lesions in man. *Neuropsychologia*, 20(3), 249–262.

[https://doi.org/Doi 10.1016/0028-3932\(82\)90100-2](https://doi.org/Doi%2010.1016/0028-3932(82)90100-2)

Rasmussen, C., Soleimani, M., Carroll, A., & Hodlevskyy, O. (2009).

Neuropsychological functioning in children with Tourette syndrome (TS).

*Journal of the Canadian Academy of Child and Adolescent Psychiatry =*

*Journal de l'Académie Canadienne de Psychiatrie de l'enfant et de*

*l'adolescent*, 18(4), 307–315. Retrieved from

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383%7B%7>

Dtool=pmcentrez%7B&%7Drendertype=abstract%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383&tool=pmcentrez&rendertype=abstract

- Redick, T. S., Broadway, J. M., Meier, M. E., Kuriakose, P. S., Unsworth, N., Kane, M. J., & Engle, R. W. (2012). Measuring working memory capacity with automated complex span tasks. *European Journal of Psychological Assessment, 28*(3), 164–171. <https://doi.org/10.1027/1015-5759/a000123>
- Reitan, R. W. D. (1985). The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation. *Tucson, AZ: Neuropsychological Press.*
- Robbins, T. W. (1996). Dissociating executive functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 351*, 1463–1470.
- Robertson, M. M. (2011). Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *British Journal of Hospital Medicine (London, England : 2005), 72*(2), 100–107. <https://doi.org/10.12968/hmed.2011.72.2.100>
- Roizen, N. J., Blondis, T. A., Irwin, M., & Stein, M. (1994). Adaptive functioning in children with attention-deficit hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine, 148*(11), 1137–1142. <https://doi.org/10.1001/archpedi.1994.02170110023004>
- Ruff, R. M., Light, R. H., & Evans, R. W. (1987). The ruff figural fluency test: A normative study with adults. *Developmental Neuropsychology, 3*(1), 37–51. <https://doi.org/10.1080/87565648709540362>
- Sallee, F. R., Sethuraman, G., & Rock, C. M. (1994). Effects of pimozide on cognition in children with Tourette syndrome: interaction with comorbid attention deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica, 90*(1),



4–9. <https://doi.org/10.1111/j.1600-0447.1994.tb01546.x>

Salthouse, T. A. (1996). The Processing-Speed Theory of Adult Age Differences in Cognition. *Psychological Review*, *103*(3), 403–428.

<https://doi.org/10.1037/0033-295X.103.3.403>

Scahill, L., Erenberg, G., Berlin, C. M., Budman, C., Coffey, B. J., Jankovic, J., ... Walkup, J. (2006). Contemporary Assessment and Pharmacotherapy of Tourette

Syndrome. *NeuroRx*, *3*(2), 192–206. <https://doi.org/10.1016/j.nurx.2006.01.009>

Scahill, L., Williams, S., Schwab-Stone, M., Applegate, J., Leckman, J. F., Walkup, J. T., ... Hollenbeck, P. J. (2006). Disruptive Behavior Problems in a

Community Sample of Children with Tic Disorders. In *Advances in neurology: Tourette syndrome (Vol. 99)*. (pp. 184–190). Retrieved from

<http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2006-06768-018&site=ehost-live>

Scharf, J. M., Miller, L. L., Mathews, C. A., & Ben-Shlomo, Y. (2012). Prevalence of Tourette syndrome and chronic tics in the population-based Avon

Longitudinal Study of Parents and Children cohort. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(2), 192–201.

<https://doi.org/10.1016/j.jaac.2011.11.004>

Schuerholz, L. J., Baumgardner, T. L., Singer, H. S., Reiss, A. L., & Denckla, M. B. (1996). Neuropsychological status of children with Tourette's syndrome with

and without attention deficit hyperactivity disorder. *Neurology*, *46*(4), 958–965.

<https://doi.org/10.1212/WNL.46.4.958>

Schuerholz, L. J., Singer, H. S., & Denckla, M. B. (1998). Gender study of neuropsychological and neuromotor function in children with Tourette

syndrome with and without attention-deficit hyperactivity disorder. *Journal of*

*Child Neurology*, 13(6), 277–282.

<https://doi.org/10.1177/088307389801300607>

Schultz, R. T., Carter, A. S., Gladstone, M., Scahill, L., Leckman, J. F., Peterson, B. S., ... Pauls, D. (1998). Visual-motor integration functioning in children with Tourette syndrome. *Neuropsychology*, 12(1), 134–145.

<https://doi.org/10.1037/0894-4105.12.1.134>

Selemon, L. D. (2013). A role for synaptic plasticity in the adolescent development of executive function. *Transl Psychiatry*, 3(3), e238.

<https://doi.org/10.1038/tp.2013.7>

Shafran, R., Frampton, I., Heyman, I., Reynolds, M., Teachman, B., & Rachman, S. (2003). The preliminary development of a new self-report measure for OCD in young people. *Journal of Adolescence*, 26(1), 137–142.

[https://doi.org/10.1016/S0140-1971\(02\)00083-0](https://doi.org/10.1016/S0140-1971(02)00083-0)

Shimoni, M., Engel-Yeger, B., & Tirosh, E. (2012). Executive dysfunctions among boys with Attention Deficit Hyperactivity Disorder (ADHD): Performance-based test and parents report. *Research in Developmental Disabilities*, 33(3), 858–865.

<https://doi.org/10.1016/j.ridd.2011.12.014>

Siegel, L. S. (1994). Working Memory and Reading: A Life-span Perspective.

*International Journal of Behavioral Development*, 17(1), 109–124.

<https://doi.org/10.1177/016502549401700107>

Sikora, D. M., Vora, P., Coury, D. L., & Rosenberg, D. (2012). Attention-Deficit/Hyperactivity Disorder Symptoms, Adaptive Functioning, and Quality of Life in Children With Autism Spectrum Disorder. *Pediatrics*,

130(Supplement 2), S91–S97. <https://doi.org/10.1542/peds.2012-0900G>

Simon, H. A. (1975). The functional equivalence of problem solving skills. *Cognitive*

- Psychology*, 7(2), 268–288. [https://doi.org/10.1016/0010-0285\(75\)90012-2](https://doi.org/10.1016/0010-0285(75)90012-2)
- Singer, H. S. (2011). *Tourette syndrome and other tic disorders. Handbook of Clinical Neurology* (Vol. 100). <https://doi.org/10.1016/B978-0-444-52014-2.00046-X>
- Singer, H.S. & Harris, K. (2006) in *Neurobiology of disease*, Circuits to synapses: The pathophysiology of Tourette syndrome, ed Gilman S (Elsevier Academic, Burlington, MA), Ed 1.
- Sparrow, S. S., Cicchetti, D. V., & Saulnier, C. A. (2016). *The Vineland Adaptive Behavior Scales-third edition*. American Guidance Service; Circle Pines, MN.
- Stern, J. S., Burza, S., & Robertson, M. M. (2005). Gilles de la Tourette's syndrome and its impact in the UK. *Postgraduate Medical Journal*, 81(951), 12–19. <https://doi.org/10.1136/pgmj.2004.023614>
- Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research*, 63(3–4), 289–298. <https://doi.org/10.1007/s004269900007>
- Sukhodolsky, D. G., do Rosario-Campos, M. C., Scahill, L., Katsovich, L., Pauls, D. L., Peterson, B. S., ... Leckman, J. F. (2005). Adaptive, emotional, and family functioning of children with obsessive-compulsive disorder and comorbid attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, 162(6), 1125–1132. <https://doi.org/10.1176/appi.ajp.162.6.1125>
- Sukhodolsky, D. G., Scahill, L., Zhang, H., Peterson, B. S., King, R. A., Lombroso, P. J., ... Leckman, J. F. (2003). Disruptive behavior in children with Tourette's syndrome: Association with ADHD comorbidity, tic severity, and functional impairment. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(1), 98–105. <https://doi.org/10.1097/00004583-200301000-00016>

- Swanson, J. M. (1995). *SNAP-IV Scale*. Irvine, CA: University of California Child Development Center.
- Termine, C., Luoni, C., Fontolan, S., Selvini, C., Perego, L., Pavone, F., ... Cavanna, A. E. (2016). Impact of co-morbid attention-deficit and hyperactivity disorder on cognitive function in male children with Tourette syndrome: A controlled study. *Psychiatry Research*, *243*, 263–267.  
<https://doi.org/10.1016/j.psychres.2016.06.048>
- Toplak, M. E., Bucciarelli, S. M., Jain, U., & Tannock, R. (2009). Executive functions: Performance-based measures and the behavior rating inventory of executive function (BRIEF) in adolescents with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology*, *15*(1), 53–72.  
<https://doi.org/10.1080/09297040802070929>.
- Tranel, D., Anderson, S. W. & Benton, A. (1994). Development of the concept of ‘executive function’ and its relationship to the frontal lobes. In *Handbook of Neuropsychology* (ed. F. Boller and J. Grafman), pp. 125–148. Elsevier: Amsterdam.
- Uher, R., Heyman, I., Turner, C. M., & Shafran, R. (2008). Self-, parent-report and interview measures of obsessive-compulsive disorder in children and adolescents. *Journal of Anxiety Disorders*, *22*(6), 979–990.  
<https://doi.org/10.1016/j.janxdis.2007.10.001>
- van't Hooft, I., Andersson, K., Bergman, B., Sejersen, T., von Wendt, L., & Bartfai, A. (2005). Beneficial effect from a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study. *Brain Injury*, *19*(7), 511–518. <https://doi.org/10.1080/02699050400025224>
- Verté, S., Geurts, H. M., Roeyers, H., Oosterlaan, J., & Sergeant, J. A. (2005).

Executive functioning in children with autism and Tourette syndrome.

*Development and Psychopathology.*

<https://doi.org/10.1017/S0954579405050200>

Vriezen, E. R., & Pigott, S. E. (2002a). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Child Neuropsychology*, 8(4), 296–303. <https://doi.org/10.1076/chin.8.4.296.13505>

Vriezen, E. R., & Pigott, S. E. (2002b). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Special Issue: Behavior Rating Inventory of Executive Function (BRIEF).*, 8(4), 296–303.

<https://doi.org/http://dx.doi.org/10.1076/chin.8.4.296.13505>

Wählstedt, C., Thorell, L. B., & Bohlin, G. (2009). Heterogeneity in ADHD: Neuropsychological pathways, comorbidity and symptom domains. *Journal of Abnormal Child Psychology*, 37(4), 551–564. <https://doi.org/10.1007/s10802-008-9286-9>

Watkins, L. H., Sahakian, B. J., Robertson, M. M., Veale, D. M., Rogers, R. D., Pickard, K. M., ... Robbins T. W. (2005). Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychological Medicine*, 35(4), 571–582. <https://doi.org/10.1017/S0033291704003691>

Wechsler, D. (n.d.). *Wechsler intelligence scale for children-fifth edition.*

Bloomington, MN: Pearson.

Weisman, H., Qureshi, I. A., Leckman, J. F., Scahill, L., & Bloch, M. H. (2013). Systematic review: Pharmacological treatment of tic disorders - Efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neuroscience and*

*Biobehavioral Reviews*. <https://doi.org/10.1016/j.neubiorev.2012.09.008>

Welsh, M. C., Pennington, B. F., & Groisser, D. B. (1991). A Normative-Developmental Study of Executive Function: A Window on Prefrontal Function in Children. *Developmental Neuropsychology*, 7(2), 131–149.  
<https://doi.org/10.1080/87565649109540483>

White, S. J., Burgess, P. W., & Hill, E. L. (2009). Impairments on “open-ended” executive function tests in Autism. *Autism Research*, 2(3), 138–147.  
<https://doi.org/10.1002/aur.78>

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H. and Evans, J. J. (1996). *Behavioural Assessment of Dysexecutive Syndrome*. Bury St. Edmunds, , UK: Thames Valley Test Company.

Wilson, BA; Alderman, N; Burgess, PW; Emslie, H; Evans, J. (1996). The behavioural assessment of the dysexecutive syndrome. *Thames Valley Company; Bury St Edmunds*.

Yaniv, A., Benaroya-Milshtein, N., Steinberg, T., Ruhrrman, D., Apter, A., & Lavidor, M. (2017). Specific executive control impairments in Tourette syndrome: The role of response inhibition. *Research in Developmental Disabilities*, 61, 1–10. <https://doi.org/10.1016/j.ridd.2016.12.007>

Zandt, F., Prior, M., & Kyrios, M. (2009). Similarities and differences between children and adolescents with autism spectrum disorder and those with obsessive compulsive disorder. *Autism*, 13(1), 43–57.  
<https://doi.org/10.1177/1362361308097120>

## **Part 2: Empirical Paper**

### **The relative impact of distinct executive functioning abilities on adaptive functioning in children with Tourette Syndrome**

#### **2.1. Abstract**

**Aims:** This study aimed to test whether children with Tourette Syndrome (TS) show deficits in executive functioning (EF), comparing performance across parent-report, ecologically-valid and selected experimental measures, and examining if performance on these measures is related to adaptive functioning. Also of interest was to test whether there are deficits on tests assessing inhibition, as has been suggested (Morand-Beaulieu, Grot, Lavoie, Leclerc, Luck, & Lavoie, 2017), and if effects are mediated by severity of comorbid ADHD or OCD.

**Method:** Forty-seven children with TS were assessed on a comprehensive, hypothesis-driven neuropsychological test battery. The assessment included objective and subjective measures of executive function, adaptive and intellectual functioning, and selected clinical factors (ADHD, OCD and tic severity).

**Results:** The group was significantly impaired across domains of adaptive and parent-report executive functioning. There was also evidence of impaired performance on objective tests of planning, monitoring, sustained and switching attention compared to normative means. Impairments in adaptive, parent-report EF and on objective EF measures were also found in a sub-group of participants without co-morbid ADHD. Performance on the BADS-C zoo map 1 test, parent-report EF and IQ significantly impacted adaptive functioning scores, after controlling for clinical variables. Of the objective EF tests, BADS-C zoo map 2 and TEA-*Ch* II reds, blues, bags and shoes (RBBS) performance was significantly associated with parent-report EF scores, independent of clinical factors.

**Conclusions:** The current findings provide evidence of profound executive and adaptive functioning impairments in children with TS, and suggest that these constructs are causally associated. The results have important clinical implications, in suggesting that neuropsychological intervention to improve EF may lead to

generalised treatment gains in adaptive functioning, potentially improving quality of life and independent functioning in children with TS.



## **2.2. Introduction**

Tourette Syndrome (TS) is an inherited, highly heterogeneous (with Attention-Deficit Hyperactivity Disorder, ADHD and Obsessive Compulsive Disorder, OCD in particular, Eddy, Rizzo, & Cavanna, 2009), neurodevelopmental disorder defined by the presence of vocal and motor tics. Clinicians at a specialist clinic at Great Ormond Street Hospital (GOSH) have observed a high prevalence of adaptive functioning problems in children with TS, although current research in this area, along with research into the neuropsychological deficits that might give rise to this pattern, is limited. Intuitively, executive functioning (EF), involving planning, problem-solving and organisation skills, may be related to adaptive functioning (the conceptual, social and practical skills needed for everyday independent living), and there is some evidence to suggest that these abilities may be associated in other neurodevelopmental populations (e.g. children with Autism Spectrum Disorder, ASD, Gilotty, Kenworthy, Wagner, Sirian, & Black, 2002; Happé, Booth, Charlton, & Hughes, 2006). The current study investigated executive and adaptive functioning, across a range of subtests and domains, in a large sample, which included children with TS and co-occurring ADHD / OCD along with a subgroup of children with uncomplicated TS.

### ***2.2.1. Executive functioning in children with TS***

#### ***2.2.1.1. Planning***

Two studies of children with uncomplicated TS showed impaired planning performance on Tower tests (Rasmussen et al., 2009; Termine et al., 2016) whereas only one of three studies using heterogeneous TS groups showed impairment (planning deficit was indicated in a TS+ADHD group in Termine et al., 2016; but not in two

heterogeneous TS groups: Ozonoff & Jensen, 1999; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005). There was little evidence of planning deficits on the other measures, with all five groups assessed over three studies on Rey Complex Figure Test (RCFT) organisation showing preserved performance (Chang, McCracken, & Piacentini, 2007; Schuerholz, Baumgardner, Singer, Reiss, & Denckla, 1996; Schuerholz, Singer, & Denckla, 1998), and only one of the three groups assessed on a planning task involving multi-tasking demonstrated impairment (TS+ADHD showed deficient performance on the Six Elements Task, but not uncomplicated TS or TS+OCD in Channon, Pratt, & Robertson, 2003).

#### ***2.2.1.2. Set shifting***

Set shifting in children with TS appeared to be preserved across the included studies, with only one set shifting measure showing deficient performance (involving intra and extra- dimensional set-shifting, IED) in an uncomplicated TS group (Rasmussen et al., 2009). Six groups tested on set shifting ability found performance within normal ranges across the TS child groups (uncomplicated TS, TS+ADHD, TS+OCD in Channon, Crawford, Vakili, & Robertson, 2003; and heterogeneous TS groups in Ozonoff & Jensen, 1999; Verté et al., 2005).

#### ***2.2.1.3. Working memory***

Studies assessing working memory task performance showed mixed results, with two studies finding evidence of impairment (Jeter et al., 2015; Rasmussen et al., 2009), and four finding unimpaired performance (Crawford et al., 2005; Ozonoff & Strayer, 2001; Verté et al., 2005).

#### **2.2.1.4. Fluency**

The review indicated a fairly consistent profile of impaired phonological fluency, that persisted across heterogeneous (in 3/4 studies reviewed: Crawford et al., 2005; Drury, Shah, Stern, Crawford, & Channon, 2017; Harris, Schuerholz, Singer, Reader, Brown, Cox, ... & Denckla, 1995; Schuerholz et al., 1998; but not Verté et al., 2005) and uncomplicated TS groups (in 3/4 studies reviewed: Channon et al., 2003; Crawford et al., 2005; Harris et al., 1995; but not Mahone, Koth, Cutting, Singer, & Denckla, 2001). These findings were observed in the context of unanimously preserved semantic (in all studies reviewed, across uncomplicated and heterogeneous groups, Drury et al., 2017; Mahone et al., 2001; Schuerholz et al., 1996; Schuerholz et al., 1998; Verté et al., 2005) and figural fluency (though data was available from only one, uncomplicated TS study (Mahone et al., 2001). These results suggested a specific phonological fluency deficit in children with TS.

#### **2.2.1.5. Inhibition**

Inhibitory control in children (and adults) with TS has been recently reviewed in a comprehensive meta-analysis (Morand-Beaulieu et al., 2017). The analysis revealed inhibition deficits in children with TS ( $d=0.30$ ,  $Z=4.20$ ,  $p<.001$ ). Children with uncomplicated and heterogeneous TS were combined in this analysis and effect size analysis for children with uncomplicated TS were not available. However, when data from children and adults were analysed together, there was a small effect of greater inhibitory deficits in uncomplicated TS compared to controls ( $d=0.26$ ), whereas a medium effect size ( $d=0.51$ ) was returned for groups with TS and comorbid ADHD. The data were derived from studies assessing performance on a range of measures of cognitive inhibition: circle tracing, Go/No-go, sentence completion (e.g. Hayling test),

stimulus-response compatibility paradigms, stop-signal and Stroop tasks. In terms of performance across the measures, the largest overall effect sizes were found in tasks necessitating a verbal response (e.g. sentence completion and Stroop).

### ***2.2.2. Summary of evidence on EF in TS***

There appear to be inhibitory deficits in children with TS, and if child TS profiles are similar to that of adult TS, these impairments may be present in uncomplicated TS, exacerbated by comorbid ADHD, and be most visible on sentence completion and Stroop tasks (Morand-Beaulieu et al., 2017). In terms of other executive functioning components, the systematic review in Part 1 showed a mixed profile of executive performance in children with TS, with instances of impaired group performance in both uncomplicated and heterogeneous TS, and convincing evidence for impaired performance in phonological fluency and in uncomplicated TS tower performance (planning).

### ***2.2.3 Ecologically-valid and parent-report executive functioning assessment***

Several studies have assessed children with TS and related neurodevelopmental conditions on a range of executive measures, making comparisons between parent-report, ecologically-valid and experimental tests possible. For instance, Rasmussen et al. (2009) examined performance on experimental and parent-report executive measures, using the CANTAB (Cambridge Neuropsychological Test Automated Battery, Cambridge Cognition, 2017) and the BRIEF (Behaviour Rating Inventory of Executive Function, Gioia, Isquith, Guy, & Kenworthy, 2000) a parent-report measure of the everyday application of executive functioning skills. The study found deficits on the CANTAB as well as in most domains of the BRIEF (except organisation

of materials), suggesting that children with TS have executive function deficits that impact on a wide range of areas in their everyday life.

The performance of children on ecologically-valid tests of executive functioning is under-reported in the TS literature. However, there has been some attempt to investigate this in children with ADHD. Shimoni et al (Shimoni, Engel-Yeger, & Tirosh, 2012) analysed the performance of children with ADHD on an executive functioning measure with high ecological validity (BADS-C: the Behaviour Assessment of Dysexecutive Syndrome for Children, Emslie, Wilson, Burden, Nimmo-Smith, & Wilson, 2003), along with the BRIEF. The authors found impairment on most subtests of the BADS-C except for the playing card assessing cognitive flexibility) and six-part (assessing planning, scheduling and monitoring) subtests (and all domains of the BRIEF) in the ADHD group, relative to matched controls.

In summary, reports of executive abilities on objective neuropsychological testing vary, and there is increasing evidence for executive deficits on parent-report and ecologically-valid measures of executive functioning in both TS and similar neurodevelopmental conditions (e.g. ADHD). Taken together, these findings suggest that there may be executive functioning impairments that are impacting on the everyday lives of children with TS, but that are not readily detected by most experimental tests, and may be more visible on ecologically-valid assessments of EF.

#### ***2.2.4. Adaptive functioning in children with TS***

Adaptive functioning skills, defined as the application of cognitive abilities as necessary to navigate daily life (including the initiation and completion of daily

activities), are crucial for achieving independence. There are several studies of adaptive functioning in children with related neurodevelopmental conditions such as ASD, but reports on adaptive functioning in TS are sparse. One study found relative weaknesses in socialisation and domestic skills components of adaptive functioning in children with TS, in the context of IQ in the average range, but as this was not a primary focus of the paper, the authors did not comment on whether these weaknesses indicated impairment compared to normative samples (Dykens, Leckman, Riddle, Hardin, Schwartz, & Cohen, 1990).

The most frequently used measure of adaptive functioning used in the literature is the Vineland Adaptive Behaviour Scale (VABS), a parent-rated measure assessing communication, daily living, socialisation and motor skills (Sparrow, Cicchetti, & Saulnier, 2016). Several studies have found VABS performance to be preserved in children with uncomplicated TS, but impaired in comparison groups with comorbid and pure ADHD (Carter, O'Donnell, Schultz, Scahill, Leckman, & Pauls, 2000; Sukhodolsky et al., 2003) suggesting that adaptive functioning deficits may be moderated by presence of ADHD in TS samples. However, impairment in children with TS on the socialisation domain that was maintained after controlling for ADHD has been reported elsewhere (Gorman, Thompson, Plessen, Robertson, Leckman, & Peterson, 2010).

Many adaptive behaviours appear intuitively to involve executive functioning. No existing studies have investigated the interaction between adaptive and executive functioning in children with TS. However, this important area has been explored in the ASD literature. One study demonstrated that performance on the working memory and initiation domains of the BRIEF contributed to the majority of adaptive functioning indices of the VABS in children with ASD, and that several executive functions were

important in the adaptive skills of communication and socialisation (Gilotty et al., 2002). These findings are consistent with another study that reported specific deficits in areas of executive functioning that are associated with the adaptive functioning skills of socialisation and communication in both ASD and ADHD (Happé et al., 2006). It is difficult to ascertain the direction of causality, and it is possible that problems in adaptive functioning could contribute to poor performance on EF tasks rather than vice versa.

### **2.2.5. Summary**

The move towards fractionating executive functioning skills in the neuropsychological literature has emphasised the value of examining specific, separable executive abilities to determine the locus of executive functioning difficulties. Some accounts of executive function assessment (e.g. Isquith, Crawford, Espy, & Gioia, 2005) emphasise the use of ecologically-valid measures, which may help resolve the findings of preserved experimental test performance with clinical and parental reports of problematic executive and adaptive functioning in TS. Studies using a parent-report measure (BRIEF) have provided some evidence for deficient executive functioning in children with TS, but the deficits that might underlie impairments on this parent-report measure are currently unclear from the literature, and the application of executive functioning tests with high ecological validity (such as the BADS-C) may help elucidate this. Studies using experimental measures of executive functioning have found inconsistent results in children. In adult samples, impaired performance on the Hayling sentence completion test (Burgess & Shallice, 1997) have been observed fairly consistently, but child studies using similar tests are sparse generally, and non-

existent in the TS literature, probably due to the current absence of published sentence completion tests that are suitable for use with children.

Adaptive functioning appears to be largely preserved in children with uncomplicated TS (although socialisation may be more problematic), and impaired in comparison groups with comorbid and pure ADHD (Carter et al., 2000; Gorman et al., 2010; Sukhodolsky et al., 2003), suggesting that adaptive functioning deficits may be moderated by levels of ADHD in TS samples. This idea is partially supported by evidence from a Transcranial Magnetic Stimulation (TMS) study that indicated strengths in cognitive control mechanisms that may *improve* adaptive functioning in TS without comorbid ADHD (Jackson, Parkinson, Manfredi, Millon, Hollis, & Jackson, 2013). Clinically, the team at GOSH has observed high rates of impaired adaptive functioning in children with TS, and evidence from the study of other neurodevelopmental disorders suggests that executive functioning (including those assessed by the BRIEF) and adaptive functioning abilities may be associated.

#### **2.2.6. Study aims**

The current study aimed to address the following questions through testing a group of children with TS on a comprehensive, hypothesis-driven neuropsychological assessment battery:

- (i) To test whether children with TS show deficient executive and adaptive functioning compared to normative data, by contrasting group means and determining rates of clinical impairment.
- (ii) To compare performance across the various subtests and domains of parent-report (BRIEF), ecologically-valid (BADSC) and experimental measures



of executive functioning (TEA-*Ch* II, Hayling sentence completion test: child version).

- (iii) To examine whether deficits in executive functioning are more identifiable on ecologically-valid measures than experimental tests.
- (iv) To explore whether there are difficulties in inhibition on a test necessitating a verbal response, as has been suggested (e.g. Morand-Beaulieu et al., 2017), and if there are greater associations between inhibition performance and adaptive functioning than other experimental tests of executive functioning.
- (v) To test the impact of clinical factors (ADHD and OCD) on adaptive functioning and on a parental report measure of executive functioning (BRIEF).
- (vi) To investigate differences in performance of children with TS across several domains of adaptive functioning (i.e. socialisation, communication, and daily living subtests of the VABS-3), to test the hypothesis suggested by the literature that the adaptive functioning skills of socialisation are disproportionately impaired, relative to other domains, in children with TS.
- (vii) To test whether performance on specific executive functioning abilities as assessed by experimental, ecologically-valid and parent-report measures are associated with domains of adaptive behaviour, in children with TS, while controlling for levels of ADHD, OCD and tic severity.
- (viii) To investigate which objective neuropsychological tests of executive functioning are associated with parent-report executive functioning scores, controlling for levels of ADHD, OCD and tic severity.

### **2.3. Method**

The work described was conducted jointly with a colleague (please see Appendix B for details of joint working).

#### ***2.3.1. Participants***

Participants were recruited through a specialist clinic at GOSH. These records were screened against the following study inclusion criteria: that children were aged between 7-14 years, and had received a diagnosis of TS. Forty-seven child participants with TS were recruited. Descriptive information about the sample, including the proportion of participants meeting clinical thresholds for impairment on the ADHD and OCD measures in the heterogeneous overall group, along with the two subgroups: TS with and without ADHD, are provided in Tables 2.1 and 2.2.

*Table 2.1: Participant characteristics*

	<b>Heterogeneous (overall) group</b>	<b>TS without ADHD subgroup</b>	<b>TS with ADHD subgroup</b>
<b><i>N</i></b>	47	15	32
<b>Gender (<i>N</i> male: female)</b>	35: 12	10: 5	25: 7
<b>Age (months)</b>	<i>M</i> age months: 142.15 <i>SD</i> : 25.36 Range (months): 74- 186 <i>M</i> age years: 11.85 <i>SD</i> : 2.11 Range (years): 6-15	<i>M</i> age months: 143.53 <i>SD</i> : 29.46 Range (months): 74- 186 <i>M</i> age years: 11.96 <i>SD</i> : 2.46 Range (years): 6-15	<i>M</i> age months: 141.5 <i>SD</i> : 23.61 Range (months): 98- 182 <i>M</i> age years: 11.79 <i>SD</i> : 1.97 Range (years): 8-15
<b>IQ</b>	<i>M</i> : 98.74 <i>SD</i> : 14.81	<i>M</i> : 99.2 <i>SD</i> : 13.70	<i>M</i> : 97.47 <i>SD</i> : 14.69
<b>Clinical diagnosis (<i>N</i>)</b>	TS+ADHD: 11 TS+OCD: 5 TS+ADHD+OCD: 1	Uncomplicated TS: 13 TS+OCD: 2	TS+ADHD: 11 TS+OCD (and clinical impairment on the ADHD measure): 3 TS+ADHD+OCD: 1

To test for differences in mean age and IQ across the TS with and without ADHD subgroups, independent *t*-tests were performed on the data. No group contrasts were significant in the IQ ( $p=.887$ ) or the age (in months,  $p=.801$ ) data, indicating roughly equivalent IQ and ages across the groups.

*Table 2.2.* <sup>3</sup> *Number of cases classified as having symptoms of impairment on the clinical measures*

<b>Domain</b>	<b>Measure</b>	<b>N impaired (% of sample)</b>
<b>ADHD</b>	SNAP-IV inattention	22 (46.80)
	SNAP-IV hyperactivity	20 (42.55)
	SNAP-IV inattention or hyperactivity	30 (63.83)
	SNAP-IV oppositional / defiant behaviour	11 (23.40)
<b>OCD</b>	<i>CHOCI-R-P</i> Total impairment	17 (36.17)

### **2.3.2. Materials**

A comprehensive neuropsychology assessment battery was used, involving standardised measures of intellectual and executive functioning, along with clinical measures of tic severity, and parent-report indices of adaptive functioning and potential comorbid conditions (ADHD and OCD).

#### **2.3.2.1. Battery of neuropsychology tests - child performance measures**

*Intellectual functioning: Wechsler Intelligence Scale for Children (WISC-V, Wechsler, 2014):* The WISC-V is comprised of several subtests across five domains (Verbal Comprehension, Visual Spatial, Fluid Reasoning, Working Memory and Processing Speed), from which a full scale IQ (FSIQ) index score can be generated.

*Executive Functioning: Behavioural Assessment of the Dysexecutive Syndrome in Children (BADS-C, Emslie et al., 2003):* An abbreviated version of the BADS-C

<sup>3</sup> 'Impaired' classifications were given if average scores were  $\geq 1.78$  on SNAP Inattention and  $\geq 1.44$  on Hyperactivity;  $\geq 1.88$  on Oppositional/Defiance Behaviour, consistent with published 5% cut off scores, and total impairment on the CHOCI-R-P (obsessional and compulsive impairment scores summed)  $\geq 17$ .

involving (i) the zoo map test (1 and 2): to assess children's visual-spatial and planning abilities where structure is minimal, increasing planning demands (1) and provided, reducing planning demands (2), and (ii) the six parts test: to assess planning, organisation and monitoring abilities.

*Hayling sentence completion test using child stimuli (Burgess & Shallice, 1997; White, Burgess, & Hill, 2009)*: The Hayling test was employed to assess inhibition (please see White et al., 2009 for full methodological details). The methodology is based on the adult Hayling test procedure, as described in the manual, but using sentence stimuli that is more suitable for use with children. The test is comprised of two parts: (part 1: sensible completion; part 2: non-sensical completion), with participants being required to generate a word that is unrelated to the sentence in Part 2, increasing inhibition demands (e.g. 'After eating you clean your teeth with a cat'). Accuracy rates, response latencies and error type data can be derived from test performance. For part 2, errors were coded based on whether the work was unrelated (correct), a semantic match (the response completes the sentence sensibly, error type 1) or semantically related (the response is from the same or a related semantic category to the semantic match, error type 2).

*Test of Everyday Attention for Children—second edition (TEA-Ch II, Manly, Anderson, Crawford, George, Underbjerg, & Robertson, 2016)*: An abbreviated version of this computerised test was used in order to give measures of selective and sustained attention. The Simple RT subtest involves responding with a button press as soon as a visual stimulus appears on the screen, and was used to assess sustained attention and response inhibition. The Vigil test requires participants to keep count of an auditory stimulus over trials, and is designed to assess sustained attention. The Reds, Blues, Bags and Shoes (RBBS) test involves making colour and object decisions about stimuli

appearing on the screen, and switching between these two types of decisions. This measure was used to assess task switching and inhibition.

### ***2.3.2.2. Battery of neuropsychology tests – parent-rated measures***

While the researcher worked with the child participant, the child's parent was asked to complete the following scales:

*Behaviour Rating Inventory of Executive Function (BRIEF)*: The parent-rated version of the BRIEF (Gioia et al., 2000) was used to assess EF behaviours at home. The items assessed performance across three behavioural regulation domains (inhibitory control; shifting; emotion regulation) and five metacognition domains (initiation; working memory; planning; organisation of materials; monitoring). Combinations of the above domains can be summed to generate indexes of behavioural regulation (BRI), metacognition (MI) and global executive composite (GEC).

*Vineland Adaptive Behaviour Scales–third edition (VABS-3)*: The VABS-3 (Sparrow, Cicchetti, & Saulnier, 2016) is a widely-used measure of adaptive functioning across communication; daily living, socialisation and motor domains, which also allows computation of an adaptive behaviour composite (ABC).

*Swanson, Nolan and Pelham (SNAP)–IV*: The SNAP-IV (Swanson, 1995) is a parent-rated scale, comprised of items based on the DSM-IV criteria for ADHD.

*Yale Global Tic Severity Scale (YGTSS)*: The YGTSS (Leckman, Riddle, Hardin, Ort, Swartz, Stevenson, & Cohen, 1989) is a clinician interview assessing tic severity over the past week.

*OCD: Child Obsessional Compulsive Inventory – Revised (CHOCI-R-P)*: The CHOCI-R-P (Uher, Heyman, Turner, & Shafran, 2008) is a parent-rated questionnaire to assess the type and severity of OCD symptoms in children and adolescents.

### **2.3.3. Procedure**

Ethical approval from the appropriate Research and Development Department for GOSH and an NHS Research Ethics Committee was obtained before the study commenced (IRAS reference: 220775, Appendix C). Individuals meeting the criteria for inclusion and their families were sent written information about the study. This included an invitation letter (Appendix D) and participant information sheets, including a version tailored to the age of the child (Appendix E). Interested participants were then offered either a testing session at GOSH (and reimbursed for travel costs), or a visit by the researcher to the family home, depending on participant preferences, to maximise recruitment. Written consent/child assent was acquired before testing (Appendix E). The battery outlined above was administered by one of two Trainee Clinical Psychologists conducting the research. In addition to the measures listed in the previous section, child participants also completed four experimental conditions of a time processing task, which was the focus of a colleague's project. The length of the testing sessions varied, but were always completed within three hours (including breaks). Participants completed the testing session at home or in a private room within GOSH. Breaks were offered and participating families were sent reports (in both adult and child-friendly formats, report templates for parents, older children and younger children are provided in Appendices F, G and H, respectively) summarising the child's performance on the measures.

#### **2.3.4. General statistical method**

Statistical analysis was conducted using SPSS (version 24.0). Where possible, both categorical and dimensional analyses were conducted on standard scores from a comprehensive neuropsychology battery. For the categorical analyses, on tests for which normative data are available (BRIEF, TEA-*Ch* II, BADS-C, VABS-3), the child TS scores were compared with the published standardised test norms by conducting one-sample *t*-tests using the means from the child TS group and the means published in the standardised test norms, for each measure. This approach has been widely used, and published studies exist by the current authors (e.g. investigating neuropsychological performance in children with Arterial Ischaemic Stroke (O'Keeffe, Liégeois, Eve, Ganesan, King, & Murphy, 2014)), and several other research groups (e.g. neuropsychological performance in ADHD, (Lambek, Tannock, Dalsgaard, Trillingsgaard, Damm, & Thomsen, 2010; Wåhlstedt, Thorell, & Bohlin, 2009); EF performance in children with TBI, (Vriezen & Pigott, 2002a); adaptive functioning in ADHD, (Roizen, Blondis, Irwin, & Stein, 1994)).

The number of participants obtaining scores suggestive of clinical impairment were assessed. Participant scores were classified as impaired if index scores (WISC-V – V and VABS-3) were lower than 70, if *t* scores were higher than 65 (BRIEF, with higher scores indicating more problematic functioning on this measure), and if scaled scores were equal to or less than 4 (BADS-C and TEA-*Ch* II), consistent with test interpretation guidelines (e.g. Gioia et al., 2000) and psychometric conversion scales. To determine the proportion of participants with scores suggestive of ADHD and OCD symptoms, ‘impaired’ classifications were given if average scores were equal to or greater than 1.78 on SNAP-IV Inattention, 1.44 on Hyperactivity; and 1.88 on SNAP-IV Oppositional/Defiance Behaviour, consistent with published 5% cut off scores, and



if total impairment on the CHOCI-R-P (obsessional and compulsive impairment scores summed) was equal to or greater than 17 (Uher et al., 2008).

The normative contrasts were repeated using a TS without ADHD subgroup, having excluded those participants with ADHD diagnoses and those who scored above the 5% cut off on any of the SNAP-IV components. For the analyses of impairment rates, the participants were characterised in terms of whether they had received ADHD diagnoses or showed impairment in any of the SNAP-IV domains, to create two participant groups: TS with ADHD and TS without ADHD (but with OCD).

For the dimensional analyses, regression and correlation tests were used to examine which factors were associated with levels of executive and adaptive functioning. This enabled the analysis of relations between the different neuropsychological (intellectual and executive functioning) and clinical variables (e.g. tic severity and levels of comorbid ADHD and OCD). Regression analyses made possible the investigation of specific associations while keeping other variables (including levels of comorbid ADHD and OCD) constant (at their means). Tic severity (YGTSS) was also controlled for, to limit the impact of tics disrupting test performance across the sample. Hierarchical stepwise regression was used to control for clinical variables and intellectual functioning when investigating relationships between the various domains of executive and adaptive functioning. For instance, to assess the association between overall adaptive functioning (VABS-3) and EF (BRIEF), clinical variables and intellectual functioning data were entered as independent variables in the first step, and EF test data were entered as an independent variable in the next step in the regression. All regression analyses controlled for the following variables in this way: ADHD (SNAP-IV), OCD (CHOCI-R-P), tic severity (YGTSS) and intellectual functioning (WISC-V FSIQ). Between-domain dimensional analyses were explored

using correlation tests, which explored broad associations between the neuropsychological and clinical variables.

## **2.4. Results**

### ***2.4.1. Contrasts between the child TS group and normative data, across tests of executive and adaptive functioning***

Table 2.3 provides group means and standard deviations for the TS and normative groups, effect sizes, and results from one sample *t*-tests comparing TS and normative group performance across intellectual, executive and adaptive functioning measures.

Table 2.3. <sup>4</sup>Neuropsychological measures for the heterogeneous clinical sample compared to normative means

Domain	Measure	Variable	N	Test population mean (SD)	Sample mean (SD)	Sample range	t	p	Effect size (Cohen's d)	N impaired (% of sample)	
<b>Intellectual Functioning</b>	WISC-V	Full Scale IQ (FSIQ)	47		98.74 (14.81)	69-129	-.581	<b>.564</b>	0.084	1 (2.13)	
		Verbal Comprehension Index (VCI)	47		97.89 (13.50)	68-124	-1.069	<b>.290</b>	0.148	1 (2.13)	
		Visual Spatial Index (VSI)	47	100 (15)		98.43 (14.16)	69-132	-.762	<b>.450</b>	0.108	2 (4.26)
		Fluid Reasoning Index (FRI)	47			100.96 (15.40)	72-134	.426	<b>.672</b>	0.063	0 (0)
		Working Memory Index (WMI)	47			99.55 (18.11)	65-138	-.169	<b>.866</b>	0.027	3 (6.38)
		Processing Speed Index (PSI)	47			93.26 (16.93)	66-129	-2.731	<b>.009</b>	0.421	3 (6.38)
<b>Executive Functioning (parent-report)</b>	BRIEF	Inhibit	47		62.74 (14.13)	37-91	6.185	<b>&lt;.001</b>	1.041	22 (46.81)	
		Shift	47		66.91 (14.89)	40-91	7.788	<b>&lt;.001</b>	1.333	26 (55.32)	
		Emotional Control	47		66.04 (13.51)	40-91	8.138	<b>&lt;.001</b>	1.350	24 (51.06)	
		Initiate	47		64.49 (11.79)	35-89	8.423	<b>&lt;.001</b>	1.326	25 (53.19)	
		Working Memory	47		69.63 (12.20)	40-90	11.039	<b>&lt;.001</b>	1.760	32 (68.09)	
		Planning / organisation	47	50 (10)		66.77 (9.40)	40-84	12.231	<b>&lt;.001</b>	1.728	32 (68.09)
		Organisation of Materials	47			62.09 (8.26)	34-76	10.025	<b>&lt;.001</b>	1.318	21 (44.68)
		Monitor	47			61.66 (11.50)	37-81	6.949	<b>&lt;.001</b>	1.082	21 (44.68)
		Behaviour Regulation Index	47			66.79 (13.82)	43-95	8.326	<b>&lt;.001</b>	1.392	23 (48.94)
		Metacognition Index	43			68.30 (9.60)	37-86	12.504	<b>&lt;.001</b>	1.867	28 (65.12)
Global Executive Composite	43			69.19 (11.36)	42-90	11.579	<b>&lt;.001</b>	1.793	34 (79.07)		
<b>Executive Functioning (ecologically-valid)</b>	BADs-C	Zoo Map 1 (low planning demands)	47		9.83 (3.50)	2-16	-.334	<b>.740</b>	0.052	3 (6.38)	
		Zoo Map 2 (high planning demands)	47	10 (3)		9.72 (3.27)	1-14	-.579	<b>.565</b>	0.089	4 (8.51)
		Six Parts Test (planning, multi-tasking, scheduling, monitoring)	47			7.38 (2.12)	3-12	-8.455	<b>&lt;.001</b>	1.008	5 (10.64)
<b>Executive Functioning (experimental)</b>	TEA-Ch II	Vigil (sustained attention)	44		9 (3.03)	4-15	-2.186	<b>.034</b>	0.332	6 (13.64)	
		Simple RT(sustained attention)	44	10 (3)		9.93 (4.55)	1-19	-.099	<b>.921</b>	0.018	11 (25.00)
		RBBS (switching attention)	43			7.86 (3.90)	1-15	-3.596	<b>.001</b>	0.615	13 (30.23)
<b>Adaptive Functioning</b>	VABS-3	Communication	46		86.30 (17.47)	36-122	-5.315	<b>&lt;.001</b>	0.841	6 (13.04)	
		Daily Living Skills	43	100 (15)		82.53 (17.82)	20-114	-6.427	<b>&lt;.001</b>	1.060	11 (25.58)
		Socialisation	45			86.28 (21.22)	34-126	-4.335	<b>&lt;.001</b>	0.747	8 (17.78)
		Adaptive Behaviour Composite	43			84.09 (15.95)	48-109	-6.542	<b>&lt;.001</b>	1.028	11 (25.58)

<sup>4</sup> Effect sizes were computed using means, SD and N from the clinical sample and test population (N: WISC-V=2200; BRIEF=1419; BADs-C=265; TEA-Ch-II=293; VABS-3=3000). 'Impaired' classifications were given if index scores were <70 on the WISC-V and the VABS-3, t-scores > 65 on the BRIEF, and scaled scores =/ <4 on the BADs-C and TEA-Ch-II. Data points from the BRIEF were lost due to data collection error, TEA-Ch data points were lost due to technical errors with the programme, and VABS-3 data points were lost to participants' error in completing the forms. RBBS=Reds, Blues, Bags and Shoes.

Mean scores from the heterogeneous child TS group were significantly lower than normative means across all domains of the parent-report executive (BRIEF) and the adaptive functioning measures (VABS-3, Table 2.3). A high proportion of the sample scored in the clinically impaired test ranges across these indices, with 79.07% and 25.58% of participants obtaining impaired global composite scores on the BRIEF and VABS-3, respectively. Large to extremely large effect sizes were found across domains in the parent-report executive and adaptive functioning data (range:  $d=0.747$ – $1.867$ , Table 2.3).

When the analyses were repeated using data from the subgroup of children with TS without ADHD, patterns of impairment on the BRIEF and VABS-3 were broadly similar: The TS without ADHD group were reported to have significantly poorer scores (all  $p$ 's $<.05$ ) than normative means across BRIEF (except inhibit  $p=.247$ ) and VABS-3 domains (except socialisation:  $p=.619$ , and the adaptive behaviour composite scores, which approached significance:  $p=.051$ ). Statistical information on the normative contrasts for the TS group without comorbid ADHD are provided in Appendix I.

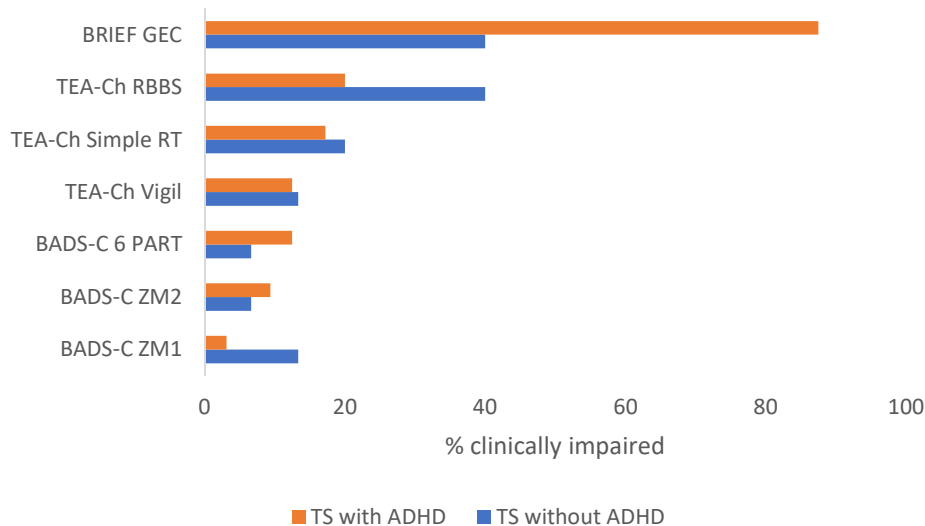
There was also evidence for poorer performance in children with heterogeneous TS on select ecologically-valid (BADS-C, six parts,  $p<.001$ , 10.64% impaired, large effect size:  $d=1.108$ ) and experimental (TEA-*Ch* II, vigil,  $p=.034$ , 13.64% impaired, medium effect size:  $d=0.332$  and RBBS,  $p<.001$ , 30.23% impaired, medium-large effect size:  $d=0.615$ , Table 2.3) executive functioning tests. A high proportion of the sample was impaired on the TEA-*Ch* II simple RT test (25%), though the result from test population and normative mean contrasts on this measure was not statistically significant ( $p=.921$ ). For the TS without ADHD group, participants were

similarly impaired on the BADS-C six parts test ( $t(14)=-2.965, p=.003$ ) and TEA-Ch II RBBS ( $t(14)=-3.572, p=.0004$ , Appendix I).

These differences were observed in the context of largely preserved intellectual functioning across both TS groups (WISC-V domains, all normative contrasts  $p$ 's > .290), except for processing speed in the heterogeneous TS group (PSI,  $p=.009$ , 6.38% impaired, medium effect size:  $d=0.421$ , Table 2.3, Appendix I). However, there were some very broad ranges in the WISC-V scores, with a small number of children falling just below the normative range (1-3 children achieved impaired scores across the WISC-V domains), and some extremely high intelligence indexes were also achieved (Table 2.3).

***2.4.1.1. Comparing rates of executive functioning impairment in the child TS group across parent-report (BRIEF), ecologically-valid (BADS-C) and experimental (TEA-Ch II) measures.***

Figure 2.1 shows the proportion of participants showing clinical impairment on the BRIEF general executive composite (GEC), and combined impairment rates from the BADS-C and TEA-Ch II subtests.



*Figure 2.1. Proportion of participants (%) obtaining scores in the clinically impaired ranges on the parent-report (BRIEF), ecologically-valid (BADS-C) and experimental (TEA-Ch II) measures across TS groups with and without ADHD*

To investigate the statistical significance of differences between performance in the TS with and without ADHD groups, and across the EF measures, the cell counts of participants obtaining impaired scores across the EF tests and between the two groups were entered into a loglinear analysis. The analysis returned a significant higher order interaction (impairment  $\times$  TS group  $\times$  EF measure),  $X^2(6)=15.934$ ,  $p=.014$ . To unpack this interaction, separate Chi Square Tests were performed on data from each group. There was a significant association between test type and impairment rate for the TS with ADHD ( $X^2(6)=93.455$ ,  $p<.001$ ), but not the TS without ADHD group ( $X^2(6)=11.667$ ,  $p=.070$ ). The significant association in the TS+ADHD data reflected significantly greater impairment in BRIEF GEC compared to other tests (all  $p$ 's  $<.001$ ), where no significant associations existed between the objective EF tests ( $p=.512$ ).

In terms of associations between the two TS groups across the EF measures, separate Chi Square tests were performed across the groups for each EF measure. There was a strong association between the two groups in the BRIEF GEC data ( $X^2(1)=11.516, p=.001$ ), reflecting greater rates of impairment in the TS with ADHD (87.5%) than the TS without ADHD group (40%). For the objective tests, an association between scores across the two groups in the RBBS data approached significance (40% and 20% in the TS without ADHD and TS with ADHD groups respectively,  $X^2(1)=2.948, p=.086$ ), and no other associations were significant (all  $p$ 's  $>.182$ ).

#### **2.4.1.2. Hayling performance**

Normative data are not currently available for the child version of the Hayling test and so contrasts to explore degree of impairment in the TS group were not possible. The Hayling test is comprised of a sensible completion (part 1), and a matched non-sensible completion (part 2) component, enabling comparisons of the data to examine performance differences where high cognitive inhibition demands are introduced (part 2). Table 2.4 shows mean accuracy, response latency, and error type data in the child TS group, over the two test conditions.

*Table 2.4. Hayling test performance in the child TS group*

<b>Hayling test component</b>	<b>N</b>	<b>Sample mean (SD)</b>	<b>Sample range</b>
<b>Part 1 (reduced inhibition demand)</b>			
Sensible Completion (Accuracy)	47	9.89 (0.312)	9-10
Sensible Completion (RT)	47	1.21 (0.44)	0.51-2.29
<b>Part 2 (increased inhibition demand)</b>			
Non-sensible completion (Accuracy)	47	6.60 (2.54)	0-10
Non-sensible completion (RT)	47	2.04 (1.21)	0.62-5.84
Non-sensible completion Type 1 error (semantic match)	47	.085 (.28)	0-1
Non-sensible completion: Type 2 error (semantically related)	47	3.36 (2.51)	0-9

To investigate the statistical significance of differences in TS group performance between parts 1 and 2, a paired *t*-test was conducted on the mean accuracy data, revealing a highly significant difference ( $t(46)=-8.683$ ,  $p<.001$ ). A Wilcoxon signed-rank test performed on the RT data was also highly significant ( $Z=-4.720$ ,  $p<.001$ ). Although it is unclear whether these differences are disproportionate compared with normative performance on these tests, the results reflect significantly lower accuracy rates, and substantially longer response latencies when inhibition demands were increased.

#### ***2.4.1.3. Investigation of differences in performance across the adaptive functioning domains (VABS-3)***

A one-way repeated measures ANOVA with a Greenhouse-Geisser correction was conducted on the VABS-3 scores, with domain type (communication, daily living skills and socialisation) entered as a factor. The analysis found no significant differences in scores across the domains ( $F(1.73, 65.80)=1.268$ ,  $p=.285$ ).

#### ***2.4.1.4. Investigation of differences in performance across the parent-report executive functioning domains (BRIEF)***

A one-way repeated measures ANOVA performed on the BRIEF standardised *t*-scores with domain type (inhibit, shift, emotional control, initiate, working memory, planning, organisation of materials, monitoring, behavioural regulation index (BRI) and metacognitive index (MI)) entered as a factor. The analysis, when applying a



Greenhouse-Geisser correction, indicated significant differences in scores across the parent-report EF domains ( $F(3.95, 165.78)=5.200, p=.001$ ).

Post hoc tests using the Bonferroni correction revealed significantly greater levels of impairment on the working memory (70.85) domain compared to inhibit (63.16,  $p=.030$ ), initiate (64.95,  $p=.009$ ), organisation of materials (62.35,  $p<.001$ ), planning (67.14,  $p=.025$ ) and monitor (62.42,  $p<.001$ ) components. Scores on the planning domain (67.14) showed greater levels of impairment than organisation of materials (62.35,  $p=.015$ ), MI (68.30,  $p<.001$ ), and monitoring (62.42,  $p=.016$ ). Impairment was also greater on the MI index (68.30) than the monitor domain (62.42,  $p<.001$ ).

#### ***2.4.1.5. Summary of performance across the executive and adaptive functioning measures***

Both the heterogeneous TS group and the TS without ADHD subgroup were significantly impaired relative to normative group performance on the adaptive functioning and parent-report EF measures. In terms of adaptive functioning, no significant differences were found in heterogeneous TS group performance across communication, daily living skills and socialisation domains, indicating global difficulties rather than problems specific to particular aspects of adaptive functioning. However, for the TS without ADHD subgroup, significant impairment was found in the communication and daily living skills domains, but not on socialisation or in terms of overall adaptive behaviour composite. There were significant differences between domains on the subjective EF measure (BRIEF) in the heterogeneous TS group, where the scores indicated greater difficulties on the working memory than most other BRIEF domains, and on planning and the metacognitive index than some of the other

components. However, as in the adaptive functioning data, there was a consistent pattern of impairment across all domains (Table 2.3). For the TS without ADHD subgroup, significant impairment was found across BRIEF domains, with the exception of inhibition (Appendix I).

Results from the objective EF tests showed significantly poorer performance on an ecologically-valid planning measure (BADS-C six part test) and an experimental measure of set-shifting (TEA-*Ch* RBBS) relative to normative means in both the heterogeneous TS and the TS without ADHD subgroup. Significantly lower scores were observed on an experimental test of sustained attention (vigil) in the heterogeneous TS group, but not in the TS without ADHD subgroup.

When impairment rates were compared across participants with and without ADHD, the parent-report EF measure showed significantly greater impairment in participants with comorbid ADHD. Interestingly, no significant associations were found between the groups on the objective measures, suggesting that difficulty in objective EF test performance was not exacerbated by comorbid ADHD.

There was no evidence to suggest poorer performance on ecologically-valid (BADS-C) compared to experimental (TEA-*Ch*) performance in either group in the normative contrasts or the impairment rate analyses.

Hayling performance showed a significant, detrimental effect of increased inhibition demands on both accuracy and RT in the heterogeneous TS group, although conclusions about this finding are limited without normative data. Intellectual functioning at the group level was largely unimpaired, though a wide range of scores was observed, spanning borderline and well above-average classifications.

## ***2.4.2. The effect of clinical variables on adaptive and executive functioning***

### ***2.4.2.1. Investigation of the effect of ADHD and OCD on adaptive functioning***

A hierarchical multiple regression was used to test whether levels of ADHD (SNAP-IV inattention, hyperactivity and oppositional defiant disorder, ODD) and OCD (CHOICI-R-P obsessive and compulsive symptoms) were significantly associated with adaptive behaviour composite scores. When the SNAP-IV data was entered in the first step, a significant regression equation was found ( $F(3, 35)=4.432, p=.010$ ), explaining 27.5% of the variance ( $R^2=.275$ ). When all data (SNAP-IV and CHOICI-R-P) were included, the regression equation remained significant ( $F(5,33)=3.005, p=.024$ ). Including the CHOICI-R-P data did not lead to a significant change to the model ( $p=.415$ ) and only led to a negligible increase (3.8%) in the percentage of variance explained ( $R^2=.313$ ).

For the CHOICI-R-P scores, standardized beta weights were  $-.192$  ( $t=-1.248, p=.221$ ) for obsessive symptoms and  $-.162$  ( $t=-1.036, p=.308$ ) for compulsive symptoms. These results indicated weak associative value of OCD levels on adaptive functioning, that were not statistically significant. A low level of multicollinearity was present in the CHOICI-R-P data (tolerance =  $.858, .844$  for obsessive and compulsive symptoms, respectively). Statistical information for the resulting model is provided in Table 2.5.

*Table 2.5. Regression statistics for the ADHD and OCD data*

	<i>B</i>	<i>SE B</i>	<i>B</i>	<i>t</i>	<i>p</i>
<b>Step 1</b>					
<b>Constant</b>	102.44	5.953		17.208	.000
<b>SNAP-IV Inattention</b>	-.510	.408	-.219	-1.251	.219
<b>SNAP-IV Hyperactivity</b>	-.548	.392	-.289	-1.395	.172
<b>SNAP-IV ODD</b>	-.224	.420	-.106	-.534	.597
<b>Step 2</b>					
<b>Constant</b>	112.512	9.875		11.394	.000
<b>SNAP-IV Inattention</b>	-.456	.423	-.196	-1.078	.289
<b>SNAP-IV Hyperactivity</b>	-.555	.394	-.293	-1.410	.168
<b>SNAP-IV ODD</b>	-.060	.445	-.029	-.136	.893
<b>CHOCI-R-P Obsessive symptoms</b>	-.508	.591	-.150	-.861	.396
<b>CHOCI-R-P Compulsive symptoms</b>	-.354	.667	-.094	-.531	.599

#### **2.4.2.2. Investigation of the effect of ADHD and OCD on BRIEF scores**

A hierarchical multiple regression was used to test whether levels of ADHD (SNAP inattention, hyperactivity and ODD) and OCD (CHOCI-R-P obsessive and compulsive symptoms) significantly impacted global executive composite scores. When the SNAP data was entered in the first step, a significant regression equation was found ( $F(3, 42)=31.808, p<.001$ ) explaining 69.4% of the variance ( $R^2=.694$ ). When all data (SNAP and CHOCI-R-P) were included, the regression equation remained significant ( $F(5,40)=19.418, p<.001$ ). Including the CHOCI-R-P data did not lead to a significant change to the model ( $p=.396$ ) and again only slightly increased (1.4%) the percentage of variance explained ( $R^2=.708$ ). Standardized beta weights for the CHOCI-R-P data were  $-.001$  ( $t=-.011, p=.992$ ) for obsessive symptoms and  $.114$  ( $t=-1.211, p=.233$ ) for compulsive symptoms. These results signaled a weak effect of OCD levels on adaptive functioning, that was not significant. A low level of multicollinearity was present in

the CHOCI-R-P data (tolerance = .847, .814 for obsessive and compulsive symptoms, respectively). Statistical information for the resulting model is provided in Table 2.6.

*Table 2.6. Regression statistics for ADHD / OCD data and BRIEF global composite score*

	<i>B</i>	<i>SE B</i>	<i>B</i>	<i>t</i>	<i>p</i>
<b>Step 1</b>					
<b>Constant</b>	47.546	2.633		18.055	.000
<b>SNAP Inattention</b>	.748	.169	.430	4.422	.000
<b>SNAP Hyperactivity</b>	.187	.170	.126	1.100	.278
<b>SNAP ODD</b>	.708	.169	.463	4.196	.000
<b>Step 2</b>					
<b>Constant</b>	45.141	4.303		10.492	.000
<b>SNAP Inattention</b>	.754	.170	.433	4.448	.000
<b>SNAP Hyperactivity</b>	.181	.170	.122	1.065	.293
<b>SNAP ODD</b>	.654	.182	.428	3.593	.001
<b>CHOCI-R-P</b>	-.178	.266	-.071	-.672	.505
<b>Obsessive symptoms</b>					
<b>CHOCI-R-P</b>	.406	.294	.149	1.378	.176
<b>Compulsive symptoms</b>					

#### *2.4.2.3. Summary: Effects of ADHD and OCD on adaptive and executive functioning*

The regression analyses indicated a strong effect of ADHD on adaptive, and a particularly potent impact on executive (parent-report) performance (explaining 27.5% and 69.4% of the variance, respectively). Inattention and hyperactivity elements of ADHD appeared to be particularly important to adaptive functioning (changing adaptive functioning scores by -.219 and -.289 when SNAP scores increase by one unit, respectively). Inattention and ODD items of the SNAP were particularly important to EF (changing EF scores by .430 and .463 when SNAP scores increase by one unit, respectively). Both for the adaptive and EF analyses, levels of OCD symptoms had only negligible, non-significant influence on adaptive functioning.

### ***2.4.3. Investigation of the effect of EF measures on adaptive functioning***

To assess the effect of EF performance on adaptive functioning, a stepwise multiple regression analysis was performed. Adaptive behaviour composite scores (VABS-3 ABC) were used as the dependent variable, and the impact of levels of ADHD and OCD were controlled for by entering these factors (SNAP Inattention, hyperactivity and ODD; CHOCI-R-P obsessive and compulsive symptoms) at block 1. To control for tic severity, YGTSS global impairment score was also included in block 1. A range of EF measures were entered at block 2 (Hayling (part 1 and part 2 accuracy and RT), BADS-C (zoo maps 1 and 2, and the six parts test, TEA-*Ch* II (vigil, simple RT and RBBS), and the BRIEF (BRI, MI and GEC)). To assess the contribution of intellectual functioning to adaptive behaviour, WISC-V-V FSIQ was also added in block 2.

The first model, used to control for the impact of the clinical variables on adaptive functioning, produced a significant model equation ( $F(6,24)=3.025, p=.024$ ) and accounted for 43.1% of the variance ( $R=.656, R^2=.431$ ). The second model included WISC-V FSIQ performance ( $F(7,23)=5.847, p=.001$ ), resulting in a significant change to the model ( $p=.001$ ) and this model including the clinical variables and WISC-V FSIQ data accounted for 64% of the variance ( $R=.800, R^2=.640$ ). The third model included BADS-C Zoo Map 2 scores with the above variables ( $F(7,23)=7.235, p<.001$ ), resulting in a significant change to the model ( $p=.016$ ), and the model accounted for 72.5% of the variance ( $R=.851, R^2=.725$ ). The final model included the clinical variables, WISC-V FSIQ, BADS-C zoo map 2 scores and BRIEF GEC, resulting in a significant model equation ( $F(9,21)=8.239, p<.001$ ), and a significant change to the model ( $p=.033$ ), which accounted for 77.9% of the variance ( $R=.883, R^2=.779$ ).

As such, results of the regression analysis provided partial confirmation for the research hypothesis: BADS-C zoo map 2 scores and the BRIEF general composite scores, as well as WISC-V FSIQ are a linear function of the participants' adaptive functioning scores ( $R = .883$ ,  $R^2 = .779$ ), with all other variables failing to pass the entry test ( $F$  tests: all  $p$ 's  $> .05$ ). Standardized beta weights were  $-.260$  ( $t = 3.727$ ,  $p = .023$ ) for BADS-C zoo map 2 scores,  $.449$  ( $t = -2.282$ ,  $p = .033$ ) for BRIEF general executive composite scores and  $.488$  ( $t = 3.727$ ,  $p = .001$ ) for WISC-V FSIQ. Tests for multicollinearity indicated that a low level of multicollinearity was present (tolerance =  $.614$ ,  $.935$  and  $.271$  for FSIQ, BADS-C zoo map 2 and BRIEF general executive composite scores, respectively). Statistical information for the resulting model is provided in Table 2.7.

*Table 2.7. Resulting model for the executive and adaptive functioning analyses<sup>5</sup>*

	<i>B</i>	<i>SE B</i>	<i>B</i>	<i>T</i>	<i>p</i>
<b>Final model</b>					
<b>Constant</b>	61.852	26.040		2.375	.027
<b>SNAP Inattention</b>	-.453	.377	-.197	-1.203	.242
<b>SNAP Hyperactivity</b>	.124	.292	.064	.426	.675
<b>SNAP ODD</b>	.244	.362	.120	.674	.508
<b>CHOCI-R-P Obsessive symptoms</b>	-1.337	.445	-.402	-3.008	.007
<b>CHOCI-R-P Compulsive Symptoms</b>	.481	.483	.139	.995	.331
<b>YGTSS Global Impairment Score</b>	.079	.111	.095	.715	.483
<b>WISC-V FSIQ</b>	.588	.158	.488	3.727	.001
<b>BADS-C Zoo Map 2</b>	1.308	.534	.260	2.451	.023
<b>BRIEF Global executive composite</b>	-.578	.253	-.449	-2.282	.033

<sup>5</sup> Excluded variables: Hayling part 1 (accuracy and RT), Hayling part 2 (accuracy and RT), BADS-C Zoo map 1 and Six Part test, TEA-Ch II Vigil, Simple RT and RBBS, BRIEF BRI and MI.

### 2.4.3.1. Correlational analyses

To test for associations between the various domains and subtests, correlational analyses were performed on the executive and adaptive functioning data. For brevity, only correlations between the executive and adaptive functioning measures are reported here. However, statistical information (Pearson's  $r$  statistics and significance indicators) on all combinations of correlational analyses performed are provided in Appendix J.

In terms of the objective neuropsychological executive measures, there was a significant positive correlation between TEA-*Ch* II Vigil performance and VABS-3 communication ( $r=.414$ ,  $N=41$ ,  $p=.004$ ) and daily living skills ( $r=.313$ ,  $N=37$ ,  $p=.030$ ). The TEA-*Ch* II simple RT data correlated positively with VABS-3 socialisation ( $r=.294$ ,  $N=40$ ,  $p=.033$ ). No other objective neuropsychological executive measures (BADS-C tests or TEA-*Ch* II RBBS) correlated with the adaptive functioning domains.

For the parent-report executive measure, several positive correlations with the adaptive functioning data were found. Negative correlations in the following statistics reflect higher scores indicating greater levels of impairment on the BRIEF, and lower scores indicating greater levels of impairment on the VABS-3. The BRIEF indexes (BRI, MI, GEC) correlated with all adaptive functioning domains: The BRIEF BRI data was significantly associated with communication ( $r=-.334$ ,  $N=44$ ,  $p=.013$ ), daily living skills ( $r=-.417$ ,  $N=39$ ,  $p=.004$ ), socialisation ( $r=.628$ ,  $N=42$ ,  $p<.001$ ) and adaptive behaviour composite scores ( $r=-.569$ ,  $N=39$ ,  $p<.001$ ). The BRIEF MI data correlated with communication ( $r=-.504$ ,  $N=40$ ,  $p<.001$ ), daily living skills ( $r=-.569$ ,  $N=36$ ,  $p<.001$ ), socialisation ( $r=-.654$ ,  $N=38$ ,  $p<.001$ ) and adaptive behaviour composite ( $r=.676$ ,  $N=36$ ,  $p<.001$ ). BRIEF Global Executive Composite correlated



with communication ( $r=-.506$ ,  $N=43$ ,  $p<.001$ ), daily living skills ( $r=-.566$ ,  $N=38$ ,  $p<.001$ ), socialisation ( $r=-.692$ ,  $N=41$ ,  $p<.001$ ) and adaptive behaviour composite ( $r=-.695$ ,  $N=38$ ,  $p<.001$ ).

#### ***2.4.3.2. Summary: effects on adaptive functioning***

In terms of effects on adaptive functioning, WISC-V FSIQ, BADS-C zoo map 2 scores and BRIEF GEC significantly impacted adaptive behaviour composite scores, and this effect was independent of influence from the clinical variables. Full-Scale IQ and BRIEF GEC were particularly important to adaptive functioning (changing adapting functioning scores by .488 and -.449 when these data increased by one unit, respectively, Table 2.7). Interestingly, BADS-C Zoo Map 2 scores also had an important influence on the adaptive functioning composite scores (changing adaptive functioning scores by .260 with every one-unit increase in these data, Table 2.7).

For the correlational analyses, that did not control for the clinical variables, the two sustained attention measures (TEA-*Ch* II vigil and simple RT) were significantly associated with select adaptive functioning domains (communication and daily living skills were related to vigil scores, and socialisation was associated with simple RT performance). For the parent-report EF data (BRIEF), indexes were significantly correlated with adaptive functioning domains, across all combinations.

Taken together, these analyses indicate that parent-report EF has an impact on adaptive functioning in children with TS. The significant correlations found between the BRIEF and VABS-3 scores across all components suggest that these associative effects are global rather than domain-specific. For the objective EF measures, experimental measures of sustained attention correlated with adaptive functioning domains, where ecologically-valid tests (BADS-C) and an experimental attentional

switching task (RBBS) did not. Interestingly, BADS-C zoo map 2, along with FSIQ performance, exerted a significant effect on VABS-3 adaptive behaviour composite scores.

#### ***2.4.4. Investigation of the effect of performance on objective executive functioning measures on BRIEF scores***

A stepwise multiple regression was used to test whether EF performance across a range of objective neuropsychological measures (Hayling (part 1 and part 2 accuracy and RT, and Part 2 errors), BADS-C (Zoo Maps 1 and 2, and the Six Parts Test) and TEA-*Ch* II (Vigil, Simple RT and RBBS) significantly impacted BRIEF global composite scores. The impact of levels of ADHD, OCD and tic severity were controlled for by entering these variables (SNAP Inattention, Hyperactivity and ODD; CHOCI-R-P obsessive and compulsive symptoms; and YGTSS global impairment score) at block 1. The contribution of intellectual functioning to EF was assessed by adding WISC-V FSIQ to the EF measures in block 2.

The first model, used to control for the impact of the clinical variables on EF, produced a significant model equation ( $F(6,31)=14.500, p<.001$ ) and accounted for 73.7% of the variance ( $R=.859, R^2=.737$ ). The second step produced a model that included BADS-C Zoo Map 1 performance ( $F(7,30)=16.323, p<.001$ ), resulting in a significant change to the model ( $p=.009$ ) and this model, comprised of the clinical variables and BADS Zoo Map 1 data accounted for 79.2% of the variance ( $R=.890, R^2=.792$ ). The final model included the TEA-*Ch* II RBBS data with the above variables ( $F(8, 29)=17.947, p<.001$ ), resulting in a significant change to the model ( $p=.014$ ), and accounting for 83.2% of the variance ( $R=.912, R^2=.832$ ).

These results suggest that BADS-C Zoo Map 1 scores and the TEA-*Ch* II RBBS data have an impact on participants' global BRIEF EF scores ( $R=.912$ ,  $R^2=.832$ ), with all other variables failing to pass the entry test for inclusion ( $F$  tests: all  $p$ 's  $>.05$ ). Standardized beta weights were  $-.975$  ( $t=-3.628$ ,  $p=.001$ ) for BADS-C zoo map 1 scores and  $-.666$  ( $t=2.625$ ,  $p=.014$ ) for TEA-*Ch* II RBBS scores. Tests for multicollinearity indicated a low level of multicollinearity (tolerance =  $.861$  and  $.904$  for BADS-C Zoo Map 1 and TEA-*Ch* II RBBS scores, respectively). Statistical information for the resulting model is provided in Table 2.8.

*Table 2.8. Resulting model for the objective executive test data and BRIEF analyses<sup>6</sup>*

	<i>B</i>	<i>SE B</i>	<i>B</i>	<i>t</i>	<i>p</i>
<b>Final model</b>					
<b>Constant</b>	57.809	5.278		10.952	.000
<b>SNAP Inattention</b>	.750	.149	.446	5.026	.000
<b>SNAP Hyperactivity</b>	.199	.178	.134	1.118	.273
<b>SNAP ODD</b>	.566	.180	.381	3.138	.004
<b>CHOCI-R-P Obsessive symptoms</b>	-.043	.246	-.018	-.175	.863
<b>CHOCI-R-P Compulsive Symptoms</b>	.281	.268	.105	1.048	.303
<b>YGTSS Global Impairment Score</b>	.050	.053	.080	.944	.353
<b>BADS-C Zoo Map 1</b>	-.975	.269	-.298	-3.628	.001
<b>TEA-<i>Ch</i> II RBBS</b>	-.666	.254	-.210	-2.625	.014

#### *2.4.4.1. Summary: effects of objective EF measures on parent-report EF*

Of all the objective executive measures, an ecologically-valid test under conditions of high planning demands (BADS-C Zoo Map 1) and a cognitively-taxing attentional switching task (TEA-*Ch* II RBBS) had strong, statistically significant impact on global BRIEF EF. These effects persisted after controlling for clinical variables, suggesting that these associations were not mediated by levels of (e.g.) ADHD. Interestingly,

<sup>6</sup> Excluded variables: Hayling part 1 (accuracy and RT), Hayling part 2 (accuracy, RT, type 1 and 2 errors), BADS-C Zoo Map 2 and Six Part test, TEA-*Ch* II Vigil, Simple RT and WISC-V FSIQ.

where WISC-V FSIQ significantly adaptive functioning, this factor did not have any significant effect on a parent-report EF measure.

#### ***2.4.5. Correlational analyses between the Hayling test and other executive functioning and adaptive functioning measures***

As normative data for the child version of the Hayling test were not available, correlational analyses were performed on the Hayling, parent-report EF (BRIEF) and adaptive functioning data, to explore any associative effects. The analyses used Hayling difference scores (part 2 minus part 1) for both accuracy and RT, the domains of the parent-report parent-report EF measure (BRIEF: BRI, MI, GEC and inhibit, as the Hayling task is designed to tap inhibition) and the adaptive functioning domains (VABS-3: communication, daily living skills, socialisation, and adaptive functioning composite). Pearson's  $r$  statistics for these analyses are provided in Table 2.9.

*Table 2.9. Pearson's r statistics for the Hayling, BRIEF and VABS-3 analyses<sup>7</sup>*

	<b>Hayling accuracy</b>	<b>Hayling RT</b>	<b>BRIEF Inhibit</b>	<b>BRIEF Behaviour Regulation Index</b>	<b>BRIEF Metacognition Index</b>	<b>BRIEF Global Executive Composite</b>	<b>VABS-3 Communication</b>	<b>VABS-3 Daily Living Skills</b>	<b>VABS-3 Socialisation</b>	<b>VABS-3 Adaptive Behaviour Composite</b>
<b>Hayling accuracy</b>	-	-.218	-.104	-.170	-.181	-.209	.180	.243	.138	.229
<b>Hayling RT</b>		-	.191	.086	.221	.170	.011	-.157	-.266*	-.126

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\* Correlation is significant at the 0.05 level (1-tailed).

Hayling RT difference scores were significantly negatively correlated with Vineland socialisation scores ( $r=-.266$ ,  $N=47$ ,  $p=.045$ ), reflecting lower socialisation indexes associated with greater RT cost when inhibition demands were increased. No other correlations were statistically significant (Table 2.9).

## **2.5. Discussion**

The current study aimed to investigate executive and adaptive functioning in a group of children with TS using a comprehensive, hypothesis-driven neuropsychology battery that also incorporated measures of clinical variables. The discussion points throughout this section correspond to the initial aims outlined in the Introduction.

### ***2.5.1. Do children with TS show impairment in adaptive and executive functioning compared to normative data?***

The heterogeneous group showed global adaptive functioning impairments, corroborating clinical observations of high prevalence rates of adaptive functioning in this population at a specialist clinic at GOSH. Domain-specific adaptive functioning impairments were observed in a subgroup of children without comorbid ADHD. The heterogeneous group was also impaired on a parent-report measure of EF (BRIEF), and the TS without ADHD group was also largely impaired on the BRIEF (on all domains with the exception of inhibition) which is consistent with previous findings (Mahone, Cirino, Cutting, Cerrone, Hagelthom, Hiemenz, 2002; Rasmussen et al., 2009).

In terms of objective measures of EF, deficient performance was found on an ecologically-valid test of planning, monitoring and scheduling (six parts test), but not on tests of route planning (zoo maps 1 & 2, BADS-C), in both heterogeneous and TS without ADHD groups. This pattern of performance might reflect differences in the skills recruited for these different planning tasks: For instance, zoo map tasks may enlist future-oriented aspects of planning such as prospection, involving skills in WM and updating (Ballhausen et al., 2017), whereas six part performance may relate to multi-tasking elements of planning (as in the adult version of the test, e.g. Bertens, Frankenmolen, Boelen, Kessels, & Fasotti, 2015). Studies testing planning abilities in children with TS using a six elements task (SET: Wilson, Alderman, Burgess, Emslie, & Evans, 1996), analogous to the BADS-C six part test, have found evidence of impairment in TS+ADHD, but not in uncomplicated TS, or TS+OCD (Channon et al., 2003). The current data are consistent with these findings, and suggest difficulties in multi-tasking, but not prospective aspects of planning in children with heterogeneous TS.

For the experimental EF measures, the heterogeneous TS group showed significantly reduced abilities on two experimental tests, designed to assess sustained and switching attention (TEA-*Ch* II vigil and RBBS, respectively), but not on another sustained attention test (simple RT), compared to normative means. The TS without ADHD group also showed impairment on the switching attention measure (RBBS), but not on either assessment of sustained attention. The finding of sustained attention impairment in the heterogeneous but not the TS without ADHD group could be attributed to ADHD exerting a particularly significant effect on measures of sustained attention (as suggested in Manly et al., 2001). No published studies reporting TEA-*Ch* II data in children with TS are available, but existing studies using other set-shifting

measures have generally shown preserved abilities in children with TS (Channon et al., 2003; Ozonoff & Jensen, 1999; Verté et al., 2005). Problematic performance in children with TS has been shown on a task involving intra-extra dimensional (IED) shifts (Rasmussen et al., 2009). Tasks requiring IED shifts involve acquisition of an initial rule relating to one dimension, followed by rule reversal to respond to a separate dimension of test stimuli. Although the RBBS test involves switching between decision type, participants are informed of the rule change, negating the need to acquire the rule independently. The finding that children with TS were impaired on this measure is interesting, and could be attributed to sensitivity of these computerised TEA-*Ch* II tasks in detecting deficits in set-shifting and inhibition in children with TS. The pattern of results observed in the EF data also indicates that the degree of EF deficit is likely to vary, depending on how EF is measured.

### ***2.5.2. Are deficits in executive functioning more identifiable on ecologically-valid measures than experimental tests?***

There was no evidence for significantly greater rates of impairment on ecologically-valid relative to experimental tests, either in the normative contrasts, or the comparisons of impairment rates. A large effect size was found on one of the ecologically valid tests (six parts, BADS-C), compared to medium effect sizes observed in the heterogenous TS TEA-*Ch* II data. The TS without ADHD group also showed a large effect size on the Six Part Test. The relative contributions of ecologically-valid and experimental executive test performance to parent-report executive functioning and adaptive functioning, under analysis conditions where levels of comorbid ADHD are controlled, are discussed later in this section (1.5.6. and 1.5.7.).



### ***2.5.3. Is inhibition impaired in children with TS?***

A recent meta-analysis demonstrated impaired cognitive inhibition in children (and adults) with TS (Morand-Beaulieu et al., 2017). The authors also found that these deficits were particularly visible on tasks requiring a verbal response. A child version of the Hayling sentence completion task employed in the current study showed a significant detrimental effect of increased cognitive inhibition demands on both accuracy and response latencies. However, without normative data for this measure, which is under development, any conclusions about whether this significant effect of higher inhibition demands is disproportionate in children with TS are limited.

The parent-report executive functioning results did not suggest more pronounced inhibition impairments compared to other EF components: BRIEF scores were globally impaired in the current sample, and greater impairment was evidenced on WM over the other indices, including inhibition. One possibility is that, although BRIEF inhibition was impaired compared to normative groups, there may be relative strengths in inhibition compared to other executive skills in children with TS. Strengths in inhibitory control in children with TS have been documented elsewhere (Jackson et al., 2011, 2013; Mueller et al., 2006), and it may be that well-developed tic suppression skills in children with TS could improve inhibitory control.

### ***2.5.4. What is the impact of clinical factors (ADHD, OCD, tic severity) on adaptive functioning and on a parental report measure of executive functioning (BRIEF)?***

Levels of ADHD had significant and strong effects on global indices of parent-report executive (BRIEF GEC) and adaptive (VABS-3 ABC) functioning, with particularly

strong effects on parent-report EF. Elevated scores on the BRIEF in young people with ADHD have been reported previously (Toplak, Bucciarelli, Jain, & Tannock, 2009). In contrast, levels of OCD exerted only weak, non-significant effects on these measures, a finding that appears at odds with existing studies reporting BRIEF impairment in OCD (Zandt, Prior, & Kyrios, 2009). In terms of adaptive functioning, deficits in children with ADHD are well-established (Sikora, Vora, Coury, & Rosenberg, 2012; Vriezen & Pigott, 2002b), and previous research has shown impaired scores on all VABS-3 domains (communication, daily living skills and socialisation) in children with OCD (Sukhodolsky et al., 2005).

#### ***2.5.5. Are there differences in performance of children with TS between domains of adaptive functioning?***

The child TS group were globally impaired on all domains of adaptive functioning, and no differences existed in scores across adaptive functioning domains. This result is at odds with the limited research in this area, which had demonstrated disproportionate impairment on socialisation relative to other domains (Gorman et al., 2010). However, the results are broadly consistent with these previous findings of adaptive functioning impairments in TS, and with clinical observations by the wider research team.

#### ***2.5.6. Is performance on specific executive functioning tests associated with adaptive behaviour?***

Independent of the impact of clinical variables (ADHD, OCD, tic severity), global executive composite scores (BRIEF GEC), ecologically-valid executive subtest performance (BADS-C zoo map 2), and WISC-V FSIQ exerted causal effects on

adaptive functioning. BRIEF executive composite score had an especially potent effect on adaptive functioning, indicating that executive problems negatively impact everyday adaptive skills in these children.

The finding that zoo map 2 test performance had an impact on adaptive functioning is interesting. Where zoo map 1 necessitates route planning without providing a structure, increasing planning demands, zoo map 2 performance provides a clear structure, reducing planning demands. Though the task does require the acquisition of and adherence to several rules, these same rules are already established in the previous trial. Therefore, in substantially reducing the executive component, relative to zoo map 1, performance on this task is likely to be moderated by lower-level cognitive processes, such as visual motor integration and processing speed. Visual motor integration (VMI) depends on visual perception, motor inhibition, fine motor co-ordination and sustained attention, and has been shown to be problematic in children with TS (Schultz et al., 1998). Problems with fine motor skills have also been found to predict poorer function and persistent tics in adulthood (Bloch, Sukhodolsky, Leckman, & Schultz, 2006). No studies exist that relate components of VMI to adaptive functioning in children with TS, but this has been investigated in other neurodevelopmental conditions. In children with ASD, causal associations have been found between fine motor skills and adaptive behaviour (Jasmin et al., 2009; Macdonald, Lord, & Ulrich, 2013), and this relationship may be reflected in the current pattern of results. Similarly, processing speed is likely to contribute to zoo map 2 performance. Zoo map 2 response latencies were associated with processing speed in (Oosterman, Wijers, & Kessels, 2013) while the impact of processing speed on a range of cognitive tests, including tests of executive functioning, has long been documented (Salthouse, 1996). At the group level, the only intellectual functioning domain to show

impairment in the TS group compared to normative means was processing speed. These relative weaknesses in processing speed may reflect difficulties in lower-level processing skills that are recruited during objective EF tests, and everyday adaptive behaviours.

Correlational analyses, that did not control for clinical variables, revealed significant associations between sustained attention performance and select adaptive functioning domains. The TEA-*Ch* II vigil performance was related to communication and daily living skills, and simple RT performance was related to socialisation. The finding that the two sustained attention measures correlated with separate adaptive domains is interesting, and could reflect differences inherent in the requirements of these tests. The vigil test, in assessing sustained attention under long and monotonous conditions, may assess this everyday requirement in everyday life (i.e. the necessity to complete tasks for which the child has little personal motivation) which may impact on daily living and communication skills. Simple RT performance was correlated with socialisation and this association could be mediated by the ability to attend and respond to social cues quickly. Similarly, an experimental measure of inhibition involving a verbal response (Hayling RT cost) was significantly correlated with adaptive socialisation, where successful real-world socialisation may closely depend on the ability to inhibit inappropriate verbal responses. Associations between inhibition and social competence have been observed in both typically developing children and children with ASD (McKown, Allen, Russo-Ponsaran, & Johnson, 2013; McKown, Gumbiner, Russo, & Lipton, 2009).

Interestingly, no ecologically valid tests correlated with adaptive functioning in this heterogeneous group. One possibility could be that comorbid ADHD symptoms were, disproportionately impacting data on these sustained attention measures (as

found in Manly et al., 2001), leading to associations with adaptive functioning in this heterogeneous TS group that may be mediated by ADHD.

It is interesting to consider these findings together with the result that an ecologically valid measure of EF was associated with adaptive functioning when clinical variables (including ADHD) were controlled, where the experimental measures did not. It may be that ecologically-valid tests of EF are more related to everyday adaptive abilities, and this association is more visible when effects of ADHD are minimised or controlled. Existing research offers partial support of this idea. The DKEFS battery, which incorporates the Tower tests, has high ecological validity (e.g. in associations with functional performance in the older adult population, Mitchell & Miller, 2008). On these tests, children with uncomplicated TS have shown impaired performance (Rasmussen et al., 2009; Termine et al., 2016) whereas only one of the three studies of heterogeneous child TS groups demonstrated impairment (planning deficit was indicated in a TS+ADHD group in Termine et al., 2016; but not in two heterogeneous TS groups: Ozonoff & Jensen, 1999; Verté et al., 2005). This finding warrants further research, and further emphasises the utility of including ecologically-valid tests in research studies (e.g. Isquith, Crawford, Espy, & Gioia, 2005).

The observed findings are broadly consistent with findings in the ASD literature that parent-report EF and adaptive functioning are related. However, the results suggest more global adaptive and parent-report EF deficits, and relationships between them, in children with TS, where BRIEF WM and initiation scores were selectively related to adaptive functioning in ASD (Happé et al., 2006).

### ***2.5.7. Which objective neuropsychological tests of executive functioning are associated with parent-report executive functioning scores?***

Given the strong impact of parent-report executive functioning on adaptive functioning, it was important to explore which objective neuropsychological executive measures were likely to load onto this construct. Regression analyses revealed significant effects of an ecologically-valid task where planning demands were high (BADS-C, zoo map 1) and a cognitively-taxing experimental measure of attentional shifting (TEA-Ch II, RBBS) on BRIEF global executive composite scores, independent of influence from clinical variables. These results suggest that planning and attentional shifting may be important mediators of parent-reported EF problems. Given that these tasks were among the more executively-demanding tests in the included battery, it is possible that increasing the complexity of objective tests may reveal limitations in children's executive skills, and that these difficulties may map onto executive difficulties observed at home. The findings provide evidence for convergence between objective neuropsychological and parental parent-report ratings of executive functioning, as has been demonstrated in a previous study of children with ADHD (Toplak et al., 2009), and indicate that parent-report EF measures effectively tap specific executive processes.

### ***2.5.8. Study strengths and limitations***

The current paper represents the first study to relate adaptive functioning to executive functioning in TS. The project benefitted from the use of a comprehensive participant pool, through links with a specialist clinic at GOSH. The analyses made good use of available normative data, and not requiring a control group enabled recruitment of a

large group of children with TS. The study generated some interesting and clinically relevant findings; that both adaptive and executive functioning may be impaired in children with TS, and that important relationships exist between the two abilities.

Tourette Syndrome is a highly heterogeneous condition, and existing studies in this area have often controlled for the effects of clinical variables through categorising participants in terms of uncomplicated or heterogeneous diagnoses. However, these approaches may be problematic. For instance, ADHD symptomology may be present in study groups, but these participants may be undiagnosed at the time of participation due to (e.g.) obstacles to observers noticing signs of ADHD across two settings, or where children demonstrate symptoms for less than six months, and therefore not meeting criteria for ADHD at the time of testing, despite being likely to meet diagnostic criteria in the future (DSM 5; American Psychiatric Association, 2013). Indeed, in the current sample, only 12 participants had received ADHD diagnoses, where 32 showed clinical impairment on the SNAP-IV. Measuring levels of clinical variables at the point of testing allowed for the control of these variables, and the inclusion of a TS without ADHD subgroup for the categorical analyses, while studying participants who closely represent this inherently heterogeneous clinical population.

The study was not without its limitations. Although broad contrasts with normative data were possible on most included tests to explore levels of impairment in the TS group, this was not the case for the child version of the Hayling test. Hayling data was used in the dimensional analyses, but the absence of normative data limited the conclusions about relative impairment in TS that could be drawn from these data. Across the measures, inclusion of a well-matched control group would have been ideal,

and could have enabled exploration of the correlational relationship between executive and adaptive functioning in typical development.

The study sample was recruited through a specialist national service. For this reason, although care was taken to include children at both the milder and more severe end of the spectrum, the sample may not be representative of children with TS.

The analyses included multiple comparisons (*t*-tests and correlations) that were uncorrected, and so may have increased the likelihood of type 1 error. Similarly, several potential predictors were entered into the regression analyses, which may be problematic (in increasing the possibility of suppression effects, for instance), given the relatively small sample size.

The potential impact of medication was not factored into the current study. Neuroleptics and alpha-2 agonists are often used to treat tics in TS (Scahill, Erenberg, Berlin, Budman, Coffey, Jankovic, ... & Walkup, 2006; Weisman, Qureshi, Leckman, Scahill, & Bloch, 2013), and there is evidence to suggest that neuroleptics affect performance on tests of inhibition (Sallee, Sethuraman, & Rock, 1994). Also, psychostimulants are frequently prescribed to treat ADHD (Erenberg, 2005) and these medications may improve inhibitory performance (Langleben, Monterosso, Elman, Ash, Krikorian, & Austin, 2006), but negatively impact children's set-shifting abilities (Rasmussen et al., 2009). Medication use was not controlled for in this sample, and so it is possible that these effects may have influenced results, perhaps particularly affecting performance on EF tests.



### **2.5.9. Conclusions**

The current study revealed significant impairments in adaptive functioning and executive functioning in a group of children with heterogeneous TS, and also in a subgroup of participants without ADHD. BRIEF executive functioning had a strong effect on adaptive functioning, and this relationship remained after controlling for clinical variables, including ADHD. Only one objective test of executive functioning had an effect on adaptive functioning (zoo map 2), which could be attributed to the contribution of lower-level skills related to EF (e.g. VMI and processing speed) to adaptive functioning.

In terms of correlational analyses, where clinical variables were uncontrolled, two tests of sustained attention (TEA-*Ch* II Vigil and Simple RT) and an inhibition measure (Hayling RT cost) were significantly associated with domains of adaptive functioning (vigil with communication and daily living skills, simple RT with socialisation and Hayling RT with socialisation), where no ecologically-valid executive tests were associated with adaptive functioning. Interestingly, ecologically-valid test performance was more related to adaptive functioning in TS when levels of ADHD were held constant.

These findings emphasise the importance of EF for adaptive functioning. Certainly, the parent-report measure of EF was particularly associated with adaptive functioning. However, significant associations between objective EF performance, together with findings that objective executive tests were causally associated with parent-report EF, emphasise the relevance of specific EF processes as tested by these objective neuropsychological measures, to adaptive functioning.

Taken together, the current findings suggest executive and adaptive functioning impairments in child TS, and that these constructs are associated, where

intellectual functioning was largely within normal ranges. These results have important implications for the treatment of children with TS: For instance, adopting neurocognitive strategies to improve EF may lead to generalised improvement in adaptive functioning in children with TS, positively impacting quality of life and independent functioning.

## **2.6 References**

- Alloway, T. P., & Alloway, R. G. (2013). Working memory across the lifespan: A cross-sectional approach. *Journal of Cognitive Psychology, 25*(1), 84–93.  
<https://doi.org/10.1080/20445911.2012.748027>
- American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). *Diagnostic and Statistical Manual of Mental Disorders 4th Edition TR.*, 280.  
<https://doi.org/10.1176/appi.books.9780890425596.744053>
- Anderson, V. (2001). *Developmental neuropsychology : a clinical approach. Brain damage, behaviour, and cognition.*
- Anderson, V. a, Anderson, P., Northam, E., Jacobs, R., & Catroppa, C. (2001). Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology, 20*(1), 385–406.  
[https://doi.org/10.1207/S15326942DN2001\\_5](https://doi.org/10.1207/S15326942DN2001_5)
- Ballhausen, N., Mahy, C. E. V., Hering, A., Voigt, B., Schnitzspahn, K. M., Lagner, P., ... Kliegel, M. (2017). Children’s planning performance in the Zoo Map task (BADs-C): Is it driven by general cognitive ability, executive functioning, or prospection? *Applied Neuropsychology: Child, 6*(2), 138–144.

<https://doi.org/10.1080/21622965.2015.1124276>

Berg, W. K., & Byrd, D. L. (2002). The Tower of London Spatial Problem-Solving Task: Enhancing Clinical and Research Implementation. *Journal of Clinical and Experimental Neuropsychology (Neuropsychology, Development and Cognition: Section A)*, 24(5), 586–604.

<https://doi.org/10.1076/jcen.24.5.586.1006>

Bertens, D., Frankenmolen, N., Boelen, D. H. E., Kessels, R. P. C., & Fasotti, L. (2015). Validity of an adapted scoring method for a Modified Six Elements Test in individuals with brain injury. *Archives of Clinical Neuropsychology*, 30(2), 122–129. <https://doi.org/10.1093/arclin/acu093>

Bloch, M. H., Sukhodolsky, D. G., Leckman, J. F., & Schultz, R. T. (2006). Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 47(6), 551–559.

<https://doi.org/10.1111/j.1469-7610.2005.01561.x>

Bornstein, R. A. (1990). Neuropsychological performance in children with Tourette's syndrome. *Psychiatry Res.*, 33(0165–1781 (Print)), 73–81.

Braun, A. R., Stoetter, B., Randolph, C., Hsiao, J. K., Vldar, K., Gernert, J., ... Chase, T. N. (1993). The functional neuroanatomy of Tourette's syndrome: an FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. *Neuropsychopharmacology*, 9(4), 277–291.

<https://doi.org/10.1038/npp.1993.64>

Burd, L., Kerbeshian, J., Wikenheiser, M., & Fisher, W. (1986). Prevalence of Gilles de la Tourette's syndrome in North Dakota adults. *American Journal of*

*Psychiatry*, 143(6), 787–788.

Burgess, P. & Shallice, T. (1997). *The Hayling and Brixton Tests. Test manual*. Bury St Edmunds, UK: Thames Valley Test Company.

Butler, R. W., Copeland, D. R., Fairclough, D. L., Mulhern, R. K., Katz, E. R., Kazak, A. E., ... Sahler, O. J. Z. (2008). A Multicenter, Randomized Clinical Trial of a Cognitive Remediation Program for Childhood Survivors of a Pediatric Malignancy. *Journal of Consulting and Clinical Psychology*, 76(3), 367–378. <https://doi.org/10.1037/0022-006X.76.3.367>

CANTAB (Cognitive Assessment Software). (2017), Cambridge.

Carter, A. S., O'Donnell, D. a., Schultz, R. T., Scahill, L., Leckman, J. F., & Pauls, D. L. (2000). Social and Emotional Adjustment in Children Affected with Gilles de la Tourette's Syndrome: Associations with ADHD and Family Functioning. *Journal of Child Psychology and Psychiatry*, 41(2), 215–223. <https://doi.org/10.1111/1469-7610.00602>

Case, R. (1992). The role of the frontal lobes in the regulation of cognitive development. *Brain and Cognition*, 20(1), 51–73. [https://doi.org/10.1016/0278-2626\(92\)90061-P](https://doi.org/10.1016/0278-2626(92)90061-P)

CASP. (2014). , (2015). Critical Appraisal Skills Programme (CASP). [online].

Chang, S. W., McCracken, J. T., & Piacentini, J. C. (2007). Neurocognitive correlates of child obsessive compulsive disorder and Tourette syndrome. *Journal of Clinical and Experimental Neuropsychology*, 29(7), 724–733. <https://doi.org/10.1080/13825580600966383>

Channon, S., Crawford, S., Vakili, K., & Robertson, M. M. (2003). Real-life-type problem solving in Tourette syndrome. *Cognitive and Behavioral Neurology*,

16(1), 3–15. <https://doi.org/10.1097/00146965-200303000-00002>

Channon, S., Pratt, P., & Robertson, M. M. (2003). Executive function, memory, and learning in Tourette's syndrome. *Neuropsychology, 17*(2), 247–254.

<https://doi.org/10.1037/0894-4105.17.2.247>

Channon, S., Sinclair, E., Waller, D., Healey, L., & Robertson, M. M. (2004). Social cognition in Tourette's syndrome: Intact theory of mind and impaired inhibitory functioning. *Journal of Autism and Developmental Disorders, 34*(6), 669–677.

<https://doi.org/10.1007/s10803-004-5287-x>

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991).

Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain, 114* (Pt 5), 2095–2122.

<https://doi.org/10.1093/brain/114.5.2095>

Crawford, S., Channon, S., & Robertson, M. M. (2005). Tourette's syndrome: performance on tests of behavioural inhibition, working memory and gambling. *Journal of Child Psychology and Psychiatry, 46*(12), 1327–1336.

<https://doi.org/10.1111/j.1469-7610.2005.01419.x>

Debes, N. M. M. M., Lange, T., Jessen, T. L., Hjalgrim, H., & Skov, L. (2011).

Performance on Wechsler intelligence scales in children with Tourette syndrome. *European Journal of Paediatric Neurology, 15*(2), 146–154.

<https://doi.org/10.1016/j.ejpn.2010.07.007>

Delis, DC., Kaplan, E., Kramer, J. (2001). *Examiner's Manual for the Delis-Kaplan Executive Function System. Child Neuropsychology* (Vol. 10).

<https://doi.org/10.1080/09297040490911140>

Delis, D., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan executive function system

(D-KEFS). *Canadian Journal of School Psychology*, 20(1–2), 117–128.

<https://doi.org/10.1177/0829573506295469>

Dempster, F. N. (1981). Memory span: Sources of individual and developmental differences. *Psychological Bulletin*, 89(1), 63–100.

<https://doi.org/10.1037/0033-2909.89.1.63>

Denckla, M. B. (2006). Attention deficit hyperactivity disorder: the childhood comorbidity that most influences the disability burden in Tourette syndrome. *Advances in Neurology*, 99, 17–21. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/16536349>

Diamond, A. (2014). Executive Functions. *Annual Review of Clinical Psychology*, 64, 135–168. <https://doi.org/10.1146/annurev-psych-113011-143750>. Executive

Diamond, A., & Goldman-Rakic, P. S. (1989). Comparison of human infants and rhesus monkeys on Piaget's AB task: evidence for dependence on dorsolateral prefrontal cortex. *Experimental Brain Research*, 74(1), 24–40.

<https://doi.org/10.1007/BF00248277>

Downes, JJ; Roberts, AC; Sahakian, BJ; Evenden, JL; Morris, RG & Robbins, T. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease. *Neuropsychologia*, 27, 1329–1343.

Drury, H., Shah, S., Stern, J. S., Crawford, S., & Channon, S. (2017).

Comprehension of direct and indirect sarcastic remarks in children and adolescents with Tourette's syndrome. *Child Neuropsychology*, pp. 1–20.

<https://doi.org/10.1080/09297049.2017.1284777>

Dykens, E., Leckman, J., Riddle, M., Hardin, M., Schwartz, S., & Cohen, D. (1990).

Intellectual, academic, and adaptive functioning of Tourette syndrome children with and without attention deficit disorder. *Journal of Abnormal Child Psychology*, 18(6), 607–615. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2074343>

Eddy, C. M., & Cavanna, A. E. (2015). Triangles, tricks and tics: Hyper-mentalizing in response to animated shapes in Tourette syndrome. *Cortex*, 71, 68–75. <https://doi.org/10.1016/j.cortex.2015.06.003>

Eddy, C. M., & Cavanna, A. E. (2017). Set-Shifting Deficits: A Possible Neurocognitive Endophenotype for Tourette Syndrome Without ADHD. *Journal of Attention Disorders*, 21(10), 824–834. <https://doi.org/10.1177/1087054714545536>

Eddy, C. M., Rickards, H. E., & Cavanna, A. E. (2012). Executive functions in uncomplicated Tourette syndrome. *Psychiatry Research*, 200(1), 46–48. <https://doi.org/10.1016/j.psychres.2012.05.023>

Eddy, C. M., Rizzo, R., & Cavanna, A. E. (2009). Neuropsychological aspects of Tourette syndrome: A review. *Journal of Psychosomatic Research*. <https://doi.org/10.1016/j.jpsychores.2009.08.001>

Emslie, H., Wilson, F. C., Burden, V., Nimmo-Smith, I., & Wilson, B. A. (2003). Behavioural Assessment of the Dysexecutive Syndrome (BADS). *Journal of Occupational Psychology, Employment and Disability*. <https://doi.org/10.1080/09602010802622730>

Erenberg, G. (2005). The Relationship Between Tourette Syndrome, Attention Deficit Hyperactivity Disorder, and Stimulant Medication: A Critical Review. *Seminars in Pediatric Neurology*, 12(4), 217–221.

<https://doi.org/10.1016/j.spen.2005.12.003>

- Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149. <https://doi.org/10.3758/BF03203267>
- Espy, K. A. (1997). The Shape School: Assessing Executive Function in Preschool Children. *Developmental Neuropsychology*, *13*(4), 495–499. <https://doi.org/10.1080/87565649709540690>
- Freedman, M. (1990). Object alternation and orbitofrontal system dysfunction in Alzheimer's and Parkinson's disease. *Brain and Cognition*, *14*(2), 134–143. [https://doi.org/10.1016/0278-2626\(90\)90025-J](https://doi.org/10.1016/0278-2626(90)90025-J)
- Gilotty, L., Kenworthy, L., Wagner, A. E., Sirian, L., & Black, D. O. (2002). Adaptive Skills and Executive Function in Autism Spectrum Disorders. *Child Neuropsychology (Neuropsychology, Development and Cognition: Section C)*, *8*(4), 241–248. <https://doi.org/10.1076/chin.8.4.241.13504>
- Gioia, G. a, Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Test Review: Behavior rating inventory of executive function. *Child Neuropsychology*, *6*(3), 235–238. <https://doi.org/10.1076/chin.6.3.235.3152>
- Godefroy, O., Cabaret, M., Petit-Chenal, V., Pruvo, J. P., & Rousseaux, M. (1999). Control functions of the frontal lobes. Modularity of the central-supervisory system? *Cortex*, *35*(1), 1–20. [https://doi.org/10.1016/S0010-9452\(08\)70782-2](https://doi.org/10.1016/S0010-9452(08)70782-2)
- Gorman, D. a, Thompson, N., Plessen, K. J., Robertson, M. M., Leckman, J. F., & Peterson, B. S. (2010). Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: controlled study. *The British Journal of Psychiatry : The Journal of Mental Science*, *197*(1), 36–44.



<https://doi.org/10.1192/bjp.bp.109.071050>

Goudriaan, A. E., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2006).

Neurocognitive functions in pathological gambling: A comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction*, *101*(4), 534–547. <https://doi.org/10.1111/j.1360-0443.2006.01380.x>

Grant, D. A., & Berg, E. (1948). A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem.

*Journal of Experimental Psychology*, *38*(4), 404–411.

<https://doi.org/10.1037/h0059831>

Greenberg, L. M. (2007). The Test of Variables of Attention (Version 7.3)

[Computer software]. Los Alamitos: The TOVA Company. (n.d.).

Groth, C., Mol Debes, N., Rask, C. U., Lange, T., & Skov, L. (2017). Course of

Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study.

*Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(4),

304–312. <https://doi.org/10.1016/j.jaac.2017.01.010>

Happé, F., Booth, R., Charlton, R., & Hughes, C. (2006). Executive function deficits

in autism spectrum disorders and attention-deficit/hyperactivity disorder:

Examining profiles across domains and ages. *Brain and Cognition*, *61*(1), 25–

39. <https://doi.org/10.1016/j.bandc.2006.03.004>

Harris, E.L., Schuerholz, L.J., Singer, H.S., Reader, M.J., Brown, J.E., Cox, C., et al.

(n.d.). Executive function in children with Tourette syndrome and/or attention

deficit hyperactivity disorder. *Journal of the International Neuropsychological*

*Society*, *1*(6), 511–.

Huckeba, W., Chapieski, L., Hiscock, M., & Glaze, D. (2008). Arithmetic

- performance in children with Tourette syndrome: Relative contribution of cognitive and attentional factors. *Journal of Clinical and Experimental Neuropsychology*, 30(4), 410–420. <https://doi.org/10.1080/13803390701494970>
- Isquith, P. K., Crawford, J. S., Espy, K. A., & Gioia, G. A. (2005). Assessment of executive function in preschool-aged children. *Mental Retardation and Developmental Disabilities Research Reviews*.  
<https://doi.org/10.1002/mrdd.20075>
- Jackson, S. R., Parkinson, A., Jung, J., Ryan, S. E., Morgan, P. S., Hollis, C., & Jackson, G. M. (2011). Compensatory neural reorganization in Tourette syndrome. *Current Biology*, 21(7), 580–585.  
<https://doi.org/10.1016/j.cub.2011.02.047>
- Jackson, S. R., Parkinson, A., Manfredi, V., Millon, G., Hollis, C., & Jackson, G. M. (2013). Motor excitability is reduced prior to voluntary movements in children and adolescents with Tourette syndrome. *Journal of Neuropsychology*, 7(1), 29–44. <https://doi.org/10.1111/j.1748-6653.2012.02033.x>
- Jasmin, E., Couture, M., McKinley, P., Reid, G., Fombonne, E., & Gisel, E. (2009). Sensori-motor and daily living skills of preschool children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39(2), 231–241.  
<https://doi.org/10.1007/s10803-008-0617-z>
- Jeter, C. B., Patel, S. S., Morris, J. S., Chuang, A. Z., Butler, I. J., & Sereno, A. B. (2015). Oculomotor executive function abnormalities with increased tic severity in Tourette syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 56(2), 193–202. <https://doi.org/10.1111/jcpp.12298>
- Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A

review of our current understanding. *Neuropsychology Review*.

<https://doi.org/10.1007/s11065-007-9040-z>

Kesler, S. R., Lacayo, N. J., & Jo, B. (2011). A pilot study of an online cognitive rehabilitation program for executive function skills in children with cancer-related brain injury. *Brain Injury*, 25(1), 101–112.

<https://doi.org/10.3109/02699052.2010.536194>

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, 55(4), 352–358.

<https://doi.org/10.1037/h0043688>

Klingberg, T., Vaidya, C. J., Gabrieli, J. D. E., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. *NeuroReport*, 10(13), 2817–2821.

<https://doi.org/10.1097/00001756-199909090-00022>

Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders*.

<https://doi.org/10.1002/mds.23868>

Lambek, R., Tannock, R., Dalsgaard, S., Trillingsgaard, A., Damm, D., & Thomsen, P. H. (2010). Validating neuropsychological subtypes of ADHD: How do children with and without an executive function deficit differ? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 51(8), 895–904.

<https://doi.org/10.1111/j.1469-7610.2010.02248.x>

Langleben, D. D., Monterosso, J., Elman, I., Ash, B., Krikorian, G., & Austin, G. (2006). Effect of methylphenidate on Stroop Color-Word task performance in children with attention deficit hyperactivity disorder. *Psychiatry Research*,

141(3), 315–320. <https://doi.org/10.1016/j.psychres.2005.09.007>

Larry, B., Jacob, K., Mark, W., & Wayne, F. (1986). A prevalence study of Gilles de la Tourette syndrome in North Dakota school-age children. *Journal of the American Academy of Child Psychiatry*, 25(4), 552–553. Retrieved from <http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=1987-28535-001&site=ehost-live&scope=site>

Lavoie, M. E., Thibault, G., Stip, E., & O'Connor, K. P. (2007). Memory and executive functions in adults with Gilles de la Tourette syndrome and chronic tic disorder. *Cognitive Neuropsychiatry*, 12(2), 165–181. <https://doi.org/10.1080/13546800600826371>

LECKMAN, J. F., RIDDLE, M. A., HARDIN, M. T., ORT, S. I., SWARTZ, K. L., STEVENSON, J., & COHEN, D. J. (1989). The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. *Journal of the American Academy of Child and Adolescent Psychiatry*, 28(4), 566–573. <https://doi.org/10.1097/00004583-198907000-00015>

Leckman, J. F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., ... Peterson, B. S. (1998). Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics*, 102(1 Pt 1), 14–19. <https://doi.org/10.1542/peds.102.1.14>

Lehto, J. (1996). Are Executive Function Tests Dependent on Working Memory Capacity? *The Quarterly Journal of Experimental Psychology*, 49A(1), 29–50. <https://doi.org/10.1080/713755616>

Lichter, D. G., & Finnegan, S. G. (2015). Influence of gender on Tourette syndrome beyond adolescence. *European Psychiatry*, 30(2), 334–340. <https://doi.org/10.1016/j.eurpsy.2014.07.003>

- Lombroso, P. J., & Scahill, L. (2008). Tourette syndrome and obsessive-compulsive disorder. *Brain & Development, 30*(4), 231–237.  
<https://doi.org/10.1016/j.braindev.2007.09.001>
- Luciana, M., & Nelson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia, 36*(3), 273–293. [https://doi.org/10.1016/S0028-3932\(97\)00109-7](https://doi.org/10.1016/S0028-3932(97)00109-7)
- Macdonald, M., Lord, C., & Ulrich, D. (2013). The relationship of motor skills and adaptive behavior skills in young children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 7*(11), 1383–1390.  
<https://doi.org/10.1016/j.rasd.2013.07.020>
- Mahone, E., Cirino, P., Cutting, L., Cerrone, P., Hagelthom, K., Hiemenz, J., et al. (2002). Validity of the Behavior Rating Inventory of Executive Function in children with ADHD and/or Tourette Syndrome. *Archives of Clinical Neuropsychology, 17*, 643–66.
- Manly, T., Anderson, V., Crawford, J., George, M., Underbjerg, M. & Robertson, I. (2016). *The Test of Everyday Attention for Children-II (TEA-Ch-2)*. Bury St Edmunds, UK: Thames Valley Test Company.
- Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., & Robertson, I. H. (2001). The Differential Assessment of Children's Attention: The Test of Everyday Attention for Children (TEA-Ch), Normative Sample and ADHD Performance. *Journal of Child Psychology and Psychiatry, 42*(8), 1065–1081.  
<https://doi.org/10.1111/1469-7610.00806>
- Mahone, E., Koth, C. W., Cutting, L., Singer, H. S., & Denckla, M. B. (2001).

Executive function in fluency and recall measures among children with Tourette syndrome or ADHD. *Journal of the International Neuropsychological Society*, 7(1), 102–111. <https://doi.org/10.1017/S1355617701711101>

Matsuda, N., Kono, T., Nonaka, M., Shishikura, K., Konno, C., Kuwabara, H., ... Kano, Y. (2012). Impact of obsessive-compulsive symptoms in Tourette's syndrome on neuropsychological performance. *Psychiatry and Clinical Neurosciences*, 66(3), 195–202. <https://doi.org/10.1111/j.1440-1819.2012.02319.x>

McKown, C., Allen, A., Russo-Ponsaran, N., & Johnson, J. (2013). Direct assessment of children's social-emotional comprehension. *Psychological Assessment*, 25, 1154–1166.

McKown, C., Gumbiner, L. M., Russo, N. M., & Lipton, M. (2009). Social-emotional learning skill, self-regulation, and social competence in typically developing and clinic-referred children. *Journal of Clinical Child and Adolescent Psychology*, 38(6), 858–871. <https://doi.org/10.1080/15374410903258934>

Mitchell, M., & Miller, L. S. (2008). Prediction of functional status in older adults: The ecological validity of four Delis-Kaplan Executive Function System tests. *Journal of Clinical and Experimental Neuropsychology*, 30(6), 683–690. <https://doi.org/10.1080/13803390701679893>

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*, 41(1), 49–100. <https://doi.org/10.1006/cogp.1999.0734>

- Moore, T. F., & Hollett, J. (2003). Giving voice to persons living with dementia: The researcher's opportunities and challenges. *Nursing Science Quarterly*, *16*(2), 163–167. <https://doi.org/10.1177/0894318403251793251793>
- Morand-Beaulieu, S., Grot, S., Lavoie, J., Leclerc, J. B., Luck, D., & Lavoie, M. E. (2017). The puzzling question of inhibitory control in Tourette syndrome: A meta-analysis. *Neuroscience and Biobehavioral Reviews*. <https://doi.org/10.1016/j.neubiorev.2017.05.006>
- Mueller, S. C., Jackson, G. M., Dhalla, R., Datsopoulos, S., & Hollis, C. P. (2006). Enhanced cognitive control in young people with Tourette's syndrome. *Current Biology*, *16*(6), 570–573. <https://doi.org/10.1016/j.cub.2006.01.064>
- Müller, S. V., Johannes, S., Wieringa, B., Weber, A., Müller-Vahl, K., Matzke, M., ... Münte, T. F. (2003). Disturbed monitoring and response inhibition in patients with Gilles de la Tourette syndrome and co-morbid obsessive compulsive disorder. *Behavioural Neurology*, *14*(1–2), 29–37. <https://doi.org/http://dx.doi.org/10.1155/2003/832906>
- O'Rourke, J. A., Scharf, J. M., Platko, J., Stewart, S. E., Illmann, C., Geller, D. A., ... Pauls, D. L. (2011). The familial association of Tourette's disorder and ADHD: The impact of OCD symptoms. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, *156*(5), 553–560. <https://doi.org/10.1002/ajmg.b.31195>
- Okeeffe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., & Murphy, T. (2014). Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: Attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, *20*(5), 557–582.

<https://doi.org/10.1080/09297049.2013.832740>

Oosterman, J. M., Wijers, M., & Kessels, R. P. C. (2013). Planning or something else? Examining neuropsychological predictors of zoo map performance.

*Applied Neuropsychology*, *20*(2), 103–109.

<https://doi.org/10.1080/09084282.2012.670150>

Osterrieth, P. A. (1944). Test of copying a complex figure; Contribution to the study of perception and memory. *Archives de Psychologie*, *30*, 206–356.

Ozonoff, S., & Jensen, J. (1999). Specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism and Developmental Disorders*, *29*(2), 171–177.

<https://doi.org/10.1023/A:1023052913110>

Ozonoff, S., & Strayer, D. L. (2001). Further Evidence of Intact Working Memory in Autism. *Journal of Autism and Developmental Disorders*, *31*(3), 257–263.

<https://doi.org/10.1023/A:1010794902139>

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal- lobe lesions in man. *Neuropsychologia*, *20*(3), 249–262.

[https://doi.org/10.1016/0028-3932\(82\)90100-2](https://doi.org/10.1016/0028-3932(82)90100-2)

Rasmussen, C., Soleimani, M., Carroll, A., & Hodlevskyy, O. (2009).

Neuropsychological functioning in children with Tourette syndrome (TS).

*Journal of the Canadian Academy of Child and Adolescent Psychiatry =*

*Journal de l'Académie Canadienne de Psychiatrie de l'enfant et de*

*l'adolescent*, *18*(4), 307–315. Retrieved from

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383%7B%7Dtool=pmcentrez%7B%7Drendertype=abstract%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383&tool=pmcentrez&rendertype=abst>

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383&tool=pmcentrez&rendertype=abst>

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383&tool=pmcentrez&rendertype=abst>



ract

- Redick, T. S., Broadway, J. M., Meier, M. E., Kuriakose, P. S., Unsworth, N., Kane, M. J., & Engle, R. W. (2012). Measuring working memory capacity with automated complex span tasks. *European Journal of Psychological Assessment, 28*(3), 164–171. <https://doi.org/10.1027/1015-5759/a000123>
- Reitan, R. W. D. (1985). The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation. *Tucson, AZ: Neuropsychological Press.*
- Robertson, M. M. (2011). Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *British Journal of Hospital Medicine (London, England : 2005), 72*(2), 100–107. <https://doi.org/10.12968/hmed.2011.72.2.100>
- Roizen, N. J., Blondis, T. A., Irwin, M., & Stein, M. (1994). Adaptive functioning in children with attention-deficit hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine, 148*(11), 1137–1142. <https://doi.org/10.1001/archpedi.1994.02170110023004>
- Ruff, R. M., Light, R. H., & Evans, R. W. (1987). The ruff figural fluency test: A normative study with adults. *Developmental Neuropsychology, 3*(1), 37–51. <https://doi.org/10.1080/87565648709540362>
- Sallee, F. R., Sethuraman, G., & Rock, C. M. (1994). Effects of pimozide on cognition in children with Tourette syndrome: interaction with comorbid attention deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica, 90*(1), 4–9. <https://doi.org/10.1111/j.1600-0447.1994.tb01546.x>
- Salthouse, T. A. (1996). The Processing-Speed Theory of Adult Age Differences in Cognition. *Psychological Review, 103*(3), 403–428. <https://doi.org/10.1037/0033-295X.103.3.403>

- Scahill, L., Erenberg, G., Berlin, C. M., Budman, C., Coffey, B. J., Jankovic, J., ... Walkup, J. (2006). Contemporary Assessment and Pharmacotherapy of Tourette Syndrome. *NeuroRx*, 3(2), 192–206. <https://doi.org/10.1016/j.nurx.2006.01.009>
- Scahill, L., Williams, S., Schwab-Stone, M., Applegate, J., Leckman, J. F., Walkup, J. T., ... Hollenbeck, P. J. (2006). Disruptive Behavior Problems in a Community Sample of Children with Tic Disorders. In *Advances in neurology: Tourette syndrome (Vol. 99)*. (pp. 184–190). Retrieved from <http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2006-06768-018&site=ehost-live>
- Scharf, J. M., Miller, L. L., Mathews, C. A., & Ben-Shlomo, Y. (2012). Prevalence of Tourette syndrome and chronic tics in the population-based Avon Longitudinal Study of Parents and Children cohort. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51(2), 192–201. <https://doi.org/10.1016/j.jaac.2011.11.004>
- Schuerholz, L. J., Baumgardner, T. L., Singer, H. S., Reiss, A. L., & Denckla, M. B. (1996). Neuropsychological status of children with Tourette's syndrome with and without attention deficit hyperactivity disorder. *Neurology*, 46(4), 958–965. <https://doi.org/10.1212/WNL.46.4.958>
- Schuerholz, L. J., Singer, H. S., & Denckla, M. B. (1998). Gender study of neuropsychological and neuromotor function in children with Tourette syndrome with and without attention-deficit hyperactivity disorder. *Journal of Child Neurology*, 13(6), 277–282. <https://doi.org/10.1177/088307389801300607>
- Schultz, R. T., Carter, A. S., Gladstone, M., Scahill, L., Leckman, J. F., Peterson, B.

- S., ... Pauls, D. (1998). Visual-motor integration functioning in children with Tourette syndrome. *Neuropsychology*, *12*(1), 134–145.  
<https://doi.org/10.1037/0894-4105.12.1.134>
- Selemon, L. D. (2013). A role for synaptic plasticity in the adolescent development of executive function. *Transl Psychiatry*, *3*(3), e238.  
<https://doi.org/10.1038/tp.2013.7>
- Shafran, R., Frampton, I., Heyman, I., Reynolds, M., Teachman, B., & Rachman, S. (2003). The preliminary development of a new self-report measure for OCD in young people. *Journal of Adolescence*, *26*(1), 137–142.  
[https://doi.org/10.1016/S0140-1971\(02\)00083-0](https://doi.org/10.1016/S0140-1971(02)00083-0)
- Shimoni, M., Engel-Yeger, B., & Tirosh, E. (2012). Executive dysfunctions among boys with Attention Deficit Hyperactivity Disorder (ADHD): Performance-based test and parents report. *Research in Developmental Disabilities*, *33*(3), 858–865. <https://doi.org/10.1016/j.ridd.2011.12.014>
- Siegel, L. S. (1994). Working Memory and Reading: A Life-span Perspective. *International Journal of Behavioral Development*, *17*(1), 109–124.  
<https://doi.org/10.1177/016502549401700107>
- Sikora, D. M., Vora, P., Coury, D. L., & Rosenberg, D. (2012). Attention-Deficit/Hyperactivity Disorder Symptoms, Adaptive Functioning, and Quality of Life in Children With Autism Spectrum Disorder. *Pediatrics*, *130*(Supplement 2), S91–S97. <https://doi.org/10.1542/peds.2012-0900G>
- Simon, H. A. (1975). The functional equivalence of problem solving skills. *Cognitive Psychology*, *7*(2), 268–288. [https://doi.org/10.1016/0010-0285\(75\)90012-2](https://doi.org/10.1016/0010-0285(75)90012-2)
- Singer, H. S. (2011). *Tourette syndrome and other tic disorders. Handbook of*

*Clinical Neurology* (Vol. 100). <https://doi.org/10.1016/B978-0-444-52014-2.00046-X>

Sparrow, S. S., Cicchetti, D. V., & Saulnier, C. A. (2016). *The Vineland Adaptive Behavior Scales-third edition*. American Guidance Service; Circle Pines, MN.

Stern, J. S., Burza, S., & Robertson, M. M. (2005). Gilles de la Tourette's syndrome and its impact in the UK. *Postgraduate Medical Journal*, *81*(951), 12–19.

<https://doi.org/10.1136/pgmj.2004.023614>

Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research*, *63*(3–4), 289–298.

<https://doi.org/10.1007/s004269900007>

Sukhodolsky, D. G., do Rosario-Campos, M. C., Scahill, L., Katsovich, L., Pauls, D. L., Peterson, B. S., ... Leckman, J. F. (2005). Adaptive, emotional, and family functioning of children with obsessive-compulsive disorder and comorbid attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, *162*(6), 1125–1132. <https://doi.org/10.1176/appi.ajp.162.6.1125>

Sukhodolsky, D. G., Scahill, L., Zhang, H., Peterson, B. S., King, R. A., Lombroso, P. J., ... Leckman, J. F. (2003). Disruptive behavior in children with Tourette's syndrome: Association with ADHD comorbidity, tic severity, and functional impairment. *Journal of the American Academy of Child and Adolescent Psychiatry*, *42*(1), 98–105. <https://doi.org/10.1097/00004583-200301000-00016>

Swanson, J. M. (1995). *SNAP-IV Scale*. Irvine, CA: University of California Child Development Center.

Termine, C., Luoni, C., Fontolan, S., Selvini, C., Perego, L., Pavone, F., ... Cavanna, A. E. (2016). Impact of co-morbid attention-deficit and hyperactivity disorder

on cognitive function in male children with Tourette syndrome: A controlled study. *Psychiatry Research*, 243, 263–267.

<https://doi.org/10.1016/j.psychres.2016.06.048>

Toplak, M. E., Bucciarelli, S. M., Jain, U., & Tannock, R. (2009). Executive functions: Performance-based measures and the behavior rating inventory of executive function (BRIEF) in adolescents with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology*, 15(1), 53–72.

<https://doi.org/10.1080/09297040802070929>

Uher, R., Heyman, I., Turner, C. M., & Shafran, R. (2008). Self-, parent-report and interview measures of obsessive-compulsive disorder in children and adolescents. *Journal of Anxiety Disorders*, 22(6), 979–990.

<https://doi.org/10.1016/j.janxdis.2007.10.001>

van't Hooft, I., Andersson, K., Bergman, B., Sejersen, T., von Wendt, L., & Bartfai, A. (2005). Beneficial effect from a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study. *Brain Injury*, 19(7), 511–518. <https://doi.org/10.1080/02699050400025224>

Verté, S., Geurts, H. M., Roeyers, H., Oosterlaan, J., & Sergeant, J. A. (2005). Executive functioning in children with autism and Tourette syndrome. *Development and Psychopathology*.

<https://doi.org/10.1017/S0954579405050200>

Vriezen, E. R., & Pigott, S. E. (2002a). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Child Neuropsychology*, 8(4), 296–303. <https://doi.org/10.1076/chin.8.4.296.13505>

- Vriezen, E. R., & Pigott, S. E. (2002b). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Special Issue: Behavior Rating Inventory of Executive Function (BRIEF)*, 8(4), 296–303.  
<https://doi.org/http://dx.doi.org/10.1076/chin.8.4.296.13505>
- Wåhlstedt, C., Thorell, L. B., & Bohlin, G. (2009). Heterogeneity in ADHD: Neuropsychological pathways, comorbidity and symptom domains. *Journal of Abnormal Child Psychology*, 37(4), 551–564. <https://doi.org/10.1007/s10802-008-9286-9>
- Watkins, L. H., Sahakian B. J., Robertson, M. M., Veale, D. M., Rogers, R. D., Pickard, K. M., ... Robbins, T. W. (2005). Executive function in Tourette's syndrome and obsessive–compulsive disorder. *Psychological Medicine*, 35(4), 571–582. <https://doi.org/10.1017/S0033291704003691>
- Wechsler, D. (n.d.). *Wechsler intelligence scale for children-fifth edition*.  
Bloomington, MN: Pearson.
- Weisman, H., Qureshi, I. A., Leckman, J. F., Scahill, L., & Bloch, M. H. (2013). Systematic review: Pharmacological treatment of tic disorders - Efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neuroscience and Biobehavioral Reviews*. <https://doi.org/10.1016/j.neubiorev.2012.09.008>
- Welsh, M. C., Pennington, B. F., & Groisser, D. B. (1991). A Normative-Developmental Study of Executive Function: A Window on Prefrontal Function in Children. *Developmental Neuropsychology*, 7(2), 131–149.  
<https://doi.org/10.1080/87565649109540483>
- White, S. J., Burgess, P. W., & Hill, E. L. (2009). Impairments on “open-ended”

executive function tests in Autism. *Autism Research*, 2(3), 138–147.

<https://doi.org/10.1002/aur.78>

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H. and Evans, J. J. (1996).

*Behavioural Assessment of Dysexecutive Syndrome*. Bury St. Edmunds, , UK:

Thames Valley Test Company.

Wilson, BA; Alderman, N; Burgess, PW; Emslie, H; Evans, J. (1996). The

behavioural assessment of the dysexecutive syndrome. *Thames Valley*

*Company; Bury St Edmunds*.

Yaniv, A., Benaroya-Milshtein, N., Steinberg, T., Ruhrrman, D., Apter, A., &

Lavidor, M. (2017). Specific executive control impairments in Tourette

syndrome: The role of response inhibition. *Research in Developmental*

*Disabilities*, 61, 1–10. <https://doi.org/10.1016/j.ridd.2016.12.007>

Zandt, F., Prior, M., & Kyrios, M. (2009). Similarities and differences between

children and adolescents with autism spectrum disorder and those with

obsessive compulsive disorder. *Autism*, 13(1), 43–57.

<https://doi.org/10.1177/1362361308097120>

## **Part 3: Critical Appraisal**

### **3.1. Introduction**

This appraisal outlines some of the key insights I have gained through conducting the thesis work. The first section describes some reflections on completing neuropsychological research with children and young people with Tourette Syndrome (TS) and associated neurodevelopmental conditions (ADHD), including difficulties in establishing boundaries between clinical and research work, and the process of feeding back results. The second concerns dilemmas that arose during the research, and how they were overcome. The third section appraises my experience of the research process, including discussion of joint working, ethical approval processes, applying for research funding, and data collection, and the final section outlines some limitations of quantitative research methodologies.

The motivation for conducting this research was the clinical observation that the hundreds of children with tic disorders that access the specialist clinic at Great Ormond Street Hospital each year often show signs of impaired adaptive functioning. The research aimed to test whether children with TS showed adaptive functioning deficits on objective testing, and to assess the potential contribution of executive functioning problems. The research also investigated if any observed deficits were due to TS diagnosis, or levels of comorbid conditions (e.g, ADHD).

### **3.2. Reflections on conducting neuropsychological assessment with children with TS, and associated neurodevelopmental conditions**

Prior to undertaking this research, I had not worked with children. Across the testing sessions I was struck by how enthusiastic and engaged the child participants were



during these extensive assessments. I was also impressed by the openness and knowledge of the participating families, in discussing their child's conditions and the impact they have on daily life. However, many of the child participants found at least some of the tasks difficult or tedious, and I often felt conflicted between the will to protect participants from any potential upset, fatigue or boredom and the need to collect the data. As a result, and as promised in our ethics application, I checked in with the child frequently and offering regular breaks. Surprisingly though, given my initial concerns about testing children on such a comprehensive battery, my experiences of testing showed that although there were instances of boredom, all children were motivated to complete the tests, none were distressed, and most reported having enjoyed the session.

Throughout data collection, I was concerned with the range of potential factors that may impact on neuropsychological performance and results: TS is a highly heterogeneous condition, and although the most common comorbidities were assessed and factored into the analysis (ADHD and OCD), not all conditions were measured (e.g. depression). Even controlling for the identified common comorbidities was problematic. For instance, to establish an ADHD diagnosis, clinical levels of ADHD need to be reported across two settings, e.g. home and school report reaching clinical threshold (DSM 5; American Psychiatric Association, 2013). However, ADHD symptoms may be less visible in a classroom environment, particularly where children present with ADHD symptoms which are not experienced as disruptive. It may also be that children were recruited before showing symptoms for six months, and therefore not meeting criteria for ADHD at the time of testing, despite being likely to meet diagnostic criteria in the future. The inherent heterogeneity in children with TS led me to look at levels of comorbidities at the point of testing, rather than the presence or

absence of a formal diagnosis (as adopted by group study methodologies that categorise participants in terms of uncomplicated TS and TS with other diagnoses).

One element that was not considered in this research was the potential impact of medication. Neuroleptics and alpha-2 agonists are frequently prescribed to treat tics in TS (Scahill, Erenberg, et al., 2006; Weisman et al., 2013), and there is evidence to suggest that use of neuroleptics alters inhibitory performance (Sallee et al., 1994). Similarly, psychostimulants are frequently used to treat ADHD (Erenberg, 2005) and may improve inhibitory performance (Langleben et al., 2006), but negatively impact children's ability to set-shift (Rasmussen et al., 2009). As medication use was not controlled for, it is possible that these effects may have influenced results, perhaps especially affecting performance on tests of executive functioning.

There were likely to be other confounding variables relating to differences in test conditions across the assessment sessions. For instance, the extent to which each child was comfortable in this relatively novel and artificial situation, and the quality of the working relationship between the researcher and participant likely had a bearing on results. Though both researchers were sensitive to signs of anxiety in these young participants, it is impossible to know the extent to which these factors were present at the time of testing, and how they may have influenced performance.

At the time of data collection, I was also working clinically with the team through which the participants were recruited while on placement. This presented some difficulties, whereby parents of children would (very understandably) approach me at the end of the session for advice on managing their child's condition and other presenting problems. As a team, we had established guidance for these instances (to make clear the boundary between clinical and research work, and to suggest

approaching the GP or paediatrician for a re-referral where appropriate). However, spending time with these children collecting research data where there were other presenting problems that I may have been able to offer intervention for often felt difficult.

Throughout the project, I also considered the meaning families might make of being included in a project that has hypothesised that children with TS might present with a range of difficulties that may not have been identified previously. I wondered about the anxieties that families might have about new difficulties being uncovered, and how research participation may have reinforced ideas that their child is somehow 'different' in their cognitive abilities and independent functioning. However, I was also often under the impression that families were pleased to have input from someone with some insight into TS, who was interested in finding out more.

### **3.3. Research challenges and dilemmas and how they were overcome**

I was keen to offer the participants something meaningful in return for their valued contribution to the project, and so it was decided to offer a summary of neuropsychological performance (in child and parent formats). Participating families could choose whether or not they wished to receive these reports, although families unanimously opted to receive this feedback. The reports were of clear value, potentially informing schools about areas where each child may require more support, for instance. However, most of my clinical experiences of neuropsychological assessments have involved feeding back results in face-to-face clinical sessions, and posting written reports made it more difficult to relay the results sensitively. I was concerned about alarming children and their families in instances of performance

outside of 'normal' ranges, without having the opportunity to clarify the meaning of these observations, make clinical referrals or ensure other support was put in place, as I would do clinically. To overcome these difficulties, a real effort was made to word the reports carefully, and each report was reviewed and signed off by an experienced Clinical Psychologist in the team at Great Ormond Street Hospital. Participants were also provided with a contact number for the clinical team should they wish to discuss the results, and would be encouraged to make a referral to the team through their GP should they remain concerned after this conversation.

Another dilemma that arose during the project planning stages was in balancing the number of measures I was interested in running with the amount of time that the neuropsychological testing was likely to take. In terms of theoretical and clinical interest, I was keen to run several executive functioning measures, including experimental tests (TEA-Ch II), and a specific measure of inhibition (Hayling), along with ecologically valid tests (BADSC) and a parent-report measure (BRIEF). However, this needed to be balanced with considerations of overall battery length, especially as the testing also incorporated current IQ testing (WISC) and time processing experiments, which were needed for my colleague's project with whom I was joint working. As well as wanting to make the children's experience of participating as enjoyable as possible, it was also possible that fatigue could affect the data, with executive functioning and attentional measures being perhaps especially vulnerable to this effect. To resolve these conflicting needs, we considered each measure and, in discussion with the research team, selected only the most theoretically important tests (i.e. using only select components of the BADSC and TEA-Ch batteries).

Before undertaking this project, I had only worked on neuropsychological research where a test group (typically participants who had received a given diagnosis or had suffered a neurological incident) was compared with a matched control group. However, the current project was focussed on a highly heterogeneous neurodevelopmental group, and recruiting a greater number of these participants was prioritised over the recruitment of matched controls, which would have rendered this already ambitious project unfeasible. As such, this project presented a methodological challenge. Standardised tests were used to make contrasts with published normative data possible. Statistically, this challenge was overcome by computing z scores and conducting difference testing (i.e. t tests) across the test group and test norms data. However, these comparison data were not always available (e.g. for the recently-developed child version of the Hayling). To resolve this, regression and correlation testing was used, to investigate if levels of given factors (e.g. tic severity, ADHD, OCD) moderated test performance, and whether executive test performance (e.g. on the Hayling) was associated with adaptive functioning ability. Although this approach involved learning new statistical methodology, I felt that this approach left me better able to maximise the outcomes that came from these data, and looking at levels of various comorbidities at the time of testing felt more realistic than grouping on the basis of comorbid diagnoses, given the concerns around potential under-diagnosis outlined in a previous section. This approach also helped me to benefit from the large amount of normative data already collected and reported in published test manuals, and I believe made for a much more interesting and efficient research process.

### **3.4. Reflections on the research process**

Here, I will outline some key reflections on the research process. The project was extremely ambitious, requiring NHS ethical approval, the acquisition of much-needed research funding through a grant application, learning a comprehensive child neuropsychology battery, the recruitment of 24 child participants, and entering each into a 2.5-hour assessment, usually in their homes at weekends, which required a great deal of travel. This work was completed while also needing to meet the typical various thesis written work deadlines and other course requirements, such as working on placement three days a week, completing other course-related work (e.g. case reports), and attending teaching. As such, at times it was very difficult to maintain a healthy work-life balance while completing this project, but it did help me to further develop organisation skills, and to prioritise certain tasks over others. There were several advantages of working on this project, in working with a specialist clinical team, and an experienced senior researcher at UCL, and the hope that I might be able to publish and disseminate the findings in the future. In what follows, I will discuss the practical, challenges of maintaining such a high workload, and offer some reflections on the elements that helped to lessen the demands and make the completion of the project possible.

#### **3.4.1. Ethical approval process**

Although I had had some involvement at certain levels of the ethical approval process while working on past projects, this was my first experience of co-leading (together with another trainee) an NHS ethics application and following this process through from start to end. I initially felt quite overwhelmed with the various elements of work needed (e.g. completing the IRAS (Integrated Research Application System))

application, projecting research timescales that were hard to estimate, writing age-appropriate versions of participant information and consent/assent sheets). The process involved a huge amount of continuous liaison with supervisors, a Research and Development team, and advisors at UCL, and as the application progressed, I became more comfortable with asking questions and addressing issues as they came up, which helped to speed up the process. Attending the ethics panel was interesting and it was a rare opportunity to speak to clinical professionals working in a wide range of clinical areas about the project. This helped me to learn skills in describing the project in a way that was accessible to people who do not have a background in neuropsychology, and to gain confidence in defending some of the project development decisions. The experience also raised some issues relating to participant reimbursement and incentive that I had not previously considered. For instance, we had initially proposed entering participants into a raffle to win a book token, but the panel raised concerns around this being potentially more incentivising to the parents than the children, and that having any monetary reward for participation may disproportionately pressurise those living in conditions of social deprivation into participating. The decision to offer summary reports, in a certificate format for children, and a more detailed format for adults was borne out of this discussion, as it was felt that information about children's neuropsychological abilities was similarly appealing to children and adults, and to families from different social economic backgrounds.

### **3.4.2. Applying for research funding**

In the early stages of planning the project, we realised that predicted project expenditure would not be covered by the UCL research funds available for DCLinPsy projects. This was due to the number of costly neuropsychological tests and score

sheets we needed to purchase, and travel costs involved in completing the participant visits. Consequently, we sent a preliminary application to a Tourette's charity who had an open call for research funding applications, Tourette's Action, for which we were later invited to submit a full application. This helped me to experience the reality of research work, in having to put together substantial written documents on top of an existing clinical and research workload, while tolerating the uncertainty of whether the application will be successful.

### **3.5.3. Participant recruitment**

I was able to recruit from a comprehensive database of (more than 1000) children who had accessed the specialist tic clinic at Great Ormond Street in recent years, and so identifying potential participants to contact was relatively straight-forward. However, there was great administrative burden involved in writing to these families, gauging interest, planning travel arrangements and scheduling in visits, which often took several phone calls. The visits sometimes presented greater challenges in maintaining appropriate boundaries when in families' homes. The families were often pleased to be able to talk about their child's condition with someone who had good understanding of Tourette's Syndrome and related neurodevelopmental conditions, and I was happy to provide a space to talk. However, I did feel very limited in terms of what I could offer, and found myself having to give answers that I think I would have found quite unsatisfactory (that this was part of a research session rather than a clinical appointment, and that the child could be re-referred through their GP or Paediatrician).



#### **3.4.4. Joint working**

I worked jointly on this project with a fellow trainee, Summer Fakhro. There were many practical advantages to conducting this project jointly: We recruited far more participants than we would have achieved individually, and we both benefitted from being able to share the project workload. Perhaps most beneficial though, was the working relationship we were able to develop, which was incredibly supportive, and collaborative rather than competitive from the outset. It was often useful to talk through aspects of the work together before seeking help from our supervisors, and to benefit from Summer's ideas, knowledge and expertise. I felt very much as though we were a team, in what could have been a very overwhelming and isolating experience if I had attempted the project alone. Working with clinical experts at Great Ormond Street Hospital, and a senior member of the research and teaching staff at UCL was incredibly useful, and I was able to learn a great deal about neurodevelopmental conditions, and research writing and methodology.

#### **3.5. Limitations of quantitative research**

The battery of tests employed involved several parent/carer-report measures, giving crucial measures of the levels of comorbid presentations, and an in-depth assessment of adaptive functioning. However, the use of these measures often felt restrictive, especially as many participating families reported not finding an answer category that they felt fit their child, and many wished to talk about their responses in greater detail. I was glad to offer families a space to discuss their child, and the moving challenges that they faced on a daily basis. In completing these questionnaires, listening to, empathising with, reflecting the key communication and asking the participant how this experience related each test item was effective in helping the participants feel heard while

also collecting data on these important issues (similar guidelines have been applied in dementia research, e.g. Moore & Hollett, 2003).

In conducting most of the assessments at children's homes, interacting with each child's close relatives, I was often left with perhaps a fairly thorough understanding of what life was like for each family, and the interaction styles within family systems, than if the child and one other adult relative was to attend a clinical appointment. This important information was not captured by the quantitative methodology used throughout this project, where a qualitative approach would have afforded greater flexibility to bring out these themes, that were apparent across my discussions with participating families. A qualitative approach would have represented a more collaborative research effort with participating families, in that the research focus may have evolved on the basis of what the children and families felt were salient issues. However, it is clear that a quantitative research methodology was needed in order to investigate the current research question, which was focussed on the relationship between different types of executive functioning on adaptive functioning domains.

### **3.6. References**

- Alloway, T. P., & Alloway, R. G. (2013). Working memory across the lifespan: A cross-sectional approach. *Journal of Cognitive Psychology*, 25(1), 84–93.  
<https://doi.org/10.1080/20445911.2012.748027>
- American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). *Diagnostic and Statistical Manual of Mental Disorders 4th Edition TR.*, 280.  
<https://doi.org/10.1176/appi.books.9780890425596.744053>
- Anderson, V. (2001). *Developmental neuropsychology : a clinical approach. Brain damage, behaviour, and cognition.*
- Anderson, V. a, Anderson, P., Northam, E., Jacobs, R., & Catroppa, C. (2001). Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology*, 20(1), 385–406.  
[https://doi.org/10.1207/S15326942DN2001\\_5](https://doi.org/10.1207/S15326942DN2001_5)
- Ballhausen, N., Mahy, C. E. V., Hering, A., Voigt, B., Schnitzspahn, K. M., Lagner, P., ... Kliegel, M. (2017). Children’s planning performance in the Zoo Map task (BADs-C): Is it driven by general cognitive ability, executive functioning, or prospection? *Applied Neuropsychology: Child*, 6(2), 138–144.  
<https://doi.org/10.1080/21622965.2015.1124276>
- Berg, W. K., & Byrd, D. L. (2002). The Tower of London Spatial Problem-Solving Task: Enhancing Clinical and Research Implementation. *Journal of Clinical and Experimental Neuropsychology (Neuropsychology, Development and Cognition: Section A)*, 24(5), 586–604.  
<https://doi.org/10.1076/jcen.24.5.586.1006>

- Bertens, D., Frankenmolen, N., Boelen, D. H. E., Kessels, R. P. C., & Fasotti, L. (2015). Validity of an adapted scoring method for a Modified Six Elements Test in individuals with brain injury. *Archives of Clinical Neuropsychology*, *30*(2), 122–129. <https://doi.org/10.1093/arclin/acu093>
- Bloch, M. H., Sukhodolsky, D. G., Leckman, J. F., & Schultz, R. T. (2006). Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*(6), 551–559. <https://doi.org/10.1111/j.1469-7610.2005.01561.x>
- Bornstein, R. A. (1990). Neuropsychological performance in children with Tourette's syndrome. *Psychiatry Res.*, *33*(0165–1781 (Print)), 73–81.
- Braun, A. R., Stoetter, B., Randolph, C., Hsiao, J. K., Vladar, K., Gernert, J., ... Chase, T. N. (1993). The functional neuroanatomy of Tourette's syndrome: an FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. *Neuropsychopharmacology*, *9*(4), 277–291. <https://doi.org/10.1038/npp.1993.64>
- Burd, L., Kerbeshian, J., Wikenheiser, M., & Fisher, W. (1986). Prevalence of Gilles de la Tourette's syndrome in North Dakota adults. *American Journal of Psychiatry*, *143*(6), 787–788.
- Burgess, P. & Shallice, T. (1997). *The Hayling and Brixton Tests. Test manual*. Bury St Edmunds, UK: Thames Valley Test Company.
- Butler, R. W., Copeland, D. R., Fairclough, D. L., Mulhern, R. K., Katz, E. R., Kazak, A. E., ... Sahler, O. J. Z. (2008). A Multicenter, Randomized Clinical Trial of a Cognitive Remediation Program for Childhood Survivors of a

Pediatric Malignancy. *Journal of Consulting and Clinical Psychology*, 76(3), 367–378. <https://doi.org/10.1037/0022-006X.76.3.367>

CANTAB (Cognitive Assessment Software). (2017), *Cambridge*.

Carter, A. S., O'Donnell, D. a., Schultz, R. T., Scahill, L., Leckman, J. F., & Pauls, D. L. (2000). Social and Emotional Adjustment in Children Affected with Gilles de la Tourette's Syndrome: Associations with ADHD and Family Functioning. *Journal of Child Psychology and Psychiatry*, 41(2), 215–223. <https://doi.org/10.1111/1469-7610.00602>

Case, R. (1992). The role of the frontal lobes in the regulation of cognitive development. *Brain and Cognition*, 20(1), 51–73. [https://doi.org/10.1016/0278-2626\(92\)90061-P](https://doi.org/10.1016/0278-2626(92)90061-P)

CASP. (2014). , (2015). Critical Appraisal Skills Programme (CASP). [online].

Chang, S. W., McCracken, J. T., & Piacentini, J. C. (2007). Neurocognitive correlates of child obsessive compulsive disorder and Tourette syndrome. *Journal of Clinical and Experimental Neuropsychology*, 29(7), 724–733. <https://doi.org/10.1080/13825580600966383>

Channon, S., Crawford, S., Vakili, K., & Robertson, M. M. (2003). Real-life-type problem solving in Tourette syndrome. *Cognitive and Behavioral Neurology*, 16(1), 3–15. <https://doi.org/10.1097/00146965-200303000-00002>

Channon, S., Pratt, P., & Robertson, M. M. (2003). Executive function, memory, and learning in Tourette's syndrome. *Neuropsychology*, 17(2), 247–254. <https://doi.org/10.1037/0894-4105.17.2.247>

Channon, S., Sinclair, E., Waller, D., Healey, L., & Robertson, M. M. (2004). Social

cognition in Tourette's syndrome: Intact theory of mind and impaired inhibitory functioning. *Journal of Autism and Developmental Disorders*, 34(6), 669–677.  
<https://doi.org/10.1007/s10803-004-5287-x>

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, 114 ( Pt 5, 2095–2122.  
<https://doi.org/10.1093/brain/114.5.2095>

Crawford, S., Channon, S., & Robertson, M. M. (2005). Tourette's syndrome: performance on tests of behavioural inhibition, working memory and gambling. *Journal of Child Psychology and Psychiatry*, 46(12), 1327–1336.  
<https://doi.org/10.1111/j.1469-7610.2005.01419.x>

Debes, N. M. M. M., Lange, T., Jessen, T. L., Hjalgrim, H., & Skov, L. (2011). Performance on Wechsler intelligence scales in children with Tourette syndrome. *European Journal of Paediatric Neurology*, 15(2), 146–154.  
<https://doi.org/10.1016/j.ejpn.2010.07.007>

Delis, DC., Kaplan, E., Kramer, J. (2001). *Examiner's Manual for the Delis-Kaplan Executive Function System*. *Child Neuropsychology* (Vol. 10).  
<https://doi.org/10.1080/09297040490911140>

Delis, D., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan executive function system (D-KEFS). *Canadian Journal of School Psychology*, 20(1–2), 117–128.  
<https://doi.org/10.1177/0829573506295469>

Dempster, F. N. (1981). Memory span: Sources of individual and developmental differences. *Psychological Bulletin*, 89(1), 63–100.  
<https://doi.org/10.1037/0033-2909.89.1.63>

Denckla, M. B. (2006). Attention deficit hyperactivity disorder: the childhood co-morbidity that most influences the disability burden in Tourette syndrome.

*Advances in Neurology*, 99, 17–21. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/16536349>

Diamond, A. (2014). Executive Functions. *Annual Review of Clinical*

*Psychology*, 64, 135–168. [https://doi.org/10.1146/annurev-psych-](https://doi.org/10.1146/annurev-psych-113011-143750)

113011-143750.Executive

Diamond, A., & Goldman-Rakic, P. S. (1989). Comparison of human infants and

rhesus monkeys on Piaget's AB task: evidence for dependence on dorsolateral prefrontal cortex. *Experimental Brain Research*, 74(1), 24–40.

<https://doi.org/10.1007/BF00248277>

Downes, JJ; Roberts, AC; Sahakian, BJ; Evenden, JL; Morris, RG & Robbins, T.

(1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease. *Neuropsychologia*, 27, 1329–1343.

Drury, H., Shah, S., Stern, J. S., Crawford, S., & Channon, S. (2017).

Comprehension of direct and indirect sarcastic remarks in children and adolescents with Tourette's syndrome. *Child Neuropsychology*, pp. 1–20.

<https://doi.org/10.1080/09297049.2017.1284777>

Dykens, E., Leckman, J., Riddle, M., Hardin, M., Schwartz, S., & Cohen, D. (1990).

Intellectual, academic, and adaptive functioning of Tourette syndrome children with and without attention deficit disorder. *Journal of Abnormal Child*

*Psychology*, 18(6), 607–615. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/2074343>

Eddy, C. M., & Cavanna, A. E. (2015). Triangles, tricks and tics: Hyper-mentalizing

in response to animated shapes in Tourette syndrome. *Cortex*, 71, 68–75.

<https://doi.org/10.1016/j.cortex.2015.06.003>

Eddy, C. M., & Cavanna, A. E. (2017). Set-Shifting Deficits: A Possible Neurocognitive Endophenotype for Tourette Syndrome Without ADHD. *Journal of Attention Disorders*, 21(10), 824–834.

<https://doi.org/10.1177/1087054714545536>

Eddy, C. M., Rickards, H. E., & Cavanna, A. E. (2012). Executive functions in uncomplicated Tourette syndrome. *Psychiatry Research*, 200(1), 46–48.

<https://doi.org/10.1016/j.psychres.2012.05.023>

Eddy, C. M., Rizzo, R., & Cavanna, A. E. (2009). Neuropsychological aspects of Tourette syndrome: A review. *Journal of Psychosomatic Research*.

<https://doi.org/10.1016/j.jpsychores.2009.08.001>

Emslie, H., Wilson, F. C., Burden, V., Nimmo-Smith, I., & Wilson, B. A. (2003). Behavioural Assessment of the Dysexecutive Syndrome (BADS). *Journal of Occupational Psychology, Employment and Disability*.

<https://doi.org/10.1080/09602010802622730>

Erenberg, G. (2005). The Relationship Between Tourette Syndrome, Attention Deficit Hyperactivity Disorder, and Stimulant Medication: A Critical Review. *Seminars in Pediatric Neurology*, 12(4), 217–221.

<https://doi.org/10.1016/j.spen.2005.12.003>

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, 16(1), 143–149. <https://doi.org/10.3758/BF03203267>



- Espy, K. A. (1997). The Shape School: Assessing Executive Function in Preschool Children. *Developmental Neuropsychology*, *13*(4), 495–499.  
<https://doi.org/10.1080/87565649709540690>
- Freedman, M. (1990). Object alternation and orbitofrontal system dysfunction in Alzheimer's and Parkinson's disease. *Brain and Cognition*, *14*(2), 134–143.  
[https://doi.org/10.1016/0278-2626\(90\)90025-J](https://doi.org/10.1016/0278-2626(90)90025-J)
- Gilotty, L., Kenworthy, L., Wagner, A. E., Sirian, L., & Black, D. O. (2002). Adaptive Skills and Executive Function in Autism Spectrum Disorders. *Child Neuropsychology (Neuropsychology, Development and Cognition: Section C)*, *8*(4), 241–248. <https://doi.org/10.1076/chin.8.4.241.13504>
- Gioia, G. a, Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Test Review: Behavior rating inventory of executive function. *Child Neuropsychology*, *6*(3), 235–238. <https://doi.org/10.1076/chin.6.3.235.3152>
- Godefroy, O., Cabaret, M., Petit-Chenal, V., Pruvo, J. P., & Rousseaux, M. (1999). Control functions of the frontal lobes. Modularity of the central-supervisory system? *Cortex*, *35*(1), 1–20. [https://doi.org/10.1016/S0010-9452\(08\)70782-2](https://doi.org/10.1016/S0010-9452(08)70782-2)
- Gorman, D. a, Thompson, N., Plessen, K. J., Robertson, M. M., Leckman, J. F., & Peterson, B. S. (2010). Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: controlled study. *The British Journal of Psychiatry : The Journal of Mental Science*, *197*(1), 36–44.  
<https://doi.org/10.1192/bjp.bp.109.071050>
- Goudriaan, A. E., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2006). Neurocognitive functions in pathological gambling: A comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction*, *101*(4), 534–

547. <https://doi.org/10.1111/j.1360-0443.2006.01380.x>

Grant, D. A., & Berg, E. (1948). A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem.

*Journal of Experimental Psychology*, 38(4), 404–411.

<https://doi.org/10.1037/h0059831>

Greenberg, L. M. (2007). The Test of Variables of Attention (Version 7.3)

[Computer software]. Los Alamitos: The TOVA Company. (n.d.).

Groth, C., Mol Debes, N., Rask, C. U., Lange, T., & Skov, L. (2017). Course of

Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study.

*Journal of the American Academy of Child & Adolescent Psychiatry*, 56(4),

304–312. <https://doi.org/10.1016/j.jaac.2017.01.010>

Happé, F., Booth, R., Charlton, R., & Hughes, C. (2006). Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder:

Examining profiles across domains and ages. *Brain and Cognition*, 61(1), 25–

39. <https://doi.org/10.1016/j.bandc.2006.03.004>

Harris, E.L., Schuerholz, L.J., Singer, H.S., Reader, M.J., Brown, J.E., Cox, C., et al.

(n.d.). Executive function in children with Tourette syndrome and/or attention

deficit hyperactivity disorder. *Journal of the International Neuropsychological*

*Society*, 1(6), 511–.

Huckeba, W., Chapieski, L., Hiscock, M., & Glaze, D. (2008). Arithmetic

performance in children with Tourette syndrome: Relative contribution of

cognitive and attentional factors. *Journal of Clinical and Experimental*

*Neuropsychology*, 30(4), 410–420. <https://doi.org/10.1080/13803390701494970>

- Isquith, P. K., Crawford, J. S., Espy, K. A., & Gioia, G. A. (2005). Assessment of executive function in preschool-aged children. *Mental Retardation and Developmental Disabilities Research Reviews*.  
<https://doi.org/10.1002/mrdd.20075>
- Jackson, S. R., Parkinson, A., Jung, J., Ryan, S. E., Morgan, P. S., Hollis, C., & Jackson, G. M. (2011). Compensatory neural reorganization in Tourette syndrome. *Current Biology*, *21*(7), 580–585.  
<https://doi.org/10.1016/j.cub.2011.02.047>
- Jackson, S. R., Parkinson, A., Manfredi, V., Millon, G., Hollis, C., & Jackson, G. M. (2013). Motor excitability is reduced prior to voluntary movements in children and adolescents with Tourette syndrome. *Journal of Neuropsychology*, *7*(1), 29–44. <https://doi.org/10.1111/j.1748-6653.2012.02033.x>
- Jasmin, E., Couture, M., McKinley, P., Reid, G., Fombonne, E., & Gisel, E. (2009). Sensori-motor and daily living skills of preschool children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(2), 231–241.  
<https://doi.org/10.1007/s10803-008-0617-z>
- Jeter, C. B., Patel, S. S., Morris, J. S., Chuang, A. Z., Butler, I. J., & Sereno, A. B. (2015). Oculomotor executive function abnormalities with increased tic severity in Tourette syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*(2), 193–202. <https://doi.org/10.1111/jcpp.12298>
- Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology Review*.  
<https://doi.org/10.1007/s11065-007-9040-z>
- Kesler, S. R., Lacayo, N. J., & Jo, B. (2011). A pilot study of an online cognitive

rehabilitation program for executive function skills in children with cancer-related brain injury. *Brain Injury*, 25(1), 101–112.

<https://doi.org/10.3109/02699052.2010.536194>

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, 55(4), 352–358.

<https://doi.org/10.1037/h0043688>

Klingberg, T., Vaidya, C. J., Gabrieli, J. D. E., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. *NeuroReport*, 10(13), 2817–2821.

<https://doi.org/10.1097/00001756-199909090-00022>

Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders*.

<https://doi.org/10.1002/mds.23868>

Lambek, R., Tannock, R., Dalsgaard, S., Trillingsgaard, A., Damm, D., & Thomsen, P. H. (2010). Validating neuropsychological subtypes of ADHD: How do children with and without an executive function deficit differ? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 51(8), 895–904.

<https://doi.org/10.1111/j.1469-7610.2010.02248.x>

Langleben, D. D., Monterosso, J., Elman, I., Ash, B., Krikorian, G., & Austin, G. (2006). Effect of methylphenidate on Stroop Color-Word task performance in children with attention deficit hyperactivity disorder. *Psychiatry Research*, 141(3), 315–320. <https://doi.org/10.1016/j.psychres.2005.09.007>

Larry, B., Jacob, K., Mark, W., & Wayne, F. (1986). A prevalence study of Gilles de la Tourette syndrome in North Dakota school-age children. *Journal of the*

*American Academy of Child Psychiatry*, 25(4), 552–553. Retrieved from  
<http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=1987-28535-001&site=ehost-live&scope=site>

Lavoie, M. E., Thibault, G., Stip, E., & O'Connor, K. P. (2007). Memory and executive functions in adults with Gilles de la Tourette syndrome and chronic tic disorder. *Cognitive Neuropsychiatry*, 12(2), 165–181.  
<https://doi.org/10.1080/13546800600826371>

LECKMAN, J. F., RIDDLE, M. A., HARDIN, M. T., ORT, S. I., SWARTZ, K. L., STEVENSON, J., & COHEN, D. J. (1989). The Yale Global Tic Severity Scale: Initial Testing of a Clinician-Rated Scale of Tic Severity. *Journal of the American Academy of Child and Adolescent Psychiatry*, 28(4), 566–573.  
<https://doi.org/10.1097/00004583-198907000-00015>

Leckman, J. F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., ... Peterson, B. S. (1998). Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics*, 102(1 Pt 1), 14–19. <https://doi.org/10.1542/peds.102.1.14>

Lehto, J. (1996). Are Executive Function Tests Dependent on Working Memory Capacity? *The Quarterly Journal of Experimental Psychology*, 49A(1), 29–50.  
<https://doi.org/10.1080/713755616>

Lichter, D. G., & Finnegan, S. G. (2015). Influence of gender on Tourette syndrome beyond adolescence. *European Psychiatry*, 30(2), 334–340.  
<https://doi.org/10.1016/j.eurpsy.2014.07.003>

Lombroso, P. J., & Scahill, L. (2008). Tourette syndrome and obsessive-compulsive disorder. *Brain & Development*, 30(4), 231–237.  
<https://doi.org/10.1016/j.braindev.2007.09.001>

- Luciana, M., & Nelson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia*, 36(3), 273–293. [https://doi.org/10.1016/S0028-3932\(97\)00109-7](https://doi.org/10.1016/S0028-3932(97)00109-7)
- Macdonald, M., Lord, C., & Ulrich, D. (2013). The relationship of motor skills and adaptive behavior skills in young children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, 7(11), 1383–1390. <https://doi.org/10.1016/j.rasd.2013.07.020>
- Mahone, E., Cirino, P., Cutting, L., Cerrone, P., Hagelthom, K., Hiemenz, J., et al. (2002). Validity of the Behavior Rating Inventory of Executive Function in children with ADHD and/or Tourette Syndrome. *Archives of Clinical Neuropsychology*, 17, 643–66.
- Manly, T., Anderson, V., Crawford, J., George, M., Underbjerg, M. & Robertson, I. (2016). *The Test of Everyday Attention for Children-II (TEA-Ch-2)*. Bury St Edmunds, UK: Thames Valley Test Company.
- Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., & Robertson, I. H. (2001). The Differential Assessment of Children's Attention: The Test of Everyday Attention for Children (TEA-Ch), Normative Sample and ADHD Performance. *Journal of Child Psychology and Psychiatry*, 42(8), 1065–1081. <https://doi.org/10.1111/1469-7610.00806>
- Mahone, E., Koth, C. W., Cutting, L., Singer, H. S., & Denckla, M. B. (2001). Executive function in fluency and recall measures among children with Tourette syndrome or ADHD. *Journal of the International Neuropsychological Society*, 7(1), 102–111. <https://doi.org/10.1017/S1355617701711101>

- Matsuda, N., Kono, T., Nonaka, M., Shishikura, K., Konno, C., Kuwabara, H., ...  
Kano, Y. (2012). Impact of obsessive-compulsive symptoms in Tourette's syndrome on neuropsychological performance. *Psychiatry and Clinical Neurosciences*, *66*(3), 195–202. <https://doi.org/10.1111/j.1440-1819.2012.02319.x>
- McKown, C., Allen, A., Russo-Ponsaran, N., & Johnson, J. (2013). Direct assessment of children's social-emotional comprehension. *Psychological Assessment*, *25*, 1154–1166.
- McKown, C., Gumbiner, L. M., Russo, N. M., & Lipton, M. (2009). Social-emotional learning skill, self-regulation, and social competence in typically developing and clinic-referred children. *Journal of Clinical Child and Adolescent Psychology*, *38*(6), 858–871.  
<https://doi.org/10.1080/15374410903258934>
- Mitchell, M., & Miller, L. S. (2008). Prediction of functional status in older adults: The ecological validity of four Delis-Kaplan Executive Function System tests. *Journal of Clinical and Experimental Neuropsychology*, *30*(6), 683–690.  
<https://doi.org/10.1080/13803390701679893>
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. <https://doi.org/10.1006/cogp.1999.0734>
- Moore, T. F., & Hollett, J. (2003). Giving voice to persons living with dementia: The researcher's opportunities and challenges. *Nursing Science Quarterly*, *16*(2), 163–167. <https://doi.org/10.1177/0894318403251793251793>

- Morand-Beaulieu, S., Grot, S., Lavoie, J., Leclerc, J. B., Luck, D., & Lavoie, M. E. (2017). The puzzling question of inhibitory control in Tourette syndrome: A meta-analysis. *Neuroscience and Biobehavioral Reviews*.  
<https://doi.org/10.1016/j.neubiorev.2017.05.006>
- Mueller, S. C., Jackson, G. M., Dhalla, R., Datsopoulos, S., & Hollis, C. P. (2006). Enhanced cognitive control in young people with Tourette's syndrome. *Current Biology*, *16*(6), 570–573. <https://doi.org/10.1016/j.cub.2006.01.064>
- Müller, S. V., Johannes, S., Wieringa, B., Weber, A., Müller-Vahl, K., Matzke, M., ... Münte, T. F. (2003). Disturbed monitoring and response inhibition in patients with Gilles de la Tourette syndrome and co-morbid obsessive compulsive disorder. *Behavioural Neurology*, *14*(1–2), 29–37.  
<https://doi.org/http://dx.doi.org/10.1155/2003/832906>
- O'Rourke, J. A., Scharf, J. M., Platko, J., Stewart, S. E., Illmann, C., Geller, D. A., ... Pauls, D. L. (2011). The familial association of Tourette's disorder and ADHD: The impact of OCD symptoms. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, *156*(5), 553–560.  
<https://doi.org/10.1002/ajmg.b.31195>
- Okeeffe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., & Murphy, T. (2014). Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: Attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, *20*(5), 557–582.  
<https://doi.org/10.1080/09297049.2013.832740>
- Oosterman, J. M., Wijers, M., & Kessels, R. P. C. (2013). Planning or something else? Examining neuropsychological predictors of zoo map performance.



*Applied Neuropsychology*, 20(2), 103–109.

<https://doi.org/10.1080/09084282.2012.670150>

Osterrieth, P. A. (1944). Test of copying a complex figure; Contribution to the study of perception and memory. *Archives de Psychologie*, 30, 206–356.

Ozonoff, S., & Jensen, J. (1999). Specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism and Developmental Disorders*, 29(2), 171–177. <https://doi.org/10.1023/A:1023052913110>

Ozonoff, S., & Strayer, D. L. (2001). Further Evidence of Intact Working Memory in Autism. *Journal of Autism and Developmental Disorders*, 31(3), 257–263. <https://doi.org/10.1023/A:1010794902139>

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal- lobe lesions in man. *Neuropsychologia*, 20(3), 249–262. [https://doi.org/Doi 10.1016/0028-3932\(82\)90100-2](https://doi.org/Doi%2010.1016/0028-3932(82)90100-2)

Rasmussen, C., Soleimani, M., Carroll, A., & Hodlevskyy, O. (2009). Neuropsychological functioning in children with Tourette syndrome (TS). *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Académie Canadienne de Psychiatrie de l'enfant et de l'adolescent*, 18(4), 307–315. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383&%7Drendertype=abstract%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2765383&tool=pmcentrez&rendertype=abstract>

Redick, T. S., Broadway, J. M., Meier, M. E., Kuriakose, P. S., Unsworth, N., Kane, M. J., & Engle, R. W. (2012). Measuring working memory capacity with

- automated complex span tasks. *European Journal of Psychological Assessment*, 28(3), 164–171. <https://doi.org/10.1027/1015-5759/a000123>
- Reitan, R. W. D. (1985). The Halstead-Reitan Neuropsychological Test Battery: Therapy and clinical interpretation. *Tucson, AZ: Neuropsychological Press*.
- Robertson, M. M. (2011). Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *British Journal of Hospital Medicine (London, England : 2005)*, 72(2), 100–107. <https://doi.org/10.12968/hmed.2011.72.2.100>
- Roizen, N. J., Blondis, T. A., Irwin, M., & Stein, M. (1994). Adaptive functioning in children with attention-deficit hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine*, 148(11), 1137–1142. <https://doi.org/10.1001/archpedi.1994.02170110023004>
- Ruff, R. M., Light, R. H., & Evans, R. W. (1987). The ruff figural fluency test: A normative study with adults. *Developmental Neuropsychology*, 3(1), 37–51. <https://doi.org/10.1080/87565648709540362>
- Sallee, F. R., Sethuraman, G., & Rock, C. M. (1994). Effects of pimozide on cognition in children with Tourette syndrome: interaction with comorbid attention deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica*, 90(1), 4–9. <https://doi.org/10.1111/j.1600-0447.1994.tb01546.x>
- Salthouse, T. A. (1996). The Processing-Speed Theory of Adult Age Differences in Cognition. *Psychological Review*, 103(3), 403–428. <https://doi.org/10.1037/0033-295X.103.3.403>
- Scahill, L., Erenberg, G., Berlin, C. M., Budman, C., Coffey, B. J., Jankovic, J., ... Walkup, J. (2006). Contemporary Assessment and Pharmacotherapy of Tourette

Syndrome. *NeuroRx*, 3(2), 192–206. <https://doi.org/10.1016/j.nurx.2006.01.009>

Scahill, L., Williams, S., Schwab-Stone, M., Applegate, J., Leckman, J. F., Walkup, J. T., ... Hollenbeck, P. J. (2006). Disruptive Behavior Problems in a Community Sample of Children with Tic Disorders. In *Advances in neurology: Tourette syndrome (Vol. 99)*. (pp. 184–190). Retrieved from <http://search.ebscohost.com/login.aspx?direct=true&db=psych&AN=2006-06768-018&site=ehost-live>

Scharf, J. M., Miller, L. L., Mathews, C. A., & Ben-Shlomo, Y. (2012). Prevalence of Tourette syndrome and chronic tics in the population-based Avon Longitudinal Study of Parents and Children cohort. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51(2), 192–201. <https://doi.org/10.1016/j.jaac.2011.11.004>

Schuerholz, L. J., Baumgardner, T. L., Singer, H. S., Reiss, A. L., & Denckla, M. B. (1996). Neuropsychological status of children with Tourette's syndrome with and without attention deficit hyperactivity disorder. *Neurology*, 46(4), 958–965. <https://doi.org/10.1212/WNL.46.4.958>

Schuerholz, L. J., Singer, H. S., & Denckla, M. B. (1998). Gender study of neuropsychological and neuromotor function in children with Tourette syndrome with and without attention-deficit hyperactivity disorder. *Journal of Child Neurology*, 13(6), 277–282. <https://doi.org/10.1177/088307389801300607>

Schultz, R. T., Carter, A. S., Gladstone, M., Scahill, L., Leckman, J. F., Peterson, B. S., ... Pauls, D. (1998). Visual-motor integration functioning in children with Tourette syndrome. *Neuropsychology*, 12(1), 134–145.

<https://doi.org/10.1037/0894-4105.12.1.134>

Selemon, L. D. (2013). A role for synaptic plasticity in the adolescent development of executive function. *Transl Psychiatry*, 3(3), e238.

<https://doi.org/10.1038/tp.2013.7>

Shafran, R., Frampton, I., Heyman, I., Reynolds, M., Teachman, B., & Rachman, S. (2003). The preliminary development of a new self-report measure for OCD in young people. *Journal of Adolescence*, 26(1), 137–142.

[https://doi.org/10.1016/S0140-1971\(02\)00083-0](https://doi.org/10.1016/S0140-1971(02)00083-0)

Shimoni, M., Engel-Yeger, B., & Tirosh, E. (2012). Executive dysfunctions among boys with Attention Deficit Hyperactivity Disorder (ADHD): Performance-based test and parents report. *Research in Developmental Disabilities*, 33(3), 858–865.

<https://doi.org/10.1016/j.ridd.2011.12.014>

Siegel, L. S. (1994). Working Memory and Reading: A Life-span Perspective. *International Journal of Behavioral Development*, 17(1), 109–124.

<https://doi.org/10.1177/016502549401700107>

Sikora, D. M., Vora, P., Coury, D. L., & Rosenberg, D. (2012). Attention-Deficit/Hyperactivity Disorder Symptoms, Adaptive Functioning, and Quality of Life in Children With Autism Spectrum Disorder. *Pediatrics*,

130(Supplement 2), S91–S97. <https://doi.org/10.1542/peds.2012-0900G>

Simon, H. A. (1975). The functional equivalence of problem solving skills. *Cognitive Psychology*, 7(2), 268–288. [https://doi.org/10.1016/0010-0285\(75\)90012-2](https://doi.org/10.1016/0010-0285(75)90012-2)

Singer, H. S. (2011). *Tourette syndrome and other tic disorders. Handbook of Clinical Neurology* (Vol. 100). <https://doi.org/10.1016/B978-0-444-52014->

2.00046-X

- Sparrow, S. S., Cicchetti, D. V., & Saulnier, C. A. (2016). *The Vineland Adaptive Behavior Scales-third edition*. American Guidance Service; Circle Pines, MN.
- Stern, J. S., Burza, S., & Robertson, M. M. (2005). Gilles de la Tourette's syndrome and its impact in the UK. *Postgraduate Medical Journal*, *81*(951), 12–19.  
<https://doi.org/10.1136/pgmj.2004.023614>
- Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research*, *63*(3–4), 289–298.  
<https://doi.org/10.1007/s004269900007>
- Sukhodolsky, D. G., do Rosario-Campos, M. C., Scahill, L., Katsovich, L., Pauls, D. L., Peterson, B. S., ... Leckman, J. F. (2005). Adaptive, emotional, and family functioning of children with obsessive-compulsive disorder and comorbid attention deficit hyperactivity disorder. *The American Journal of Psychiatry*, *162*(6), 1125–1132. <https://doi.org/10.1176/appi.ajp.162.6.1125>
- Sukhodolsky, D. G., Scahill, L., Zhang, H., Peterson, B. S., King, R. A., Lombroso, P. J., ... Leckman, J. F. (2003). Disruptive behavior in children with Tourette's syndrome: Association with ADHD comorbidity, tic severity, and functional impairment. *Journal of the American Academy of Child and Adolescent Psychiatry*, *42*(1), 98–105. <https://doi.org/10.1097/00004583-200301000-00016>
- Swanson, J. M. (1995). *SNAP-IV Scale*. Irvine, CA: University of California Child Development Center.
- Termine, C., Luoni, C., Fontolan, S., Selvini, C., Perego, L., Pavone, F., ... Cavanna, A. E. (2016). Impact of co-morbid attention-deficit and hyperactivity disorder

on cognitive function in male children with Tourette syndrome: A controlled study. *Psychiatry Research*, 243, 263–267.

<https://doi.org/10.1016/j.psychres.2016.06.048>

Toplak, M. E., Bucciarelli, S. M., Jain, U., & Tannock, R. (2009). Executive functions: Performance-based measures and the behavior rating inventory of executive function (BRIEF) in adolescents with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology*, 15(1), 53–72.

<https://doi.org/10.1080/09297040802070929>

Uher, R., Heyman, I., Turner, C. M., & Shafran, R. (2008). Self-, parent-report and interview measures of obsessive-compulsive disorder in children and adolescents. *Journal of Anxiety Disorders*, 22(6), 979–990.

<https://doi.org/10.1016/j.janxdis.2007.10.001>

van't Hooft, I., Andersson, K., Bergman, B., Sejersen, T., von Wendt, L., & Bartfai, A. (2005). Beneficial effect from a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study. *Brain Injury*, 19(7), 511–518. <https://doi.org/10.1080/02699050400025224>

Verté, S., Geurts, H. M., Roeyers, H., Oosterlaan, J., & Sergeant, J. A. (2005). Executive functioning in children with autism and Tourette syndrome. *Development and Psychopathology*.

<https://doi.org/10.1017/S0954579405050200>

Vriezen, E. R., & Pigott, S. E. (2002a). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Child Neuropsychology*, 8(4), 296–303. <https://doi.org/10.1076/chin.8.4.296.13505>

- Vriezen, E. R., & Pigott, S. E. (2002b). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Special Issue: Behavior Rating Inventory of Executive Function (BRIEF)*, 8(4), 296–303.  
<https://doi.org/http://dx.doi.org/10.1076/chin.8.4.296.13505>
- Wählstedt, C., Thorell, L. B., & Bohlin, G. (2009). Heterogeneity in ADHD: Neuropsychological pathways, comorbidity and symptom domains. *Journal of Abnormal Child Psychology*, 37(4), 551–564. <https://doi.org/10.1007/s10802-008-9286-9>
- WATKINS, L. H., SAHAKIAN, B. J., ROBERTSON, M. M., VEALE, D. M., ROGERS, R. D., PICKARD, K. M., ... ROBBINS, T. W. (2005). Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychological Medicine*, 35(4), 571–582.  
<https://doi.org/10.1017/S0033291704003691>
- Wechsler, D. (n.d.). *Wechsler intelligence scale for children-fifth edition*.  
Bloomington, MN: Pearson.
- Weisman, H., Qureshi, I. A., Leckman, J. F., Scahill, L., & Bloch, M. H. (2013). Systematic review: Pharmacological treatment of tic disorders - Efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neuroscience and Biobehavioral Reviews*. <https://doi.org/10.1016/j.neubiorev.2012.09.008>
- Welsh, M. C., Pennington, B. F., & Groisser, D. B. (1991). A Normative-Developmental Study of Executive Function: A Window on Prefrontal Function in Children. *Developmental Neuropsychology*, 7(2), 131–149.  
<https://doi.org/10.1080/87565649109540483>

White, S. J., Burgess, P. W., & Hill, E. L. (2009). Impairments on “open-ended” executive function tests in Autism. *Autism Research*, 2(3), 138–147.

<https://doi.org/10.1002/aur.78>

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H. and Evans, J. J. (1996).

*Behavioural Assessment of Dysexecutive Syndrome*. Bury St. Edmunds, , UK:

Thames Valley Test Company.

Wilson, BA; Alderman, N; Burgess, PW; Emslie, H; Evans, J. (1996). The

behavioural assessment of the dysexecutive syndrome. *Thames Valley*

*Company; Bury St Edmunds*.

Yaniv, A., Benaroya-Milshtein, N., Steinberg, T., Ruhrrman, D., Apter, A., &

Lavidor, M. (2017). Specific executive control impairments in Tourette

syndrome: The role of response inhibition. *Research in Developmental*

*Disabilities*, 61, 1–10. <https://doi.org/10.1016/j.ridd.2016.12.007>

Zandt, F., Prior, M., & Kyrios, M. (2009). Similarities and differences between

children and adolescents with autism spectrum disorder and those with

obsessive compulsive disorder. *Autism*, 13(1), 43–57.

<https://doi.org/10.1177/1362361308097120>



## **Appendix**

## Appendix A: Critical Appraisal Skills Programme (CASP, 2014) checklist for case control studies



**CASP Checklist:** 11 questions to help you make sense of a [Case Control Study](#)

**How to use this appraisal tool:** Three broad issues need to be considered when appraising a case control study:

- ▶ Are the results of the study valid? (Section A)
- ▶ What are the results? (Section B)
- ▶ Will the results help locally? (Section C)

The 11 questions on the following pages are designed to help you think about these issues systematically. The first three questions are screening questions and can be answered quickly. If the answer to both is “yes”, it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a “yes”, “no” or “can’t tell” to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

**About:** These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

**Referencing:** we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Case Control Study) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

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Critical Appraisal Skills Programme (CASP) part of Better Value Healthcare Ltd [www.casp-uk.net](http://www.casp-uk.net)

Section A: Are the results of the trial valid?

1. Did the study address a clearly focused issue?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: An issue can be 'focused' in terms of

- the population studied
- Whether the study tried to detect a beneficial or harmful effect
- the risk factors studied

Comments:

2. Did the authors use an appropriate method to answer their question?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- Is a case control study an appropriate way of answering the question under the circumstances
- Did it address the study question

Comments:

Is it worth continuing?

3. Were the cases recruited in an acceptable way?

Yes

Can't Tell

No

Comments:

HINT: We are looking for selection bias which might compromise validity of the findings

- are the cases defined precisely
- were the cases representative of a defined population (geographically and/or temporally)
- was there an established reliable system for selecting all the cases
  - are they incident or prevalent
- is there something special about the cases
  - is the time frame of the study relevant to disease/exposure
- was there a sufficient number of cases selected
- was there a power calculation

4. Were the controls selected in an acceptable way?

Yes

Can't Tell

No

Comments:

HINT: We are looking for selection bias which might compromise the generalisability of the findings

- were the controls representative of the defined population (geographically and/or temporally)
- was there something special about the controls
- was the non-response high, could non-respondents be different in any way
  - are they matched, population based or randomly selected
- was there a sufficient number of controls selected

5. Was the exposure accurately measured to minimise bias?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: We are looking for measurement, recall or classification bias

- was the exposure clearly defined and accurately measured
- did the authors use subjective or objective measurements
- do the measures truly reflect what they are supposed to measure (have they been validated)
- were the measurement methods similar in the cases and controls
- did the study incorporate blinding where feasible
- is the temporal relation correct (does the exposure of interest precede the outcome)

Comments:

6. (a) Aside from the experimental intervention, were the groups treated equally?

HINT: List the ones you think might be important, that the author may have missed

- genetic
- environmental
- socio-economic

List:

6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Look for

- restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

Section B: What are the results?

7. How large was the treatment effect?

Comments:

HINT: Consider

- what are the bottom line results
- is the analysis appropriate to the design
- how strong is the association between exposure and outcome (look at the odds ratio)
- are the results adjusted for confounding, and might confounding still explain the association
- has adjustment made a big difference to the OR

8. How precise was the estimate of the treatment effect?

Comments:

HINT: Consider

- size of the p-value
- size of the confidence intervals
- have the authors considered all the important variables
- how was the effect of subjects refusing to participate evaluated

9. Do you believe the results?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- big effect is hard to ignore!
  - Can it be due to chance, bias, or confounding
  - are the design and methods of this study sufficiently flawed to make the results unreliable
  - consider Bradford Hills criteria (e.g. time sequence, does-response gradient, strength, biological plausibility)

Comments:

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider whether
- the subjects covered in the study could be sufficiently different from your population to cause concern
  - your local setting is likely to differ much from that of the study
  - can you quantify the local benefits and harms

Comments:

11. Do the results of this study fit with other available evidence?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- all the available evidence from RCT's Systematic Reviews, Cohort Studies, and Case Control Studies as well, for consistency

Comments:

**Remember** One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making. However, for certain questions observational studies provide the only evidence. Recommendations from observational studies are always stronger when supported by other evidence.

## **Appendix B: Details of joint working**

The project was conducted in collaboration with Summer Fakhro (trainee Clinical Psychologist). We completed the grant application, ethics applications and recruitment activities jointly.

Regarding recruitment, we both required participants from the same specialist clinic. As such, we shared recruitment duties, which included screening a comprehensive database of potential participants and the administrative tasks involved (e.g. writing and sending invitation letters). We shared the recruitment equally, each planning and conducting roughly half of the research visits. We each ran the full battery with the participants, which included measures of intellectual functioning, adaptive functioning, clinical variables, executive functioning and time processing.

In terms of the data, the intellectual functioning, adaptive functioning and clinical variables data were common to both theses. However, data related to the main subjects of our respective studies: executive functioning in the current study, and time processing in Summer's thesis, were used exclusively by each. This method maximised the number of participants we were able to recruit, without requiring participants to repeat research work unnecessarily, or to make more than one research commitment in order to participate.



## Appendix C: Letter confirming NHS ethics approval



Health Research Authority

Dr Daniel Stark  
Department of Child and Adolescent Mental Health  
Level 4 Frontage Building  
Great Ormond Street Hospital, Great Ormond Street  
WC1N 3JH

Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)

31 August 2017

Dear Dr Stark,

### Letter of HRA Approval

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

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.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from [www.hra.nhs.uk/hra-approval](http://www.hra.nhs.uk/hra-approval).

### Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

### After HRA Approval

The document “*After Ethical Review – guidance for sponsors and investigators*”, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](#), and emailed to [hra.amendments@nhs.net](mailto:hra.amendments@nhs.net).
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](#).

### Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/>.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

### User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	220775
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procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

### **HRA Training**

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

Your IRAS project ID is **220775**. Please quote this on all correspondence.

Yours sincerely

Thomas Fairman  
HRA Assessor

Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)

Copy to: *Ms Emma Pendleton, UCL Institute of Child Health, (Sponsor Contact)*  
*Ms Anika Kadchha, Joint Research and Development Office, Division of Research and Innovation, (Lead NHS R&D Contact)*

**Appendix D: Participant Invitation Letter**

Great Ormond Street   
Hospital for Children

NHS Foundation Trust

[Name]  
[Address]

Great Ormond Street  
London WC1N 3JH

[Date]

Tel: 020 7405 9200

Dear [Name],

I am writing to invite you and your child to participate in a study which my colleagues and I are carrying out at Great Ormond Street Hospital. We are contacting you because your child has been seen at our clinic in relation to their Tourette Syndrome.

Please find enclosed an information sheet explaining the study. It outlines why this research is important and what would be asked of you and your child should you choose to participate. There is also a children's version of the information sheet included which you can discuss with your child should you wish.

One of my colleagues, Lara Harris or Summer Fakhro, will contact you by telephone in approximately one week to check you have received this information and to discuss any queries you may have.

Many thanks for taking the time to read the enclosed information.

Yours sincerely,

**Dr Daniel Stark**  
Clinical Psychologist  
Great Ormond Street Hospital for Children

## Appendix E: Participant Information and Consent / Assent Sheets

# Great Ormond Street Hospital for Children

NHS Foundation Trust

## **Patient & Carer Information Sheet**

Great Ormond Street  
London WC1N 3JH

### About the Project

Tel: 020 7405 9200

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

We work at the Tourette syndrome Clinic at Great Ormond Street Hospital (GOSH). 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 Great Ormond Street Hospital, 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 GOSH 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 effected. 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 Great Ormond Street Hospital, 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 Great Ormond Street 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 Great Ormond Street 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 Great Ormond Street Hospital (You can ring them on 020 7829 7862 or email them on [pals@gosh.nhs.uk](mailto:pals@gosh.nhs.uk)).

### **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  
Dept of Child and Adolescent Mental Health  
Level 4, Frontage Building  
Great Ormond Street Hospital  
Great Ormond Street  
London  
WC1N 3JH

Email: [lara.harris.15@ucl.ac.uk](mailto:lara.harris.15@ucl.ac.uk)  
[S.fakhro.12@ucl.ac.uk](mailto:S.fakhro.12@ucl.ac.uk)

Tel: [Insert telephone numbers]

Supervised by: Dr Daniel Stark, Clinical Psychologist, Great Ormond Street Hospital for Children [Insert telephone numbers]; Dr Tara Murphy, Consultant Clinical Psychologist, Great Ormond Street Hospital for Children [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 Great Ormond Street 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 Great Ormond Street 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?**

## **Meeting**



We would meet you and your parents or carers at your home or at Great Ormond Street Hospital. 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](mailto:lara.harris.15@ucl.ac.uk)

[s.fakhro.12@ucl.ac.uk](mailto:s.fakhro.12@ucl.ac.uk)

Tel: [Insert telephone numbers]



Supervised by: Dr Daniel Stark, Clinical Psychologist, Great Ormond Street Hospital for Children [Insert telephone numbers]; Dr Tara Murphy, Consultant Clinical Psychologist, Great Ormond Street Hospital for Children [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 Great Ormond Street 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 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 Great Ormond Street 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 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 Great Ormond Street Hospital. 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 Great Ormond Street Hospital 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](mailto:lara.harris.15@ucl.ac.uk)  
[s.fakhro.12@ucl.ac.uk](mailto:s.fakhro.12@ucl.ac.uk)

Tel: [Insert telephone numbers]



Supervised by: Dr Daniel Stark, Clinical Psychologist, Great Ormond Street Hospital for Children (Tel: ); Dr Tara Murphy, Consultant Clinical Psychologist, Great Ormond Street Hospital for Children (Tel: ); and Dr John King, Senior Lecturer and Clinical Psychologist, University College London (Tel: )



## 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 Great Ormond Street Hospital. 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 Great Ormond Street 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 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 Great Ormond Street Hospital. 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 Great Ormond Street Hospital 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](mailto:lara.harris.15@ucl.ac.uk); [s.fakhro.12@ucl.ac.uk](mailto:s.fakhro.12@ucl.ac.uk)  
Tel: [Insert telephone numbers]

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

Identification Number \_\_\_\_\_

**CONSENT FORM FOR**

Great Ormond Street  
London WC1N 3JH

**PARENT/(S) AND CARER/(S)**

Tel: 020 7405 9200

**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 \_\_\_\_\_

Identification Number \_\_\_\_\_

Great Ormond Street   
Hospital for Children

NHS Foundation Trust

Great Ormond Street  
London WC1N 3JH

Tel: 020 7405 9200

**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 \_\_\_\_\_

Great Ormond Street   
Hospital for Children

NHS Foundation Trust

Great Ormond Street  
London WC1N 3JH

Tel: 020 7405 9200

**PARTICIPANT ASSENT FORM:**

**Children and young people ages 10-12**

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

\_\_\_\_\_  
Name Date Signature

\_\_\_\_\_  
Researcher Date Signature

Identification Number \_\_\_\_\_

# Great Ormond Street Hospital for Children



NHS Foundation Trust

Great Ormond Street  
London WC1N 3JH

## **PARTICIPANT ASSENT**

Tel: 020 7405 9200

### **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



If you would like to discuss this report you can contact Daniel Stark until the end of March 2019 on 020 7829 8679 ext. 0146.

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*

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



	Scaled Score	%ile	Range
<b>Verbal Comprehension Subtests</b>			
Similarities			
Vocabulary			
<b>Visual Spatial Subtests</b>			
Block Design			
Visual Puzzles			

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
Playing Card Test			
Modified Six Elements Test			
Water Test			
Key Search Test			
Zoo Map Test 1			
Zoo Map Test 2			

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

<b>Scale/Index</b>	<b>T Score</b>	<b>%ile</b>	<b>Range</b>
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)*

<b>Domains</b>	<b>Parent Report Scores</b>	
	<b>Current Tics</b>	<b>Worst Ever</b>
Total Phonic		
Total Motor		
Impairment Classification		

Behaviour

*Vineland Adaptive Behaviour Scale - 3 (VABS)*

<b>Domains</b>	<b>Parent Report Scores</b>		
	<b>Standard Score</b>	<b>%ile</b>	<b>Classification</b>
Communication			
Daily Living Skills			
Socialisation			
Motor Skills			

## Appendix G: Example summary report for children aged 10-16

Child's Name

Date: (INSERT DATE)

### How I can help myself....

- If I do not understand what I am being 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
- When studying I should repeat things several times and test myself to help me to learn



Report Compiled by: (INSERT CLINICIAN)  
Psychological Medicine Team  
Great Ormond Street Hospital



### 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



### My Strengths

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



### 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 plan, sorting and starting big pieces of work and will do better with some extra help
- Keeping a copy of my textbooks at school will help make sure I have everything I need to learn
- I find it hard to write, especially when I have to do it quickly. A laptop will help me to complete work in school and at home



## Appendix H: Example summary report for children aged 7-9

### 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.

Compiled by: Dr Smith

Psychological Medicine Team

Date: 22/02/2017



#### Things I am good at:

Understanding what I am being asked to do

Reading and spelling words

Playing the flute

Working out problems in maths

Drawing



#### Things I find hard:

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



#### 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 plan, sorting and starting big pieces of work and will do better with some extra help

Keeping a copy of my textbooks at school will help make sure I have everything I need to learn

I find it hard to write, especially when I have to do it quickly. A laptop will help me to complete work in school and at home



#### 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 repeat something the better I get

When studying I should repeat things several times and test myself to help me to learn



**Appendix I: Neuropsychological measures for the TS without ADHD group compared to normative means**

Domain	Measure	Variable	<i>N</i>	Test population mean (SD)	Sample mean (SD)	Sample range	<i>t</i>	<i>p</i>	Effect size (Cohen's <i>d</i> )	<i>N</i> impaired (% of sample)
<b>Intellectual Functioning</b>	WISC-V	Full Scale IQ (FSIQ)	15	100 (15)	99.2 (13.71)	76-122	-.206	<b>.837</b>	.0557	0 (0.00)
		Verbal Comprehension Index (VCI)			98.8 (10.97)	73-116	-.309	<b>.757</b>	.091	0 (0.00)
		Visual Spatial Index (VSI)			102.8 (12.97)	75-126	-.721	<b>.471</b>	.199	0 (0.00)
		Fluid Reasoning Index (FRI)			103.13 (15.59)	76-134	-.805	<b>.421</b>	.205	0 (0.00)
		Working Memory Index (WMI)			100.87 (18.25)	72-138	-.224	<b>.823</b>	.052	0 (0.00)
		Processing Speed Index (PSI)			94 (16.35)	72-119	-1.543	<b>.123</b>	.382	0 (0.00)
<b>Executive Functioning (parent-report)</b>	BRIEF	Inhibit	15	50 (10)	53 (8.42)	37-67	1.158	<b>.247</b>	.071	2 (13.33)
		Shift			59.67 (9.44)	47-72	3.728	<b>.0002</b>	.994	7 (46.67)
		Emotional Control			61.13 (8.72)	42-73	4.293	<b>.0001</b>	1.186	4 (26.67)
		Initiate			58.07 (8.94)	43-73	3.112	<b>.0019</b>	.851	4 (26.67)
		Working Memory			64.60 (12.23)	40-90	5.611	<b>.0001</b>	1.307	7 (46.67)
		Planning / organisation			62.27 (7.21)	45-72	4.738	<b>.0001</b>	1.408	8 (53.33)
		Organisation of Materials			60.33 (8.35)	40-69	3.986	<b>.0001</b>	1.121	6 (40.00)
		Monitor			56 (9.73)	40-70	2.312	<b>.021</b>	.608	3 (20.00)
		Behaviour Regulation Index			58.33 (7.97)	45-70	3.215	<b>.001</b>	.921	3 (20.00)
Metacognition Index	63.43 (6.29)	53-74	5.190	<b>.0001</b>	1.608	5 (33.33)				
Global Executive Composite	61.93 (7.37)	49-73	4.607	<b>.0001</b>	1.358	6 (40.00)				
<b>Executive Functioning (ecologically-valid)</b>	BADS-C	Zoo Map 1 (low planning demands)	15	10 (3)	10.2 (4.35)	2-15	-.245	<b>.807</b>	.053	2 (13.33)
		Zoo Map 2 (high planning demands)			10.13 (2.88)	4-12	-0.164	<b>.871</b>	.044	1 (6.66)
		Six Parts Test (planning, multi-tasking, scheduling, monitoring)			7.67 (2.09)	4-11	-2.965	<b>.003</b>	.901	1 (6.66)
<b>Executive Functioning (experimental)</b>	TEA- <i>Ch</i> II	Vigil (sustained attention)	15	10 (3)	9.07 (2.53)	4-13	-1.179	<b>.239</b>	.335	2 (13.33)
		Simple RT(sustained attention)			9.67 (4.47)	2-15	-.404	<b>.686</b>	.087	3 (20.00)
		RBBS (switching attention)			7.07 (4.70)	1-15	-3.572	<b>.0004</b>	.743	6 (40.00)
<b>Adaptive Functioning</b>	VABS-3	Communication	15	100 (15)	92 (18.96)	36-120	-2.058	<b>.0397</b>	.468	1 (6.66)
		Daily Living Skills			91.21 (22.59)	20-114	-2.257	<b>.0241</b>	.458	2 (13.33)
		Socialisation			99.2 (13.71)	76-122	-.206	<b>.837</b>	.0557	0 (0.00)
		Adaptive Behaviour Composite			98.8 (10.97)	73-116	-.309	<b>.757</b>	.091	0 (0.00)

**Appendix J: Pearson's r statistics with significance indicators for correlational analyses performed across executive and adaptive domains and subtests<sup>8</sup>**

	WISC-V FSIQ	Hayling Acc difference	Hayling RT difference	BADS-C Zoo Map 1	BADS-C Zoo Map 2	BADS-C Six Part Test	TEA-Ch Vigil	TEA-Ch Simple RT	TEA-Ch RBBS	BRIEF BRI	BRIEF MI	BRIEF GEC	VABS-3 CMM	VABS-3 DLS	VABS-3 SOC	VABS-3 ABC
WISC-V FSIQ	-	.276*	-.030	0.01	0.152	-0.089	.499**	.300*	.473**	-.285*	-.362**	-.343**	.340*	.426**	0.118	.348*
Hayling Acc difference		-	-.218	-.080	-.079	-.113	.255*	.161	.149	-.170	-.181	-.209	.180	.243	.138	.229
Hayling RT difference			-	.010	.000	.048	-.250†	-.214	.095	.086	.221	.170	.011	-.157	-.266*	-.126
BADS-C Zoo Map 1				-	-.0211	-.307*	-0.04	-.276*	-.0222	-.324*	-.299*	-.372**	0.152	0.114	0.002	0.167
BADS-C Zoo Map 2					-	-0.016	-0.202	.355**	0.07	-0.142	-0.066	-0.034	-0.039	0.111	0.222	0.111
BADS-C Six Part Test						-	0.117	0.101	-0.221	-0.06	-.273*	-0.203	0.03	-0.07	0.111	0.001
TEA-Ch Vigil							-	0.149	0.254	-0.181	-.306*	-.303*	.414**	.313*	0.113	0.239
TEA-Ch Simple RT								-	.398**	-.268*	-0.187	-0.219	0.002	-0.111	.294*	0.088
TEA-Ch RBBS									-	-0.254	-0.089	-0.161	0.063	0.039	0.144	0.059
BRIEF BRI										-	.679**	.896**	-.334*	-.417**	-.628**	-.569**
BRIEF MI											-	.930**	-.504**	-.569**	-.654**	-.676**
BRIEF GEC												-	-.506**	-.566**	-.692**	-.695**
VABS-3 CMM													-	.727**	.520**	.860**
VABS-3 DLS														-	.569**	.864**
VABS-3 SOC															-	.829**

<sup>8</sup> \*\* Correlation is significant at the 0.01 level (1-tailed); \* Correlation is significant at the 0.05 level (1-tailed); † Correlation approaches significance  $p=.051$  (1-tailed).

