Tourette's syndrome: The role of attention and inhibitory mechanisms in the generation and management of tics

Leanne Nicole Hockey

University College London, UCL

PhD Clinical Neuroscience

Declaration

I, Leanne Nicole Hockey, confirm that the work presented in this thesis is my own. Where information has been derived from other sources; I confirm that this has been indicated in the thesis.

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Abstract

Tourette's syndrome (TS) is characterised by the presence of premonitory urges and involuntary movements and vocalisations known as tics. Evidence suggests that TS pathology involves a widespread neurodevelopmental abnormality, which disrupts the balance of inhibition and excitation within cortico-striato-thalamo-cortical pathways. Thus, aberrant sensation, movement and behaviour, can be explained by abnormalities of limbic, associative and motor circuitry. There is a pressing need to advance our understanding of adult TS. Therefore, cognitive, physiological and clinical features of adult TS were investigated to further the understanding of tic generation and management and thereby elucidate possible modifiable mechanisms. Thirty-three adults with TS and twenty-two healthy volunteers were recruited from specialist Tourettes clinics or the community. General cognition was characterised using premorbid IQ and the CANTAB computerised-testing battery. Novel tasks were developed to investigate attention and inhibition in parallel. Interoceptive awareness was evaluated using a heartbeat-tracking method and non-invasive transcranial magnetic stimulation explored motor system neurophysiology. In adult TS, the clinical profile was characterised and the effects of attention distraction on tic frequencies explored. Adult TS was found to have marked urge and tic severity, prominent psychopathologies and comorbidities, slower motor functioning, a specific deficit in cognitive flexibility for habitually learned behaviours and altered distribution of cortico-spinal-excitability (CSE). Passive tic control, likely arising from adaptive brain change, was found to underpin mechanisms of active tic suppression, the efficacy of distraction-based tic control, and inhibitory cognitive control. Finally, reduced interoception corresponded to reduced inhibitory mechanisms of the motor system and attention distraction significantly reduces tic frequency in uncomplicated and complicated adult TS. The results suggest that adaptive motor slowing may function to preserve attentional and inhibitory cognitions, that modulation of CSE is a likely tic control mechanism and suggest a theoretical basis for the development of new therapies in TS, based on attention distraction.

Impact Statement

There is a pressing need for increased awareness, better understanding and more efficacious treatment in adult persisting Tourettes syndrome. Our research has advanced understanding of the cognitive, physiological and clinical features of adult Tourettes, and provides a theoretical basis for the development of new therapies, based on attention distraction.

This research has undergone formal peer and regulatory review in accordance with the requirements outlined by UCL, with considerable knowledge and expertise placed in the project concept, task design and development. Furthermore, recruitment and dissemination of this research was facilitated by service user and public involvement, including advertisement amongst the community by the charity Tourettes Action UK and dissemination of research results to the general public and to service users, their families and carers by Tourette's Action UK and our funders Brain Research UK. Similarly, results of our research will be disseminated to the scientific community by publishing in peer-reviewed scientific journals and by presenting at conferences and invited talks.

The impact of our research is therefore threefold: i) promoting positive scientific communication and perception of research amongst the general public and to service users, their families and carers; ii) contributing quality research to the area of adult Tourette syndrome, to further awareness and advance understanding, to generate further interest in the field; and iii) providing a theoretical basis for the development of new therapies, based on attention distraction, to improve quality of life and clinical care in adults with Tourettes syndrome.

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Chapter 1. Introduction

1.1. Background

Tourettes syndrome

Following the first written account back in the 15th century by Jakob Sprenger and Heinrich Kraemer in 'Malleus Maleficarum', in 1885, George Gilles de la Tourette published 'Study of a Nervous Affliction' (Germiniani, Miranda, Ferenczy, Munhoz, & Teive, 2012; Teive, Chien, Munhoz, & Barbosa, 2008). Subsequently, Jean-Martin Charcot named a clinically distinct movement disorder after his resident; Gilles de la Tourette's syndrome (TS) (Rickards & Cavanna, 2009). TS is characterised by the presence of involuntary movements and vocalisations which can be simple or complex in nature (Gilles de la Tourette, 1885). Simple tics can be repetitive, localised movements (e.g. brief head, neck or eye twitch or mouth gaping) or vocalisations (e.g. cough, grunt, sniffs). Complex motor tics however, involve more global, seemingly co-ordinated movements (e.g. gestures, twisting [palipraxia]) or imitation of others (echopraxia), despite being unintentional. Complex vocal tics similarly, appear intentional utterances due to their linguistic or prolonged nature (e.g. words or sentences), yet are unintended repetitions or mimicry (e.g. palilalia and echolalia) often contradictory to self-belief or social setting (e.g. obscenity [coprolalia]) (Robertson, 2000). Throughout the course of the disorder, the severity of tics are seen to 'wax and wane' (Gilles de la Tourette, 1885).

The World Health Organisation criteria of the International Statistical Classification of Diseases and Related Health Problems (10th revision, ICD-10) specifies a diagnosis of TS following the chronic presence of two or more motor and one vocal tic (WHO, 2016), typically presenting before age 18 (APA, 2013). TS is most common in males compared to females, with 1.6-9 to 1 likelihood (Kurlan et al., 2001) and occurs worldwide, across cultures with prevalence of between .3 -1% (Freeman et al., 2000; T. Knight et al., 2012; Robertson, 2008, 2015b; Robertson, Eapen, & Cavanna, 2009; Scharf et al., 2015).

In TS, the experience of bodily sensations are often reported to precede tics (Hallett, 2015; Houghton, Capriotti, Conelea, & Woods, 2014; Kwak, Dat Vuong, & Jankovic, 2003; Patel, Jankovic, & Hallett, 2014; Prado et al., 2008) and are described as building internal tension, causing discomfort and stress (Himle, Woods, Conelea,

Bauer, & Rice, 2007; Martino, Madhusudan, Zis, & Cavanna, 2013). These premonitory urges however, can be alleviated temporarily, by the performance of tics (Steinberg et al., 2010). Premonitory urges are considered core features by individuals with TS, with variability in both urge intensity and somatotopy (Cox, Seri, & Cavanna, 2018; Ganos, Bongert, et al., 2015). Despite occurring in 93% cases, premonitory urges however, are not included in diagnostic criteria (Hollenbeck, 2001; Kane, 1994; Leckman, Walker, & Cohen, 1993).

Initial reports of premonitory urge experience occurs approximately 3 years after the onset of tics; suggesting that initially, urges may not be the cause of tic generation (Leckman, Bloch, Scahill, & King, 2006; Leckman, Bloch, Sukhodolsky, et al., 2013). However, as children have difficulty reporting conscious experiences prior to the age of 10, it is possible that urges may, in fact, precede tics (Banaschewski, Woerner, & Rothenberger, 2003; Kane, 1994). Differentiation of urge and tic phenomenon is complex and further complicated by the anxiolytic effects that tic behaviours have on urge discomfort (Hawksley, Cavanna, & Nagai, 2015; Nagai, Cavanna, & Critchley, 2009). Unfortunately, in TS, due to aberrant dopamine, the relationship between tics and urges is negatively reinforced, resulting in maladaptive habit formation over time (Albin & Mink, 2006; Bortolato & Pittenger, 2017; Capriotti, Brandt, Turkel, Lee, & Woods, 2014; Cravedi et al., 2017; Evers & van de Wetering, 1994; Godar & Bortolato, 2017; Kwak et al., 2003; Sukhodolsky et al., 2017; Woods, Piacentini, Himle, & Chang, 2005).

Previously considered a motor disorder, TS is now regarded as a neuropsychiatric disorder due to the occurrence of comorbid psychiatric conditions (Freeman & Consortium, 2007; Kurlan et al., 2002). Attentional deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) are the most common comorbidities (Zinner & Coffey, 2009) however, autism spectrum disorders, mood disorders and self-injurious behaviours are also reported (Bloch & Leckman, 2009; Cheung, Shahed, & Jankovic, 2007; McNaught & Mink, 2011). Comorbidity is noted to occur in 90% of TS cases (Freeman et al., 2000) whilst ‘pure’ or uncomplicated TS is rare in clinical presentation and considered the exception rather than the rule (Draganski et al., 2010). In accordance with the clinical heterogeneity of tic behaviours and comorbidity, TS is no longer considered a unitary disorder

(Robertson, 2015b) and often the presence of debilitating comorbidities can make TS appear refractory (Kious, Jimenez-Shahed, & Shprecher, 2016).

Genetics

The origins of TS are yet to be elucidated, however there is a strong genetic component to the disorder (Georgitsi et al., 2016; Paschou, 2013; Paschou et al., 2004) with higher incidence occurring within families (Jankovic & Kurlan, 2011; Robertson, 2000), especially first-degree relatives (Pauls, Raymond, Stevenson, & Leckman, 1991) with concordance rates of 53-77% occurring for monozygotic and 8-23% for dizygotic twins (Hyde, Aaronson, Randolph, Rickler, & Weinberger, 1992; Price, Kidd, Cohen, Pauls, & Leckman, 1985). Alternatively, environmental factors such as perinatal stress, smoking, infection, birthing complications as well as autoimmune disorders and childhood infections (PANDAS), whilst controversial (Motlagh et al., 2010; Murphy, Kurlan, & Leckman, 2010), have also been implicated as risk factors for TS (Hoekstra, Dietrich, Edwards, Elamin, & Martino, 2013; Robertson, 2000).

Whilst a strong genetic component has been highlighted, views that the TS is caused by rare single genes is outdated, applying only to few heritable cases (Knight et al., 2010) and is unable to account for sporadic emergence, clinical heterogeneity or comorbidity (Deng, Gao, & Jankovic, 2012; Grados, Mathews, & Genetics, 2008; Voelker, 2004). Genome-wide association studies and other genetic research have so far failed to identify any significant genetic risk factors implicated in TS (Davis et al., 2013; Deng et al., 2012; Yu et al., 2015). Rather, a more complex process of genetic predispositions interacting with environmental risk factors, in a cumulative nature (Singer, 2011; State et al., 2003) may be better at encapsulating phenotypic heterogeneity of the disorder (Kurlan, Eapen, Stern, McDermott, & Robertson, 1994; Olson, 2004). Complex gene and environmental interactions, that are seen to change over time can account for the wax and wane course of TS severity (Leckman et al., 2006), whereby periods of increased stress can exacerbate current or contribute to re-emergence of remitted symptoms (Kurlan, 2010). This phenomenon may be an epigenetic facet of TS, whereby environmental risk factors directly impacts clinical severity via stress-mediated alterations to gene transcription (Singer, 2011).

Natural history

TS is developmental in origin, emerging around 6 years of age, with childhood prevalence of 1% (Cohen, Leckman, & Bloch, 2013; Freeman et al., 2000; Hirschtritt et al., 2015; Leckman et al., 1998; Robertson, 2000). Initially, during childhood, simple motor tics emerge, acquiring further movements and vocalisations overtime with peak tic severity reported at adolescence onset (Cohen et al., 2013). What mediates the transition to complex tics is unknown, however maladaptive habit formation is likely acquired overtime (Ganos, 2016; Godar & Bortolato, 2017; Leckman & Riddle, 2000), facilitated by tic exacerbation due to psychosocial stress, including stigma and peer exclusion (Nagai, 2015). As emotions, both negative (stress, anxiety) and positive (relaxation, excitement) influence tic severity, this suggests that in TS, there is alterations and interplay between motor and limbic systems (Neuner & Ludolph, 2011).

Tic severity is observed to be at its worst at around approximately 10.6 years of age (Bloch et al., 2006) with decline in severity upon approach to adulthood. There is a 4-5 fold higher incidence of TS in children, compared to adults (Hariz & Robertson, 2010). Whilst less common, tics can arise later in life, with the most severe and debilitating cases occurring in adulthood (Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Crncec, et al., 2017). Such cases however, often represent exacerbation or re-emergence of tics that had onset, originally, in childhood (Jankovic, Gelineau-Kattner, & Davidson, 2010). Within the third decade of life, the majority of tics are reduced and close to complete remission from 21 years age (Hassan & Cavanna, 2012; Novotny, Valis, & Klimova, 2018). Fewer than 1 in 5 report moderate to severe tic severity in adulthood (Bloch, 2013; Leckman et al., 1998) with remission reported in 30-50% of adult cases (Bloch et al., 2006; Leckman et al., 1998).

A recent longitudinal study of the clinical course of 237 adolescents with TS reiterates significant age-related decline in tic severity (Groth, 2018), supporting the longitudinal trajectory of key symptom features, originally proposed by Leckman and colleagues (Bloch et al., 2006; Leckman et al., 1998). Interestingly, 90% adults who report they are in remission, display tics upon observation; their tics however do not appear to cause distress and do not require treatment (Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003). On the other hand, 10-20% of cases have persistent or

worsening tics throughout adulthood (Bloch, State, & Pittenger, 2011; Bloch et al., 2006; Cath et al., 2011; Hirschtritt et al., 2015; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Crncec, et al., 2017) with 24% of these cases reporting moderate to severe tic severity (Goetz, Tanner, Stebbins, Leipzig, & Carr, 1992).

Coinciding with typical reports of decreased tic severity in early adulthood (Leckman et al., 1998; Robertson, 2000) overtime patients become able to actively suppress their tics, supporting proposals that childhood tics are perhaps behavioural correlates of premature motor system tuning (Jackson, Draper, Dyke, Pépés, & Jackson, 2015; Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). However, for a subset of people, 30% of cases, TS is a chronic lifelong disorder not easily managed with therapeutic interventions (Cohen et al., 2013). Subsequently, a unique facet of TS is the ability to implement cognitive control, via effortful task engagement or voluntary suppression, to subdue involuntary action (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). Thus, there is debate regarding the extent to which TS is an involuntary motor disorder (Ganos, Asmuss, Bongert, Brandt, Münchau, et al., 2015) and suggests interplay between direct and indirect pathways of action (Cavanna & Nani, 2013).

Neuroimaging

Brain regions implicated in TS are highly interconnected networks processing motion, sensations, volition of action, emotions and cognition (Alexander, DeLong, & Strick, 1986; Draganski et al., 2010). It is therefore unsurprising that TS is associated with dysfunction to movements, interoception, premonitory urges, cognition, inhibitory control and mental health (Ganos, Garrido, Navalpotro-Gómez, et al., 2015; Leckman, Bloch, Smith, Larabi, & Hampson, 2010; Riva, Taddei, & Bulgheroni, 2018). Specifically, disruptions in the balance of inhibition and excitation, crucial to typical neural circuitry function, within cortico-striato-thalamo-cortical circuitry (CSTC) pathways has been implicated in TS pathology (Clarke & Eapen, 2014; Jackson et al., 2015; Kalanithi et al., 2005; Mink, 2001b; Parent & Hazrati, 1995; Peterson et al., 2003; Ramamoorthi & Lin, 2011; Tisch, Silberstein, Limousin-Dowsey, & Jahanshahi, 2004; Worbe et al., 2012).

Whilst dysfunctional dopamine signalling is proposed to contribute to this circuitry imbalance, due to implication of the basal ganglia in the disorder (nigrostriatal

pathways) and favourable treatment with dopamine modulation (Fraint & Pal, 2015; Graybiel, 2008; McNaught & Mink, 2011), alterations in inhibitory mechanisms involving neurotransmitter γ-aminobutyric acid (GABA) is increasingly recognised. For example disruption of GABAergic neurons within the basal ganglia are noted in TS patients, with significant reductions seen in the caudate nucleus, putamen and globus pallidus externa (Leckman et al., 2010) and significant increases seen in the globus pallidus interna (Kataoka et al., 2010). In addition, alteration of histaminergic and cholinergic systems have been observed in TS (Cox, Seri, & Cavanna, 2015; Xu et al., 2015).

In TS, tic and urge occurrence is associated with enhanced activity within cortical motor and sensorimotor areas (Biermann-Ruben et al., 2012; Biswal et al., 1998; Bohlhalter et al., 2006; Eidelberg et al., 1997; Jackson, Parkinson, Kim, Schuermann, & Eickhoff, 2011b; Neuner, Werner, Arrubla, Stocker, et al., 2014; Wang et al., 2011; Worbe, Marrakchi-Kacem, et al., 2015). Over-activation within the supplementary motor area (SMA) has been proposed to be a neural correlate of the premonitory urge, for activation within this area, precedes tic-related activity within the primary sensorimotor and motor cortices and later activation of the basal ganglia; mirroring the temporal sequence of tic-related events (Neuner, Werner, Arrubla, Stöcker, et al., 2014). Tic suppression may therefore be achieved via recruitment of compensatory mechanisms that regulate neurophysiological imbalance and reduces motor system noise. Specifically, Jackson and colleagues propose that motor system noise likely arises due to a loss of inhibitory control mechanisms within the sensorimotor and motor systems (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Plessen, Bansal, & Peterson, 2009).

Exploration into how individuals with TS gain the ability over time to control their tics has led to interesting discoveries to why tics may occur and persist in the first instance. Increased activity to cortico-striatal and fronto-striatal regions (Kawohl, Brühl, Krowatschek, Ketteler, & Herwig, 2009; Peterson et al., 1998; Raz et al., 2009) including the inferior frontal gyrus (Deckersbach et al., 2014; Ganos, Kahl, Brandt, Schunke, Bäumer, et al., 2014) are examples of observed compensatory mechanisms employed to suppress tics that may regulate global neurophysiological imbalance. Other compensatory mechanisms may involve more local, neurochemical

inhibition (via tonic inhibition of GABA) to over-excitatory primary and supplementary motor regions (Jackson et al., 2015).

Neuroimaging studies of both children and adults with TS have identified similarities in the abnormal structure and function to the pathways involving cortico-basal ganglia circuitry (Worbe, Lehericy, & Hartmann, 2015), fronto-parietal connections (Church, Fair, et al., 2009; Muellner et al., 2015), cortico-striatal networks, the anterior cingulate cortex (ACC) and the caudate nucleus (Wang et al., 2011). Such dysfunction, both structural and functional, likely represents neural signatures of deviant neurodevelopment originating in childhood (Worbe, Lehericy, et al., 2015). Thus, altering the ability to develop compensatory cognitive control mechanisms, resulting in persistent tics in adulthood. Examples of structural abnormalities include reduced cortical thickness to motor and sensorimotor areas and increased fractional anisotropy to white matter tracts, indicative of enhanced structural connectivity within the striatum, thalamus, basal ganglia and sensorimotor areas (Bohlhalter et al., 2006; Worbe, Gerardin, et al., 2010; Worbe, Lehericy, et al., 2015). Functional irregularities arising from such alterations to CSTC circuitry are associated with enhanced local connectivity and reduced long range connectivity, resulting in less efficient information transfer (Bullmore & Sporns, 2009). Structural and functional abnormalities in TS that are consistent with more severe and persistent tics (Jung, Jackson, Parkinson, & Jackson, 2013) likely exacerbates abnormalities within overly inhibitory basal ganglia structures and disinhibited motor and sensorimotor cortices (McNaught & Mink, 2011), perhaps contributing to the imbalance of crucial neurophysiology (Jackson et al., 2015).

Neurophysiology

In accordance with neuroimaging findings, evidence from transcranial magnetic stimulation (TMS) support proposals of neurophysiological imbalance in TS. Specifically, in TS there is evidence of reduced short-interval intracortical inhibition (SICI), associated with $GABA_A$ergic neurotransmission, and enhanced intracortical facilitation (ICF), associated with excitatory glutamatergic (NMDA) neurotransmission. Similarly, reductions to short-interval afferent inhibition (SAI) involving cholinergic and $GABA_A$ergic inhibition of the motor cortex by the somatosensory cortex has been found in those with TS (Orth, 2009; Orth, Amann, Robertson, & Rothwell, 2005; Orth & Rothwell, 2009). The influence of comorbidity

on corticospinal excitability has also been investigated and evidence suggests that pure TS and those with comorbid OCD have similar alterations in SICI, ICF and SAI, whilst comorbid ADHD is associated with more extensive alterations in SAI and ICF (Orth & Rothwell, 2009). It is therefore likely that premonitory urges and resulting tics may originate in TS due to neurophysiological imbalance, especially in GABAergic disinhibition within somatosensory and motor cortices (Jackson et al., 2015; Orth et al., 2005).

TMS has also revealed that corticospinal excitability appears to be altered in TS during rest (Orth, Münchau, & Rothwell, 2008). For example, when TMS is administered above established stimulation thresholds, the subsequent generated motor activity is smaller in TS than HVs (Orth, Münchau, et al., 2008). Such observations suggest that fewer additional neuronal connections are being recruited, indicating uneven distribution of corticospinal excitability (Orth, 2009). As these alterations are not evident during tonic activity (Orth et al., 2005; Orth, Münchau, et al., 2008; Ziemann, Paulus, & Rothenberger, 1997) and are more extensive with increasing tic severity (Orth, Münchau, et al., 2008) it suggests that actions that are voluntary may serve to regulate corticospinal excitability in TS (Orth, 2009). Focus on voluntary actions may therefore have therapeutic potential (Orth, Münchau, et al., 2008).

Cognition

The complex aetiology in TS, including disruption to CSTC pathways and clinical features such as urges, tics and comorbidity (Jackson et al., 2015; Ramamoorthi & Lin, 2011) strongly implicates behavioural and cognitive impairments (Channon et al., 2009; Channon, Gunning, Frankl, & Robertson, 2006; Eddy, Rizzo, & Cavanna, 2009). Whilst cognitive dysfunction has been implicated in adult TS (Channon et al., 2009; Channon et al., 2006; Eddy et al., 2009) literature is at large inconsistent due to failures to control for the effects of tic severity or tic suppression (causality issues) and due to the lack of task consensus or suitability (sensitivity issues) (Channon et al., 2009; Eddy et al., 2009; Kalsi, Tambelli, Aceto, & Lai, 2015; Robertson, 2015a). Attempts to identify whether cognitive deficits are attributable to uncomplicated TS have been undertaken, but has proven difficult due to lack of adequate characterisation and efforts to control comorbidity. Such perspectives are however outdated (Eddy et al., 2009; Kalsi et al., 2015; Robertson, 2015a); TS should not be

considered a unitary disorder (Robertson, 2015b) and complicated TS represents the majority of clinical presentations (Draganski et al., 2010). Despite these methodological issues, impairments in executive function, attention and inhibitory control are reported in adult TS (Channon et al., 2009; Robertson, 2015a) with the degree of impairment coinciding with the extent of comorbidity (Channon et al., 2009; Robertson, 2015a).

Brain networks and structures implicated in various forms of tic control (passive and active) play a key role alongside the basal ganglia in volitional action and mediation of executive functions (Jackson et al., 2015; Jahanshahi & Rothwell, 2017; Kalsi et al., 2015). In addition, different states of neural activity have been observed under voluntary tic inhibition with evidence for increased inhibitory activity upon approach of tic behaviours (Ganos et al, 2018; Hong et al, 2013; Peterson et al, 1998; Serrien et al, 2004). Thus, exploration of cognition in those with TS is further complicated by the potential influence of tic control mechanisms, both automatic and actively employed during task performance. Mechanisms of tic control that promote inhibitory neural activity may benefit aspects of cognition relating to inhibitory control (Serrien et al., 2004). Conversley, tic suppression recruiting frontal control to channel focus to prevent oneself from ticcing (Ganos et al, 2015; Misirlisoy et al., 2015) places demand on working memory and attentional capacity which likely impacts performance across several domains of cognition (Erenberg, 2005). To date, attempts to establish the effects of tic management during task performance has not occurred, limiting the inferences that can be made regarding cognition in TS. Further investigation of cognition in TS exploring the effects of tic control (tic suppression compared to free to tic conditions) are warranted.

Treatment

Treatments for TS involve pharmacological interventions to reduce tic severity and tic occurrence and involves medication with atypical and typical antipsychotics, anticonvulsants and botulinum toxin injections (McNaught & Mink, 2011; Roth, 2018; Waldon, Hill, Termine, Balottin, & Cavanna, 2013). Additionally, pharmacological treatment of symptoms associated with comorbid conditions (i.e. ADHD, OCD, anxiety, depression) are often prescribed (Jankovic, 2015). In extreme cases where tics are debilitating, surgical intervention with deep brain stimulation (DBS) is considered, yet consensus on the optimum target sites are warranted (Cavanna,

Eddy, et al., 2011; Fraint & Pal, 2015). Whilst pharmacological intervention can be of use, with reports of 25-70% reduction in tics, long-term treatment is unfavourable due to negative side effects including metabolic syndrome, weight gain, apathy and extra-pyramidal effects (Robertson, 2000; Singer, 2010; Stern, 2018).

Psychological therapy for TS is considered first line treatment alongside pharmacological intervention (Jankovic, 2015) and involves comprehensive behavioural intervention for tics (CBIT) that alongside psychoeducation, relaxation techniques and peer involvement, employs habit reversal therapy (HRT) (Frank & Cavanna, 2013; Hollis et al., 2016; Whittington et al., 2016; Woods, Piacentini, Chang, et al, 2008). HRT aims to familiarise individuals with triggers and the nature of their urges and tics. In doing so, this therapy promotes the learning of competing alternative movements, in different muscles, in response to urges, in an attempt to reduce the association between urge and tic response (Bate, Malouff, Thorsteinsson, & Bhullar, 2011; Carr, 1995; McGuire, 2016; Piacentini & Chang, 2006; Verdellen, van de Griendt, Hartmann, Murphy, & Group, 2011; Whittington et al., 2016). Whilst noted to be effective in reducing symptoms in approximately 50% of children (Dutta & Cavanna, 2013; Frank & Cavanna, 2013; Piacentini et al., 2010; Verdellen et al., 2011) the efficacy of treatment for adults is less promising, with 10 month post-treatment tic severity similar to those receiving psychotherapy (Wilhelm et al., 2012), suggesting benefits may simply be related to therapy engagement and reducing stress and anxiety (Buse, Kirschbaum, Leckman, Munchau, & Roessner, 2014; Houghton et al., 2017). Furthermore, CBIT is not suitable for the cognitively impaired (Novotny et al., 2018).

States of stress, anxiety and excitement can cause tic severity to dramatically increase (Robertson, 2000); for example, social interactions can increase tic severity and elicit inappropriate behaviours (Conelea, Woods, & Brandt, 2011; Eddy & Cavanna, 2013; Steinberg, Shmuel-Baruch, Horesh, & Apter, 2013). How emotionally salient states can modulate tic severity is not known, however perturbed interoception and autonomic function may be able to alter motor system circuitry, in a process mediated by attention (Ganos, 2016; Ganos, Garrido, Navalpotro-Gómez, et al., 2015; Misirlisoy, Brandt, Ganos, Tübing, et al., 2015; Nagai, 2015). In accordance with views that premonitory urges and tics are a product of motor system noise, arising from CSTC neural imbalance (Jackson et al., 2015), attention to these

urges and tics may boost their signal, leading to increased occurrences of involuntary behaviour (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015; O'Connor, St-Pierre-Delorme, Leclerc, Lavoie, & Blais, 2014; Woodman & Luck, 2003). It is therefore unsurprising that directing attention inwards to urges and tics has less than favourable therapeutic efficacy in adult TS.

Interoception

Brain regions implicated in TS are highly interconnected networks that process sensations and emotions (Alexander et al., 1986; Draganski et al., 2010), accordingly, TS has been associated with dysfunction in premonitory urges and interoceptive awareness (Ganos, Garrido, Navalpotro-Gómez, et al., 2015; Leckman et al., 2010). Interestingly, the perception of premonitory urges has been found to depend on an individual's capacity to perceive or be aware or their own interoceptive signals (Ganos, 2016). Subsequently, it has been proposed that the experience of premonitory urges in TS (Kwak et al., 2003; Steinberg et al., 2010) reflects aberrant interoceptive awareness (Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011). Interoceptive awareness is a measure of how aware people are to their internal body processes, with the development of such awareness important to body autonomy and self-awareness (Ganos, Garrido, Navalpotro-Gómez, et al., 2015). Emotions, both negative (stress, anxiety) and positive (relaxation, excitement) can influence tic severity suggesting alterations and interplay between motor and limbic systems in TS (Neuner & Ludolph, 2011). It is possible that interoceptive awareness can influence the valence of internal experiences, with altered awareness likely to cause stress and anxiety; in turn affecting tic severity (Paulus & Stein, 2010).

Interoceptive awareness is observed to be reduced in adults with TS, with higher awareness associated with worse premonitory urge severity (Ganos, Garrido, Navalpotro-Gómez, et al., 2015). Therefore in TS, problems with interoceptive awareness could mean that individuals have difficulties interpreting the source of their urges (Ganos, Asmuss, Bongert, Brandt, Münchau, et al., 2015) and/or have negative experiences when attending to internal physical states (Bench & Lench, 2013; Ganos, Garrido, Navalpotro-Gómez, et al., 2015; Paulus & Stein, 2010). Either way, interoception may be a negative experience that amplifies motor system noise, perhaps by interacting with the autonomic nervous system or immune pathways (Nagai, 2015; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, et al.,

2017), resulting in increased involuntary movement. How interoceptive awareness is related to tic generation and management in adult TS, is yet to be elucidated.

Role of attention

Individuals with TS possess the unique ability to implement cognitive control in order to inhibit tics, by active suppression or by focusing attention on effortful tasks (Misirlisoy, Brandt, Ganos, Tubing, et al., 2015). As voluntary action has been shown to regulate the distribution of corticospinal excitability (Orth, 2009; Orth et al., 2005; Orth, Münchau, et al., 2008), diverting attention externally or to actions of their own volition appears critical to tic management (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). Attention distraction could reduce tic frequency by limiting resources available to experience premonitory urges and decreases stress. Alternatively, attention distraction may reinforce distinctions between voluntary and involuntary motor pathways, perhaps by recruiting attentional resources to one system over the other (Ganos, 2016; Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). There appears to be an inhibitory relationship between the voluntary and involuntary motor pathways in TS that may be modulated by attention (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). Furthermore, attention distraction poses treatment potential for adults with TS who struggle with tic management, either due to a failure of compensatory mechanisms or difficulty with active tic suppression, and are prone to negative experiences, due to comorbidity and altered interoceptive awareness, when attention is diverted internally towards their urges and tics (Ganos, 2016; Misirlisoy, Brandt, Ganos, Tübing, et al., 2015; Robertson, 2015a).

Conclusion

There is a pressing need to advance our understanding of adult TS, both uncomplicated (no comorbidities) and complicated (by the presence of comorbidity) (Robertson, 2015a). By investigating cognitive, physiological and clinical features of adult TS, we will be able to advance our understanding of tic generation and management. In doing so, we hope to gain valuable insight into how such factors mediate the degree to which attention distraction therapies (harnessing voluntary action as a therapeutic tool to regulate corticospinal excitability) may benefit those with adult TS.

1.2. Rationale

There is emerging evidence that in TS there are difficulties in the ability to inhibit actions (Eddy et al., 2009; Orth & Rothwell, 2009). A proposed mechanism is that there is a disruption in the balance between inhibitory and excitatory processes in the CSTC motor circuitry (Ganos, Garrido, Navalpotro-Gómez, et al., 2015; Jackson et al., 2015). Consequently, motor noise signals that occur in the brain are not sufficiently inhibited and are perceived as meaningful. Alterations in inhibitory mechanisms may therefore explain why those with TS have problems controlling movements i.e. tics. As dysfunction in CSTC is noted in children and adults with TS (Muellner et al., 2015; Wang et al., 2011), it is proposed that in some, there is a failure of neurodevelopmental mechanisms resulting in the persistence of tics in adulthood (Worbe, Lehericy, et al., 2015).

Motor and vocal tics are usually preceded by the build-up of an 'urge' (Kwak et al., 2003). At this stage some people can actively suppress the tic from developing for short periods of time (Steinberg et al., 2010). Current psychological therapy (CBIT and HRT) is aimed at producing a competing response when the urge arises, thereby enabling tic suppression (Bate et al., 2011). Such therapy is based on the hypothesis that in TS there is a problem with inhibitory mechanisms (Jackson et al., 2015). Whilst effective in reducing tic severity in children (Piacentini et al., 2010) treatment efficacy in adults is less promising (Wilhelm et al., 2012). Further, focusing attention on tics can cause stress and anxiety that may amplify deviant motor signals and generate involuntary behaviour (Clark, 1986; Nagai, 2015; Robertson, 2000). It is therefore apparent that therapies requiring attention to be focused on the urge to tic may not work or could make tics worse. Thus there is a pressing need for better treatments in adults with TS (Jankovic, 2015).

A unique facet of TS is that people often note that their tics are automatically reduced when they are distracted or concentrating on something (Robertson, 2000). This suggests that there may be an additional problem in TS with attention. Rather than focusing on urges to help prevent tics, learning distraction techniques may be a promising alternative therapy (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015) for tic control. Distraction is likely to operate by diverting resources available to attend to urges onto voluntary actions (e.g. stimulating task), thereby regulating CSTC neurophysiological imbalance (Jackson et al., 2015; Orth & Rothwell, 2009).

Further characterisation of attentional and inhibitory mechanisms in TS, and how clinical features and comorbidities (OCD, ADHD) interact with these mechanisms, is paramount for advancing our understanding of tic generation. Specifically, by investigating whether attentional and/or inhibitory mechanisms are altered in TS and if so, how these alterations influence the motor system, our research aims to provide a theoretical basis for the development of new TS therapies.

1.3. Aims

The overall aim of this research was to assess cognitive, physiological and clinical factors, which influence the severity of TS, and thereby elucidate possible modifiable mechanisms. The specific aims and objectives of each experimental chapters are as follows:

General cognition

The aim was to characterise the general cognitive profile of adults with TS by: a) measuring premorbid IQ; and b) assessing general cognitive abilities with the CANTAB computerised testing battery using tests sensitive to attention and inhibitory control, previously suggested to be associated with both uncomplicated and complicated TS.

Attention and inhibition

The aim was to explore, in detail, whether adult TS is associated with specific cognitive deficits in attention and inhibition by: a) developing tasks that are complex and sensitive to the measurement of attention and inhibition in parallel, with minimal dependence on working memory; and b) assessing attention and inhibition using these computerised cognitive tasks, to evaluate the degree of impairment in adult TS.

Interoceptive awareness

The aim was to characterise further the relationship between interoceptive awareness and adult TS by: a) assessing whether interoceptive awareness is altered

in adult TS; and b) exploring the relationship between interoceptive awareness and general cognition, clinical profiles and cognitive and neurophysiological attentional and/or inhibitory mechanisms.

Neurophysiology

The aim was to assess corticospinal excitability (CSE) of the motor system in adult TS with non-invasive Transcranial Magnetic Stimulation (TMS) and explore the impact of tic control mechanisms on motor system neurophysiology by: a) obtaining measures of CSE at rest and during target muscle activity; b) assessing neurophysiological balance of inhibitory and excitatory mechanisms in the motor system; and c) observe CSE during instructions to tic freely or suppress tics.

Clinical profile

The aim was to assess the clinical profile of adult TS by; a) characterising i) urge and tic severity ii) psychopathology; and iii) comorbid conditions and; b) assess the relevance of clinical features and comorbid symptoms to interoceptive awareness and cognitive and neurophysiological indices of attention and inhibition.

Comorbidity subgroups

The aim was to assess the extent and severity of comorbid conditions by: a) characterising and assigning individuals to comorbidity subgroups based on clinical rating scales; and b) exploring whether differences exist across comorbidity subgroups in medication, general cognition, interoceptive awareness and cognitive and neurophysiological indices of attention and inhibition.

Attention distraction

The aim was to explore the effects of attention distraction and voluntary tic suppression on tic frequency during the performance of a CPT task by: a) assessing the individual and summative influence on tic frequency of i) voluntary tic suppression and ii) attention distraction load; and b) evaluating the impact of these tic control processes on task performance indices of attention and inhibition.

Chapter 2. Methodology

2.1. Study design

Ethics

The presented studies have been reviewed and approved by the London Queen Square Research Ethics Committee and the Health Research Authority 16/LO/1417. IRAS project ID 200509.

Funding

This research was funded by a personal award by Brain Research UK to Leanne Nicole Hockey as part of the Institute of Neurology (UCL) Clinical Neuroscience PhD programme.

Design

This research consisted of an observational case-control study, requiring participants to attend on one or two occasions according to their preference.

Participants

Tourette's syndrome

Adults with TS were recruited either from a University College London Hospital (UCLH) specialist Tourette clinic or from the community via advertisement by the UK charity Tourette's Action.

Healthy volunteers

Age-matched healthy volunteers (HVs) were recruited by advertisement on a UCL volunteer database.

Inclusion Criteria

Inclusion criteria were: intellectual capacity of IQ above 70; fluency in English; and age 18- 65 years and for participants with TS, a current or past diagnosis of

Tourette's syndrome (ICD-10; F95.2) requiring the presence of two or more motor tics and at least one vocal tic for the duration of over one year (WHO, 2016).

Exclusion Criteria

Exclusion criteria were: the presence of physical or neurological disorders known to affect brain function, including organic mental behaviours and disorders (ICD-10; F00-F09), diseases of the nervous system (ICD-10; G00-G99), schizophrenia, schizotypal and delusional disorders (ICD-10; F20-F29), mental retardation (ICD-10; F70-F79) and mental and behavioural disorders due to psychoactive substance use (ICD-10; F10-F19). Additionally, for healthy volunteers a family history of TS (ICD-10; F95.2) or related comorbid conditions, ADHD (ICD-10; F90.0) or OCD (ICD-10; F42), incurred exclusion (WHO, 2016). The Mini International Neuropsychiatric Interview (MINI) (see Chapter 2) was used to screen and confirm eligibility.

Sample size

Power analyses using G*Power (version 3.1.9.2) based on previous neuropsychological findings (Channon et al., 2009) indicated that there will be a 75% chance of detecting a medium effect size (Cohen's d= 0.75) for a primary outcome measure at the 5% significance level (one-tailed) between two groups with 20 participants in each group (e.g. healthy volunteers vs. TS or medicated vs. non medicated).

Additionally, for comparisons amongst subgroups of TS there will be a 95% chance to detect a medium effect size (d= 0.75) in a primary outcome measure between three groups (by comorbidity) at the 5% significance level (one-tailed) with 11 participants in each group.

Taking power calculations, the number of participants recruited previously for similar research (Orth, Münchau, et al., 2008; Orth & Rothwell, 2009), the requirements of the clinical population and the resources of the study (PhD researcher) into consideration, the aim was to recruit 50 participants (20 healthy volunteers; 30 TS).

Only 20% of participants with TS continue to show symptoms in and throughout adulthood (Bloch et al., 2011; Bloch et al., 2006) therefore the aim to recruit 30 TS

participants is realistic, considering the rarity of adulthood presentation (Yaniv et al., 2017).

2.2. Experimental assessments

Neuropsychological assessment

Participants were seated in a quiet room and given detailed, standardised instructions before the completion of tasks. Participants were given the opportunity to clarify instructions before testing began. In between blocks and tasks, participants were able to take breaks if required.

General cognition

Premorbid intelligence quotient (IQ)

The Wechsler Test of Adult Reading (WTAR)

The WTAR (Holdnack, 2001) was used to assess general intelligence. This neuropsychological assessment requires the correct pronunciation of 50 words of increasing difficulty that do not conform to regular grapheme-to-phoneme rules of the English language. Test success is therefore due to previously learned language intelligence (how to pronounce irregular words) known to correlate with intelligence quotient (IQ). Such language abilities are shown to remain intact following neurological injury and are therefore a reliable method for estimating premorbid intelligence. The WTAR is therefore a useful measure to compare HVs and those with neuropsychiatric conditions such as TS. Subsequently, use of the WTAR in our study ensures that alterations to neurodevelopment, implicated in TS pathology, does not affect estimates of premorbid intelligence

Participants were provided with the list of 50 words, and instructed to read each word aloud when ready. If participants did not recognise the word they were instructed to attempt to pronounce the word. Participants were marked on correct pronunciation and individual raw scores were standardised based on age norms and a premorbid IQ estimate is derived.

See Appendix 1 for WTAR materials.

The Cambridge Automated Neuropsychological Test Battery (CANTAB)

The CANTAB (Sahakian et al., 1988) has been developed and validated with over 30 years of neuropsychological expertise and is a highly sensitive computerised neuropsychological assessment tool. This easy to administer battery of assessments investigates a range of cognitive abilities using non-verbal visual stimuli designed for cross-culture use, that utilises automatic randomisation as well as tailoring task dynamics to individual performance. The CANTAB was designed in conjunction with fMRI to validate brain circuity and neurochemical systems and has been extensively validated across a range of abilities and neuropsychiatric disorders. The use of the CANTAB is therefore considered the gold standard for precise, objective measurement of general cognition.

The CANTAB battery was run on an IBM compatible touch-screen computer with additional use of compatible button-box equipment. Participants were seated in a quiet room and placed in front of the tablet device and button-box equipment delivering the computerised cognitive assessment. Participants received standardised instructions and when ready proceeded with each experiment.

The following CANTAB tests were administered to characterise the cognitive profile of adult TS. The chosen tasks assess general cognition essential for everyday life as well as domains that may be altered in TS and associated with comorbid ADHD and OCD.

Intra-Extra Dimensional Shift (IED)

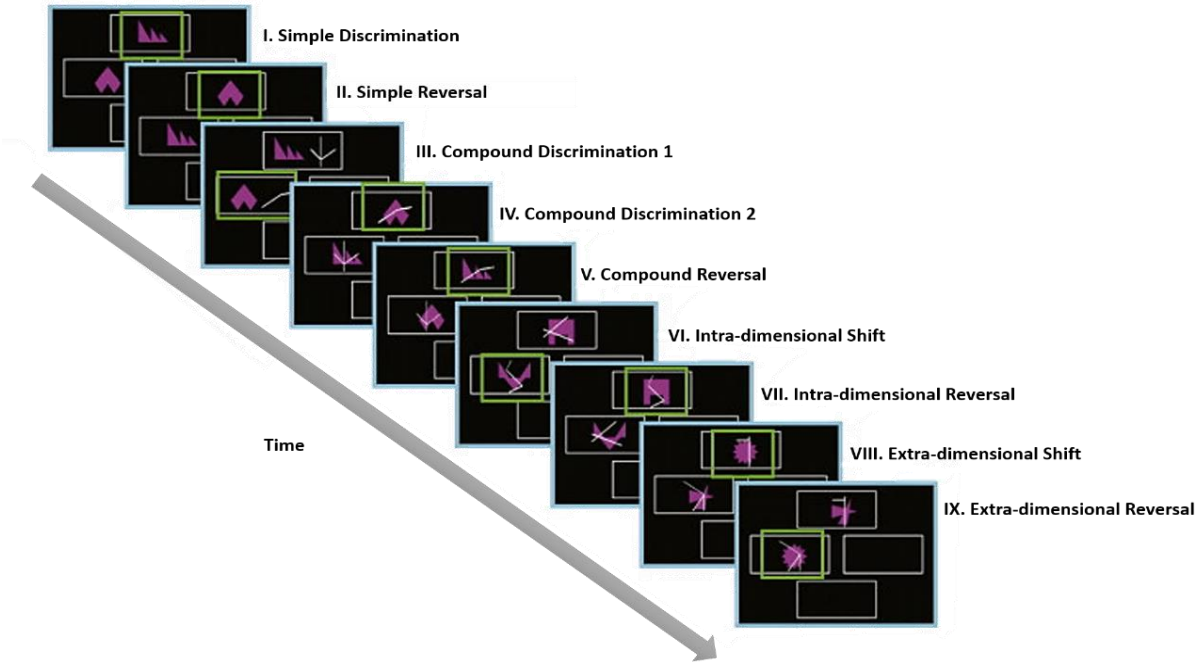


Figure 1. Schematic of the CANTAB IED subtest. Pink shapes are the main stimulus dimension that rules are based on from stage 1- stage 7. At stage 8, the white shapes become the stimulus dimension on which rule learning is based.

The IED test (see Figure 1) consists of 9 stages. Each stage measures the ability to learn a rule governing responding and the ability to reverse responding when the rule changes. During the task, two stimuli are presented simultaneously on the screen and the participant is asked to work out which stimulus is correct, based on the computer feedback (on-screen RIGHT or WRONG). Once the rule has been acquired, based on 6 consecutively correct responses, the rule is reversed.

The first response is based on chance and participants receive on-screen feedback as to whether they are correct or not. Participants are instructed to continue making selections based on the rule guided by the on-screen feedback. They are told that the rule will change from time to time, and when this occurs, that they will need to learn the new rule. Initially, a single stimulus dimension is introduced, followed by compound stimuli consisting of two dimensions. The first 5 stages test simple and compound discrimination learning and reversal. Stages 6 and 7 test the rule

abstraction and reversal when different forms of the dimensions are introduced. The 'correct' dimension remains the same throughout these stages (intra-dimensional set shifting stage). In stages 8 and 9, the rules changes so that the second stimulus dimension becomes correct. This requires an attentional shift from the previously learned correct dimension to the new dimension and is a stringent test of cognitive flexibility (extra-dimensional set shifting stage).

The main outcome measures are: a) the number of errors made; b) the number of trials completed; and c) the number of stages completed. Alongside the raw outcome measures, scores are also adjusted to compensate for participants that fail to complete a stage. As failure to complete a stage means less opportunity to make errors, a score of 25 is added for each stage not attempted, which corresponds to responding by chance as completing 50 trials results in task failure. Successful task performance relies on the learning and reversal of rules (flexibility) and the shifting of attention to relevant stimuli dimensions.

For the IED task, the number of errors made for HVs and those with TS at each IED stage is data shown for participants that attempted that particular stage, having passed the previous stage. Therefore, these are unadjusted scores.

Stockings of Cambridge (SOC)

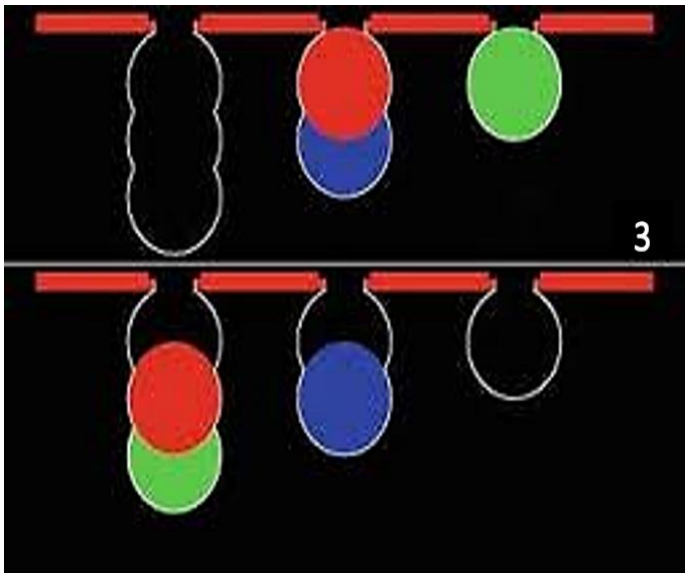


Figure 2. Schematic of the CANTAB SOC subtest.

The SOC test (see Figure 2) is used to measure executive functioning, with specific focus on spatial planning and working memory. During this task, there are two displays of three suspended stockings at the top and bottom half of the screen. In the top half of the screen the display has an arrangement of three coloured balls hanging in the stockings. At the bottom half of the screen the same coloured balls are arranged in the stockings, but in a different order to the top half of the screen. The participant is required to move the balls on the bottom half of the screen to match those displayed on the top half of the screen. Balls are moved one at a time by selecting the required ball and then selecting on-screen the position to which it should be moved.

Participants are told on each trial the minimum number of moves needed to solve the problem. They are instructed to plan their solutions before starting and aim to solve each problem in as few moves as possible. Over time, task difficulty is varied by increasing the number of minimum moves required to solve a problem (3, 4 or 5 moves). In the next phase, the computer generates, on the top half of the screen, the moves made by the participant for each solution. Participants are asked to copy these moves, on the bottom half of the screen. This allows assessment of motor times, which are subtracted from the time taken to make each move during problem solutions, to give a measure of thinking time.

The main outcome measures are: a) the number of perfect solutions achieved (problems solved in the minimum number of moves); b) mean initial thinking time, representing how long it takes for a participant to plan their moves before selecting their first ball; and c) mean subsequent thinking time, representing how long it takes them per move during completion of the problem.

Spatial Working Memory (SWM)

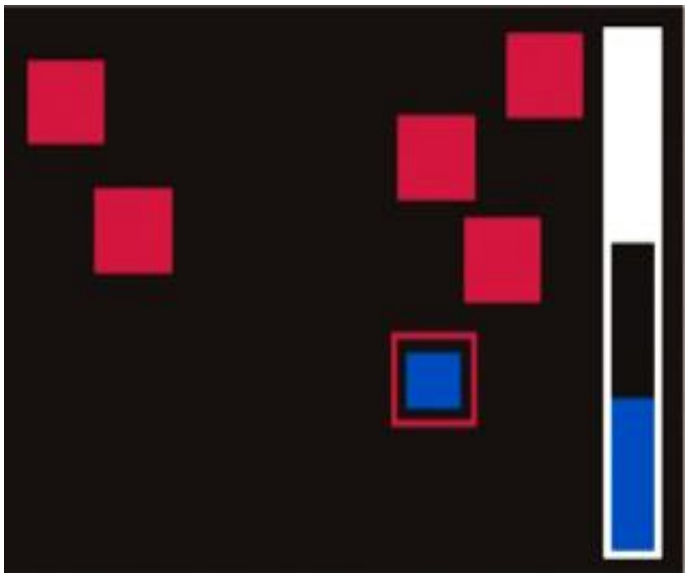


Figure 3. Schematic of the CANTAB SWM subtest.

The SWM test (see Figure 3) was used to measure working memory and requires the manipulation of visuospatial information and strategy development. During this task, participants are required to search through boxes located in different positions on the screen in order to find a hidden blue token. Task difficulty is increased overtime based on the total number of boxes required to search through (4, 6 or 8 boxes). Participants are required to find as many tokens as there are boxes on screen, e.g. during 4-box difficulty, a total of 4 tokens are to be found.

On each trial, the computer hides one token and participants must search through boxes until they locate the token. Participants are instructed that, once a token is found, the computer will not use that box again to hide a token on that trial. Successful task completion requires adoption of systematic search strategies and avoidance of boxes previously hiding a token.

The main outcome measures are: a) total errors made, including within-errors representing selecting boxes already found to be empty, between-errors representing revisiting boxes already containing a token and double-errors; and b) a strategy score, representing whether participants employed systematic search patterns.

Rapid Visual Information Processing (RVP)

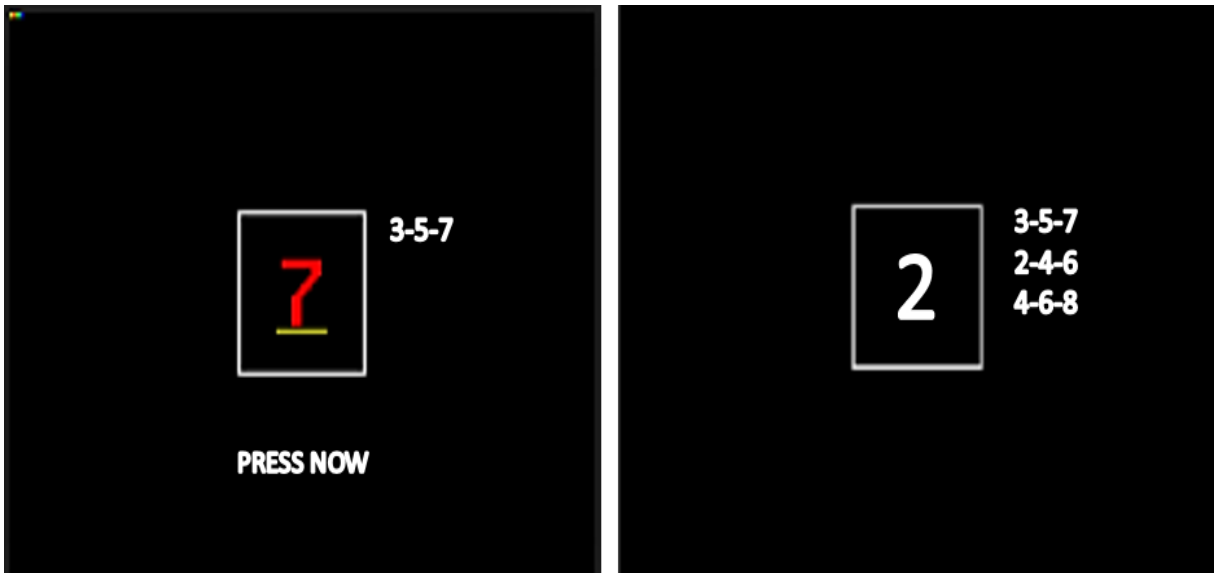


Figure 4. Schematic of the CANTAB RVP subtest. The first example (left) shows the use of colour, underlining and instructions to help participants learn sequences and correct times to respond. The second example (right) of the main task provides no on-screen assistance, other than a visual reminder of the three target sequences.

The RVP test (see Figure 4) measures sustained attention and impulsivity. During this task, at the centre of the screen individual numbers ranging from 2 to 9, appear one at a time within a box (100 digits per minute) in a pseudo-randomised order.

Participants are instructed to detect and respond to the sequential presentation of three-digit targets such as 3-5-7. Upon presentation of the third digit in the correct target sequence, participants are asked to press a button as quickly as possible.

Initially, during a practice round participants are provided with cues and feedback to ensure responses occur at the correct time (third digit of sequence). Cues and feedback are gradually withdrawn so that participants practice detecting and responding to target sequences unassisted.

During the main task participants are require to detect and respond to three different target sequences, each consisting of three digits (3-5-7, 2-4-6 and 4-6-8), for four minutes.

The main outcome measures are: a) RVP *A'* which is a signal detection measure of sensitivity to target regardless of response tendency; b) RVP *B'* which is another signal detection measure of the likelihood/bias to respond i.e. false alarms; c) total hits; d) total misses; e) total false alarms; f) total correct rejections; g) probability of a hit; h) probability of a false alarm and i) mean latency.

Stop-signal Task (SST)

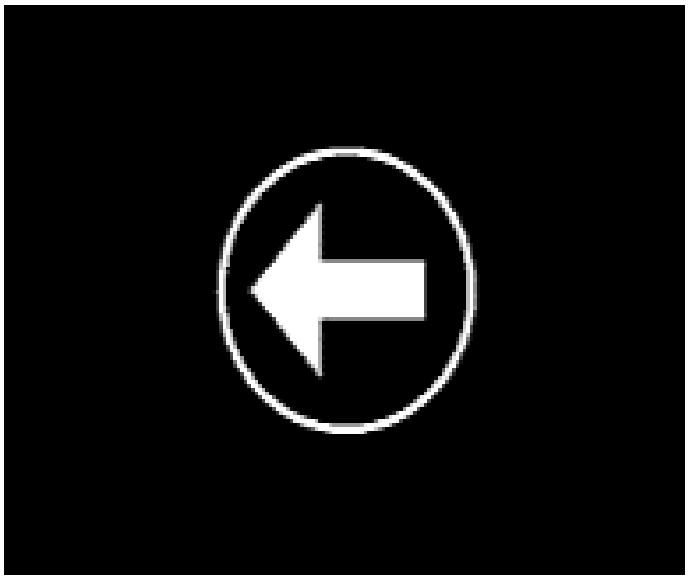


Figure 5. Schematic of the CANTAB SST subtest.

The SST test (see Figure 5) is considered a 'pure' measure of response inhibition (Jahanshahi & Rothwell, 2017; Kalsi et al., 2015; Miyake et al., 2000). During this task, at the centre of the screen, an arrow appears within a circle. Participants are instructed to press, on a dual-button box, responses corresponding to the direction the arrow is pointing, with left button responses for left-pointing arrows and the right button responses for right-pointing arrows.

During the first block, participants are required to perform this task for 16 trials, under instruction to respond as quickly and accurately as possible. For the remainder of the task participants are instructed to respond to the arrow with the appropriate button responses as before. However, they are instructed that if they hear an auditory beep signal, they are to prevent themselves from pressing the button in response to the

arrow. The auditory beep, known as the stop signal, is varied across five blocks with the stop signal delays (SSD) between arrow and beep presented in a staircase design, which adapts to an individual's performance, in order to identify the 50% success rate for inhibition.

The main outcome measures are: a) reaction time on GO trials; b) direction errors; c) proportion of successful stops; d) stop signal delay (SSD); and e) stop signal reaction time (SSRT).

Attention and inhibition

In order to investigate in more depth attention and inhibition mechanisms, the following tasks were administered.

Continuous Performance Task (CPT)

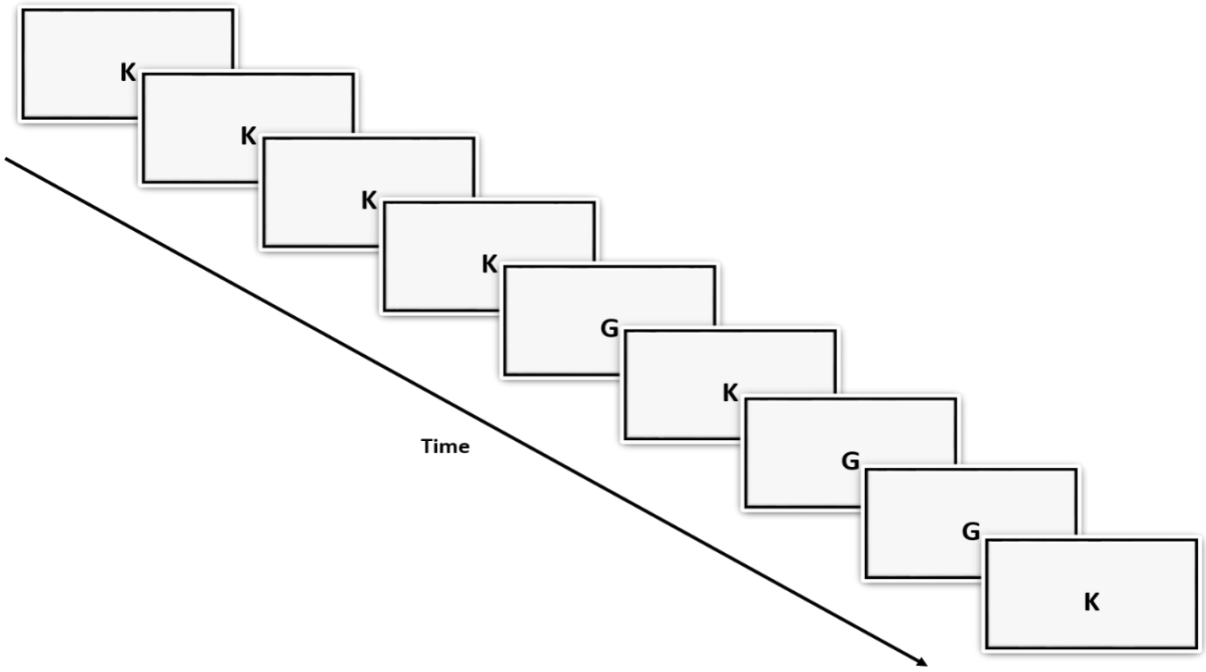


Figure 6. Schematic of the CPT task.

This CPT task variant (see Figure 6) was developed specifically for the use in TS to measure sustained attention and inhibitory control. CPT tasks require the performance of a prepotent motor action in response to simple visual stimuli and inhibition of this response is required on demand. These inhibitory paradigms require

participants to be alert over a continuous period and are therefore able to measure sustained attention and inhibitory control in parallel (Beck, Bransome, Mirksy, Rosvold, & Sarason, 1956; Riccio, Reynolds, Lowe, & Moore, 2002). Specifically, CPT tasks can be used to obtain objective measures of inattentiveness, impulsivity, sustained attention and vigilance (Huang-Pollock, Karalunas, Tam, & Moore, 2012; Riccio et al., 2002).

During this task, individual letters are presented at the centre of the screen and participants are instructed to press a button in response to target letters and to prevent themselves from pressing the button in response to non-target letters. On each trial, a blank screen is presented for an inter-stimulus interval (ISI) of either 250, 500, 750, 1000 or 1500ms (order randomised) followed by the presentation of an individual letter for 250ms. Letters were presented in a mono-spaced font, Lucida console in 30 point font size. For each experiment, of the 26 letters in the alphabet, 13 of these letters were targets and the other 13 letters were non-targets. Across blocks, letters were quasi-randomised so that visually similar letters (i.e. D, O) did not appear together. Additionally, each letter is assigned as either a targets or non-target for the duration of the entire experiment.

The experiment involves 8 individual blocks each consisting of 72 trials. Before each block on-screen instructions notified participants of target set-size and which letters will be targets. The block order of the experiment was quasi-randomised whereby the first block was predetermined to either have a set size of 1 or 2 targets. This was designed to help prevent poor initial task performance due to ceiling effects. The next 3 blocks are randomised regarding target set-size. In a ‘sandwich’ arrangement the second half of the experiment, consisting of 4 blocks is ordered in the mirror image of the first half order. Thus, if the first 4 blocks were target set sizes of: 1, 4, 3, 2 the second half would be 2, 3, 4, 1. By presenting blocks in this format we could attribute differences in performance to varying set-sizes and not effects of learning and/or practice effects. Initially, participants undergo practice blocks for target set-sizes of 1 and 2, each repeated on a loop until 60% accuracy criteria is reached. In order to assess sustained attention this task takes approximately 20 minutes to complete. This task was designed and presented using Superlab v5 (Cedrus Corporation) on a Dell laptop using a compatible button-box (Cedrus Corportation).

Furthermore, for adults with TS, one-half of the experiment (4 of the 8 blocks of the CPT task) was performed under instruction to actively suppress their tics and the other half of the experiment performed under instruction to tic freely (order counterbalanced across participants). Tic-related instructions were presented on-screen for participants with TS. Subsequently, in chapter 4, CPT scores for adults with TS are an amalgamation of free to tic and tic suppression blocks. In chapter 9, differences in CPT task performance under free to tic compared to during tic suppression is explored.

The main outcome measures of this CPT task are: a) reaction times; b) omission errors (not responding to a target); c) commission errors (responding to a non-target); d) perseverative errors (RT < 100ms); e) multiple responses; f) detectability *d* (signal detection measure of how well participant discriminates targets from non-targets); g) and response style *c* (signal detection statistic representing trade-off between speed and accuracy). Signal detection statistics were calculated using an online calculator (ComputerPsych LLC, 2011) using standard signal detection formulas (Macmillan & Creelman, 2005). Alongside these measures, evaluation of the type and number of errors and RTs for different attentional loads (target set-size), ISI durations and experimental block allows the estimation of inattentiveness, inhibitory control, impulsivity, sustained attention and vigilance.

Response Conflict Flanker (RCF)

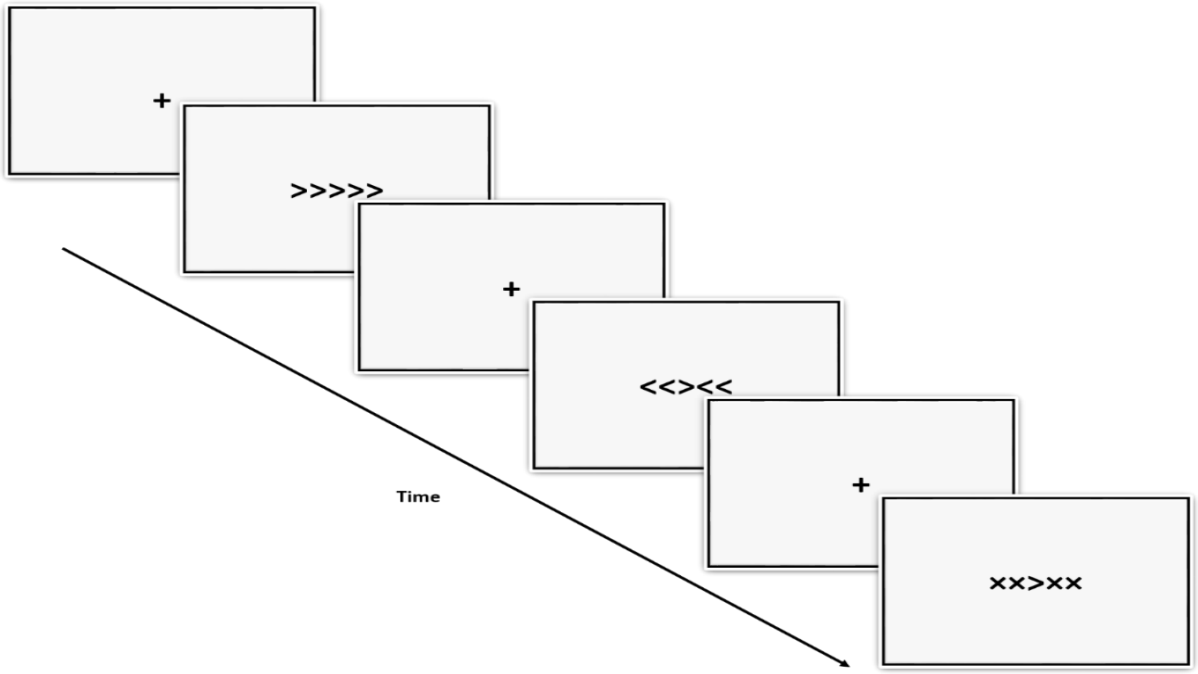


Figure 7. Schematic of the RCF task.

This variant of an Eriksen flanker task (see Figure 7) was developed for use in TS to examine selective attention and inhibitory control. This task will also explore basal-ganglia dependent action selection and ACC-dependent conflict detection (Beste, Saft, Andrich, Gold, & Falkenstein, 2008; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Eriksen & Eriksen, 1974; Mink, 1996).

During this task, on each trial, a fixation cross appears at the centre of the screen for 1200ms. Following this, an array of five items appears briefly at the centre of the screen for 400ms. The central item of the array is a target arrow and participants are required to make button box responses that are compatible with the direction that the target is pointing; i.e. left button press for left pointing arrows (and *vice versa*). The target arrows are presented alongside non-target stimuli that are compatible (congruent flankers, e.g. >>>>>), incompatible (incongruent flankers, e.g. <<><<) or neutral to target direction (neutral flankers, e.g. ××>××). Stimuli were presented in a mono-spaced font, Lucida console in 30 point font size and the fixation cross presented in 18 point font size. Participants began the task with a practice block

which repeats on a loop until 60% accuracy criteria is reached. Following this, participants undergo 3 blocks each containing 42 trials with flanker type (equal probability) and target arrow direction randomised. This task was designed and presented using Superlab v5 (Cedrus Corporation) and presented on a Dell laptop using a compatible button-box (Cedrus Corporation).

The main outcome measures are: a) reaction times; b) the number of correct responses; and c) the number of errors, made in response to each flanker type.

Transcranial Magnetic Stimulation (TMS)

Rationale

Transcranial magnetic stimulation (TMS) is a non-invasive method used to examine the corticospinal excitability (CSE) of the motor system (Hallett, 2007; Rossini et al., 2015). In adults with TS, this tool can be used to explore neurophysiological imbalance in inhibitory and excitatory mechanisms of the motor system and characterise differences in CSE during rest, voluntary action and tic management (Grados, Huselid, & Duque-Serrano, 2018; Orth, 2009)

Application of TMS to the motor cortex (M1) in the form of pulses of magnetic stimulation induces electrical currents within the brain and upon reaching threshold can depolarise neurons. Subsequently, neural signals are transmitted down the spinal cord to the target muscle, eliciting motor-evoked potentials (MEPs), which is seen as muscle movement (Hallett, 2007; Rossini et al., 2015). MEPs are recorded using electromyography via electrodes and the variability in the stimulation intensity needed to evoke MEPs provides information about motor system CSE. Furthermore, the differences in peak-peak amplitude of MEPs recorded under different conditions provides insight into CSE and functioning of inhibitory and excitatory mechanisms of the motor system.

Characterisation of motor thresholds, that being the ease and extent to which MEPs can be induced, at rest during active states and above stimulation thresholds provides insight into motor system CSE and its distribution. MEPs generated at rest may reflect activation of low-threshold, small and slowly propagating pyramidal tract neurons at the cortical level (Rossini et al., 2015). MEPs generated during voluntary action may reflect changes to axonal excitability of higher threshold central and

peripheral pyramidal neurons as their synapses become highly excitable during movement (Orth, 2009). Stimulation intensities needed to generate MEPs are higher during rest compared to voluntary action, with activity thresholds typically 80% of the intensity needed to evoke movement at rest. This occurs due to the fact that spinal motor neurons are active and randomly firing during movement and excitatory input synchronises and summates the spinal motor neuron firing (Day et al., 1989; Rossini et al., 2015). Additionally, MEPs evoked above thresholds provide insight into the distribution CSE. For example, if an increase above threshold intensity produces a large MEP then all components of the corticospinal system are equally excitable; smaller MEPs on the other hand, suggests alteration in the distribution of CSE excitability.

Stimulus-response (S-R) curves display the relationship between stimulation intensity and MEP amplitude and are typically sigmoid in shape. Initially, the slope is relatively flat, becoming linear with increasing stimulation intensities (Hallett, 2007). The gradient of this slope represents increases in the number of corticospinal fibres that are recruited by stronger descending excitatory volleys, with resulting MEP amplitudes proportionate to the sum of all synchronised propagating spikes along cortico-motor pathways (Rossini et al., 2015). Eventually, at higher stimulus intensities and due to longer conduction distance from the brain, motor units are activated more asynchronously, resulting in phase cancellation, seen as a plateau on the S-R slope (Kukke, Paine, Chao, de Campos, & Hallett, 2014; Rossini et al., 2015). The S-R curve is dynamic and representative of the physiological state of the motor system. However, due to experimental time constraints, establishing a recruitment curve is difficult. Therefore, to examine neurophysiological properties associated with the rising phase of the S-R curve, TMS intensities of 115-125% resting motor threshold (RMT) are used (Kukke et al., 2014). To investigate the S-R relationship of CSE the threshold to elicit MEPs with peak-peak amplitudes of 1mV, which is typically 120% of RMT, was established. Coincidently, this intensity also corresponds to the S50, approximately the half way point on the ascending line which is the logically optimal intensity to be used to investigate inhibition and facilitation, and will therefore be the test pulse stimulation intensity used during our TMS paradigms (Kukke et al., 2014).

Excitatory and inhibitory mechanisms of intracortical interneurons can be assessed using paired-pulse TMS protocols. Specifically, short-interval intracortical inhibition (SICI) assesses inhibitory GABAergic (GABAA receptor) mechanisms and intracortical facilitation (ICF) assesses excitatory glutamatergic (NMDA receptor) mechanisms (Hallett, 2007). These paired-pulse protocols are based on the premise that intracortical interneurons can be conditioned, by a sub-threshold TMS pulse, that modulates the amplitudes of subsequent MEPs, evoked by a second supra-threshold TMS test pulse (Hallett, 2007; Rossini et al., 2015). When a short interval of approx. 2.5ms occurs between paired-pulses, MEPs are found to be inhibited. In this instance, it is believed that sub-threshold pre-activation of intracortical neurons leads to the release of an inhibitory neurotransmitter which acts to dampen the amplitude of the successive MEP generated by the subsequent test pulse. Thus, SICI is thought to reflect inhibitory mechanisms of intracortical $GABA_A$ergic receptors as drugs known to enhance $GABA_A$ergic neurotransmission increases SICI (Orth, 2009; Orth & Rothwell, 2009; Rossini et al., 2015). When longer intervals (8-30ms) occur between paired-pulses, MEPs are facilitated. The physiological mechanisms of ICF, however, remain to be elucidated. ICF is thought to represent how glutamatergic (NMDA receptor) circuits of M1 influence the excitability of motor neurons and may reflect the recruitment of higher-threshold cortical circuits that are not activated in single pulse paradigms (Orth, 2009; Orth & Rothwell, 2009; Rossini et al., 2015).

Alongside intra-cortical inhibitory and excitatory mechanisms, the paired-pulse paradigm short-interval afferent inhibition (SAI) investigates inter-cortical inhibition of the motor cortex by the sensorimotor cortex (Hallett, 2007; Rossini et al., 2015; Tokimura et al., 2000). The N20 component of the somatosensory evoked potential (SEP) represents the duration in which afferent stimulation reaches the somatosensory cortex to be processed. Typically, this occurs approximately 20ms after sensory stimulation. MEPs evoked following peripheral stimulation are noted to be inhibited, when TMS is administered close to the N20 component. This suggests that there is inter-cortical inhibition of the motor cortex by the somatosensory cortex. To investigate SAI, peripheral sensory stimulation is delivered to the median nerve at the wrist preceding a TMS pulse to contralateral M1 (FDI hotspot) delivered at inter-stimulus intervals (ISIs) relative to the N20 SEP component. The degree of SAI evoked appears dependent on the ISIs between the conditioning sensory stimulus

and the TMS test pulse, with maximum inhibition occurring between ISIs relative to N20 – $N20^{+6ms}$. SAI is thought to represent cholinergic and $GABA_A$ergic mechanisms (Tokimura et al., 2000).

TMS is an essential tool that can allow us to explore in adult TS whether there is neurophysiological imbalance in inhibitory and excitatory mechanisms of the motor system (Grados et al., 2018; Orth, 2009).

Technical set-up

Safety

Prior to TMS experiments, participants were screened using a TMS safety tool comprised of questions to identify individuals that may be at higher risk from the procedure, despite the risk of syncope and fainting being very rare (Rossi, Hallett, Rossini, & Pascual-Leone, 2011).

See Appendix 2 for TMS screening tool.

Magnetic Stimulators

Two high-power Magstim 200 stimulators (Magstim Co., Whitland, Dyfed, UK) joined by a connecting module in a Magstim BiStim set-up were used to deliver magnetic stimulation. By using this experimental set-up, both single and paired-pulses can be delivered using the same coil under identical set-up conditions.

Coil

Magnetic stimulation was delivered to participants using a hand-held figure-of-eight coil (outer winding diameter 9mm) using a Magstim 200 stimulator. Figure-of-eight coils composed of two small copper wire coils with oppositely directed currents can achieve shallow but intense focal neural stimulation to brain regions in a selective manner (smaller coil diameter, more focal) (Ueno & Matsuda, 1992). TMS is dependent on coil orientation and the membrane properties of the axons impacted by the TMS-induced electrical field. Therefore, magnetic pulses were monophasic in waveform, inducing in the brain a current with posterior-anterior (PA) flow. To

achieve this, the coil handle was positioned at an angle of 45° pointing backwards, guaranteeing current flow perpendicular to the central sulcus (Hallett, 2007).

Surface Electromyography (EMG)

During TMS, electromyography (EMG) recordings were made from the target muscles using electrodes to measures the strength of the TMS-generated motor-evoked potentials (MEPs). EMG recordings from the scalp to measure somatosensory-evoked potentials (SEPs) were also taken (described later). EMG signals relating to the strength of the MEPs (or SEPs) were amplified with a gain of 1000 (Digitimer, UK), band-pass filtered (5-3000 Hz), digitised to 5 kHz (1401; CED, Cambridge, UK) with a Digitimer D150 amplifier (Digitimer, Welwyn Garden City, UK) and analysed off-line with Signal v5.10/v6 software (Cambridge Electronic Devices, Cambridge). If EMG signals from target muscles at rest had peak-peak amplitudes of >0.03mV then the electrodes were re-applied and interference were assessed.

Motor-evoked Potentials (MEPs)

Motor-evoked potentials (MEPs) were recorded using surface electromyogram (EMG) electrodes (WhiteSensor 40713, Ambu®, Denmark) placed in a bipolar belly-tendon arrangement. The active electrode was placed over the first dorsal interosseous (FDI) muscle of the dominant hand, the reference electrode placed on the metacarpophalangeal joint of the index finger and the ground electrode placed over the back of the hand. MEP peak-peak amplitude was our main neurophysiological measurement of interest. Further for acquisition of SEPs the active electrode was placed on the abductor pollicis brevis (APB) muscle.

Somatosensory-evoked potentials (SEPs)

Somatosensory-evoked potentials (SEPs) are electrical activity recorded from the scalp and representative of the somatosensory cortex processing afferent nerve stimulation. Specifically, the N20 latency represents the arrival of afferent nerve impulses to the primary somatosensory cortex (S1) that originate from peripheral sensory stimulation, taking approximately 20ms. The N20 latency of the SEP can

therefore be used to assess somatosensory system function and can be used to investigate inter-cortical inhibition mechanisms such as short-latency afferent inhibition (SAI).

SEPs were recorded from the scalp using disposable silver/silver-chloride Ag-AgCl electrodes. The active electrode was placed over the somatosensory cortex, 3cm posterior to C3 and the reference electrode placed 3cm posterior to C4 using the 10-20 system (Tokimura et al., 2000). The ground electrode was placed behind the ear over the mastoid process; all placed contralateral to the dominant hand. Peripheral electrical stimulation (details below) to the median nerve at an intensity (mA) needed to produce a visible APB muscle twitch (MEP of 0.2mV) was administered 500 times. An average of 500 generated SEPs was used to calculate the latency of the N20 peak for each participant. Where SEP could not be recorded, the SEP N20 latency will be assumed to be 20ms (Tokimura et al., 2000).

Peripheral Electrical stimulation

Median nerve stimulation was used to induce contraction of the thenar muscles, specifically the abductor pollicis brevis (APB). To stimulate the APB muscle, pulses of electrical stimulation (1000μs) generated by a constant-current variable stimulator (DS7A, Digitimer, UK) was applied parallel to the median nerve at the wrist via bipolar electrodes with the cathode positioned proximally. Median nerve stimulation was administered to establish SEP N20 latency and as conditioning sensory stimulation during short-latency afferent inhibition (SAI).

Sensory Threshold

An individual's sensory threshold is the minimum intensity (mA) of electrical stimulation to the median nerve (as above) needed to be felt by the participant. Stimulation intensity (mA) was decreased from above sensory threshold until the participant reported no sensation; this was then increased in small increments until sensation was reported to have returned. Establishing the sensory threshold for each individual ensured that the SAI investigation was tailored to each individual's sensory requirements.

Locating the First Dorsal Interosseous (FDI) hotspot

During all TMS experiments participants were seated in a comfortable chair and asked to relax as much as possible unless instructed otherwise. TMS was applied over the motor cortex area M1, contralateral to the target hand muscle of the participant's dominant hand, the first dorsal interosseous (FDI) with the figure-of-eight coil positioned as above (PA orientation at an angle of 45°).

To locate the FDI 'hotspot' a coordinate spatial method relative to a skull landmark, the vertex, a reference point midway between the ear canals and between the nasion (in-between the eyes) and inion (bony ridge at back of the head), was used. To find this, on the head of the participant a marking is made at 50% of the nasion to inion distance. Perpendicular to this a marking is also made at 50% of the distance between the left and the right pre-auricular (tragus) points. In order to identify the FDI hotspot, relative to the vertex (intersection of the nasion-inion and pre-auricular distances) a measurement of 5cm laterally and then 1cm anteriorly was made and this was the reference point of M1 in which locating the FDI hotspot would start.

Magnetic stimulation was applied starting at 35% maximal output stimulation intensity and moved in a medial-lateral plane, then anterior-posterior plane until the FDI target muscle was activated, as seen by index finger movement. When consistent MEPs were evoked in the FDI, the exact location was identified with markings and referred to as the FDI 'hot spot'. All TMS experimental application was administered in this exact location.

Experiments

Motor Thresholding

Resting Motor Threshold (RMT)

RMT was defined as the minimum intensity needed to evoke an MEP of >50μV (peak-peak amplitude) in five out of ten consecutive trials in the relaxed FDI target muscle.

To begin with, stimulation intensity was set to 35% of maximal stimulator output and gradually increased in steps of 5% until TMS consistently evoked MEPs of >50 μV on all trials. Thresholding was then approached from above threshold in steps of 1%

stimulator output. When MEPs failed to be generated, intensity was increased in steps of 1% stimulator output until an MEP of >50μV occurs in five out of ten consecutive trials (50% trials). The required stimulation intensity was then defined as RMT.

Active Motor Threshold (AMT)

AMT was defined as the minimum intensity needed to evoke an MEP of >200μV (peak-peak amplitude) in five out of ten consecutive trials in the tonically active FDI muscle.

Participants were asked to squeeze their index finger and thumb together at maximum force, with MEP recordings recorded. From this recording, participants were then presented visually on a screen, via an oscilloscope guidelines corresponding to 10% of their maximum force. Participants were asked to contract their index finger muscle to maintain FDI muscle activity within these 10% guidelines whilst TMS was administered. Stimulation intensity was set at RMT and decreased in 1% increments until the stimulator intensity was able to evoke MEPs of >200 μV in five out of ten consecutive trials (50%). The required stimulation intensity was defined as the AMT; AMT is usually 80% of RMT (Rossini et al., 2015).

1mV threshold

This was defined as the minimum intensity needed to evoke an MEP of > 1mV in five out of 10 consecutive trials in the resting FDI muscle. Stimulation intensity was set at RMT and increased and/or decreased as described previously until TMS consistently evoked MEPs of >1mV in five out of ten consecutive trials (50% trials). The required stimulation intensity was then defined as the 1mV threshold; 1mV threshold is typically 20% of RMT (Rossini et al., 2015).

Cortico-spinal excitability

1mV baseline

Once the 1mV threshold has been identified 15-20 consecutive MEPs were recorded from the FDI muscle at rest in all participants. No tic-related instructions were given

during 1mV baseline acquisition and trails with movement in the FDI were excluded on-line.

1mV tic management

For those with TS, participants were asked to either allow their tics to happen or to inhibit their tics to the best of their ability during the application of above threshold TMS test pulse intensity (1mV threshold).

In each block 15-20 consecutive MEPs were recorded from the FDI muscle at rest. In total 4 blocks, will be recorded with 2 blocks during tic suppression and 2 blocks during allowing tics to occur. The order of blocks was counterbalanced/randomised and 2 minutes of rest were given in between blocks. Trials with FDI movement were excluded on-line.

Short Interval Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF)

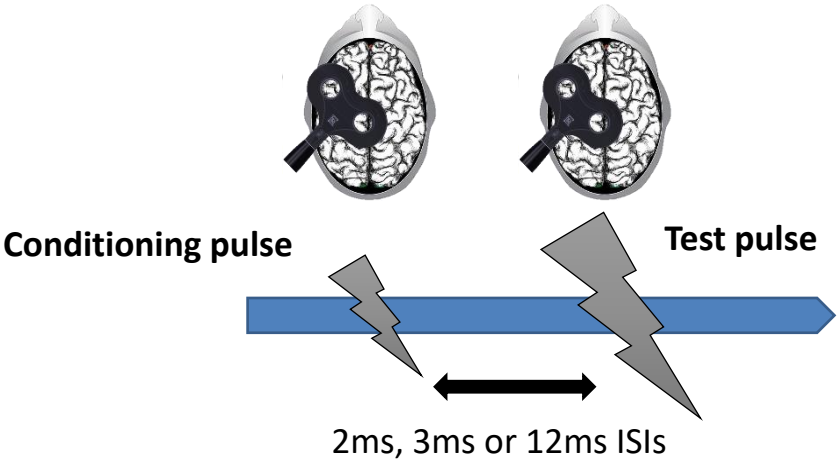


Figure 8. Schematic of the paired-pulse paradigm used to evoke SICI and ICF.

SICI and ICF (see Figure 8) are paired-pulse TMS protocols that examine mechanisms of intra-cortical inhibition (SICI) and facilitation (ICF) (Hallett, 2007). During this procedure, a subthreshold conditioning stimulus (CS) is followed by a suprathreshold test pulse with variations to interstimulus interval (ISI) duration. For this paired-pulse paradigm, the test TMS pulse intensity is set to evoke an MEP of 1mV (see rationale section). The subthreshold CS intensity was varied between 70, 80 and 90% AMT with each CS intensity forming an experimental block. During statistical analysis, only trials using 90% AMT CS intensity were used due to this being the intensity most robust at eliciting inhibition across all participants. During each block either a 2ms, 3ms or 12ms ISI between CS and test pulse was administered in a randomised order. The shorter ISIs examine SICI and the latter ICF. All test pulses occurred 100ms into the frame with CS at ISIs prior to this. For each block, 10 conditioned MEPs were recorded for each ISI and 20 non-conditioned MEPs (test pulse only) were recorded. All conditioned MEPs were averaged and normalised to non-conditioned (test pulse only) MEPs.

Short-latency Afferent Inhibition (SAI)

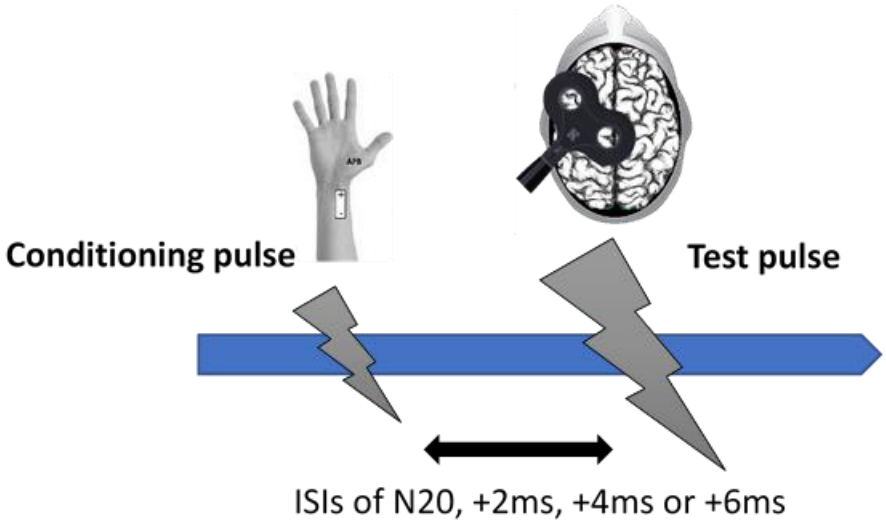


Figure 9. Schematic of the paired-pulse paradigm used to evoke SAI.

The paired-pulse short-latency afferent inhibition (SAI) TMS procedure (see Figure 9) was used to assess inter-cortical inhibitory mechanisms of the sensorimotor cortex. During this procedure, TMS was applied to the FDI hotspot 100ms into the frame at an intensity to elicit MEPs of 1mV peak-peak amplitude. Prior to this and relative to the participants' SEP N20 component (i.e. 70ms into frame for ISIs of N20 =100-20ms) participants received median nerve stimulation at the wrist (as detailed above) at an intensity (mA) of 2-3x sensory threshold (Kukke et al., 2014). The ISIs between sensory stimulation and TMS corresponded to N20, $N20^{+2ms}$, $N20^{+4ms}$ and $N20^{+6ms}$, which are approximately 20, 22, 24 and 26ms prior to the TMS test pulse. During this experiment ISIs were randomised and 30 MEPs were obtained from test pulse only conditions and 15 MEPs conditioned by a sensory stimulus were recorded at each ISI. All conditioned MEPs of different ISIs were averaged and normalised to non-conditioned (test pulse only) MEPs.

Clinical assessment

Tic Severity

Video recordings and tic frequency measures alongside validated questionnaires were acquired to measure tic severity.

Tic video recordings

Participants were recorded via video camera (Sony HDR CX240 full HD camcorder) alone in a quiet room for five minutes with no tic related instructions; these 'baseline' recordings were used to rate tic severity. Assessment of these videos was conducted independently by myself and independently by a trained clinician; consensus was used, where appropriate to reach agreements.

The Yale Global Tic Severity Scale (YGTSS)

The YGTSS (Leckman et al., 1989) is a semi-structured interview using questions and clinical observation to assess tic severity. Due to its good internal consistency (Storch et al., 2005), convergent and divergent validity (Leckman et al., 1989) and inter-rater reliability (Walkup, Rosenberg, Brown, & Singer, 1992) the YGTSS is the most comprehensive and reliable tic severity measure (Martino, Pringsheim, et al., 2017). Furthermore subscales of total severity can also be used to identify clinically relevant exacerbation of tics (Leckman et al., 1989; Lin et al., 2002; Martino, Pringsheim, et al., 2017; Storch et al., 2005). YGTSS is therefore considered the gold-standard for tic severity assessment and is the most frequently used tic rating scale worldwide (Martino, Pringsheim, et al., 2017).

Participants were asked to complete a self-report checklist detailing which motor and vocal tics they have ever and currently experience. Additionally, they are asked to note the age at which their first motor and vocal tics occurred.

Using the tic baseline video (as described above) assessment of tic number, frequency, intensity, complexity and interference were made on a severity rating scale ranging from 0-5 for both motor and vocal tics. These scores are combined to provide a Total Tic Severity Score out of 50. Further, a rating of functional impairment based off interaction with the participant and their semi-structured interview answers were calculated on a severity scale ranging from 0-50. This score was then added to the total tic severity score to provide a total YGTSS score out of 100, reflective of tic severity and associated functional impairment.

YGTSS assessment was conducted independently by myself, and then verified with a trained clinician, who independently assessed each participant, using the baseline video recordings, to produce a total tic severity score. Functional impairment rating scores were discussed and reached upon agreement with a trained clinician.

See Appendix 3 for the YGTSS materials.

Modified Rush Video-Based Rating Scale (MRVS)

The MRVS is regarded as an excellent objective assessment of tic severity (Goetz, Pappert, Louis, Raman, & Leurgans, 1999; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Crncec, et al., 2017; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Črnčec, et al., 2017). The MRVS is based upon five domains of disability: number of body areas, motor tic frequency (tics/min), phonic tic frequency, severity of motor tics and severity of phonic tics (Goetz et al., 1999). Unlike the original Rush rating scale, psychometric properties all of the domains are rated on a scale of 0-4 and are therefore internally comparable. Additionally, the modified version provides a total score of impairment; the sum of the assessed domains.

Video recordings of tic baseline videos (as described above) were used to rate tic severity using this measure. MRVS assessment of videos was done independently by myself, and then verified with a trained clinician, who independently assessed each participant, using the baseline tic video recordings. All MRVS scores were verified with a trained clinician.

See Appendix 4 for the MRVS materials.

Premonitory Urges

The Premonitory Urge for Tics Scale (PUTS)

The PUTS is a fully validated instrument (Martino, Pringsheim, et al., 2017) for assessment of the sensory premonitory phenomena preceding tics in children and adults (Banaschewski et al., 2003; Crossley, Seri, Stern, Robertson, & Cavanna, 2014; Reese et al., 2014). The PUTS assesses the intensity and quantity of urges as well as the subjective experience of control over their tics and urges (Brandt, Beck,

Sajin, Anders, & Munchau, 2016). The scale has great internal consistency correlating with total, number, complexity and interference measures of the YGTSS (Woods et al., 2005), convergent validity with assessments of tic and urge severity in real-time, and divergent consistency with measures of ADHD, OCD (Cavanna, Black, Hallett, & Voon, 2017; Woods et al., 2005). The PUTS is an excellent tool for assessment of premonitory urges, however it is difficult to cross-validate as identified biological markers are yet to be found (Banaschewski et al., 2003).

In this study, the PUTS (Woods et al., 2005) was used to assess the severity and qualitative nature of the premonitory urges participants with TS may experience prior to tics. This self-report questionnaire requires individuals to rate on a scale (1-4) the extent to which they experience the urge related phenomenon described in the 10 items. A total PUTS score was then calculated from the sum of the first 9 items.

See Appendix 5 for the PUTS materials.

Interoceptive awareness

Heartbeat mental tracking method

Interoceptive awareness was assessed using a heartbeat “mental tracking method” (Ganos, Garrido, Navalpotro-Gómez, et al., 2015) requiring participants to report from sensation alone the number of heartbeats felt during short intervals of time. Comparisons to actual heartbeat rate, recorded with a heart rate monitor were used to establish interoceptive awareness using the following formulae for each block: 1/3 ∑ (|recorded heartbeats – counted heartbeats| / recorded heartbeats).

Participants were fitted with the Polar A300 Activity Tracker heart rate chest monitor and seated comfortably in a quiet room. After a period of relaxation participants were instructed to concentrate and try to estimate the number of times their heart beats during time intervals initiated and ceased by the experimenter by saying ‘start’ and ‘stop’. At the end of each interval participants reported the number of times they have estimated their heart having beat. Participants were reminded not to take any physical pulse measurements.

There were three blocks in total, each with 25, 35 and 45 second intervals; the order of intervals were randomised in each block and rest periods were given between

blocks. Actual heart rate recordings were recorded on the Polar A300 Wrist Monitor (in possession of experimenter) and Polar FlowSync software was used to analyse the data. The start of each interval was noted by the experimenter and matched up with the monitor recordings using the software.

The main outcome measure of interoceptive awareness was an average of all blocks and ranges from a value of 0 to 1, with higher scores indicating higher interoceptive awareness.

Attentional Deficit Hyperactivity Disorder (ADHD)

The Adult ADHD Self-Report Scale (ASRS) Symptom Checklist

The ASRS Symptom Checklist (Kessler et al., 2005) is a self-report 18 item questionnaire that was used to screen for the presence of comorbid ADHD and evaluate ADHD severity. This tool is used to screen for ADHD in adults with the questions being consistent with DSM-IV criteria and address the manifestation of ADHD symptoms in adults. Participants are asked to rate how frequently the symptoms detailed in each question have occurred during the past 6 months. Ratings ask whether symptoms are experienced ‘never’, ‘rarely’, ‘sometimes’, ‘often’ or ‘very often’. For section A, if four or more items are scored as ‘sometimes’, ‘often’ or ‘very often’ for questions 1-3 or ‘often’ and ‘very often’ for questions 4-6 then it is suggestive that the participant has symptoms highly consistent with ADHD. Section B can be used to provide more information about the qualitative nature of the ADHD if present, whereby any score of ‘often’ and ‘very often’ for the remaining 12 questions as well as a rating of ‘sometimes’ for items 9, 12, 16 and 18 indicates more severe/frequent ADHD symptoms.

Participants completed this questionnaire during their research session and the main outcome measure is their total ASRS score.

See Appendix 6 for ASRS symptom checklist.

The Barkley Adult ADHD Rating Scale-IV (BAARS-IV)

The BAARS-IV (Barkley, 2011) is a self-report questionnaire used to assess current ADHD symptoms and domains of impairment including inattention, hyperactivity,

impulsivity and sluggish cognitive tempo. This tool is consistent with DSM-IV diagnostic criteria and includes recollection of childhood ADHD symptoms. Furthermore, the BAARS-IV is used to evaluate ADHD symptom severity, thus identifying individuals with likely comorbid ADHD.

For the assessment of current symptoms, individuals are required to rate the frequency of behaviour, detailed in each question, in reference to the last 6 months. Frequency ratings are ‘never or rarely’, ‘sometimes’, ‘often’ and ‘very often’. There are 27 items to be rated for frequency in this section followed by 3 questions asking if any items were rated ‘often’ or higher, questions probing age symptoms began and the degree that these symptoms impair school, home, work and social relationship functioning.

The recollection of childhood symptoms requires participants to rate the frequency of behaviours detailed in 18 questions in reference to their behaviour as a child prior to 12 years of age. There are 9 questions related to inattention and 9 related to hyperactivity. Finally, they are questioned if any childhood items were rated ‘often’ or higher and asked about the degree that these symptoms impaired home, school and social relationship functioning.

Participant completed this questionnaire during their research session and the main outcome measures are their total BAARS-IV and subscales raw scores. Importantly, the BAARS-IV raw scores are then tailored to age, with normalised percentiles calculated. Any individual scoring in the 93rd percentile or higher in the total BAARS-IV current domains of inattention, hyperactivity or impulsivity or total score, who report onset of symptoms prior to age 16 years, with impairment in at least one domain (e.g. home, work, social) is identified as likely to have comorbid ADHD.

See Appendix 7 for the BAARS-IV rating scale.

Obsessive-Compulsive Disorder (OCD)

The combined use of multiple measures is recommended to assess the complexity of OCD phenomena in those with TS (Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Črnčec, et al., 2017). The following measures are frequently used robust, validated measures suitable for exploration of OCD features (Anholt et al., 2009):

The Padau Inventory Long Version (Padua-L)

The Padau Inventory, long version (Sanavio, 1988), is a self-report questionnaire that was used to confirm the diagnosis of comorbid OCD and, due to the extensive dimensional assessment of core obsessive-compulsive features, the use of this measure additionally provides culturally sensitive insight into OCD symptom severity.

The Padua-L has 60 statements and participants are asked to score the degree of disturbance the thoughts or behaviours mentioned creates for the individuals' everyday life. The disturbance ratings are 'not at all', 'a little', 'quite a lot', 'a lot' and 'very much'. Such scores correspond with a 0-4 scale of increasing disorder intensity. A total Padua Inventory score is out of 240 with a higher score indicating the presence of obsessive-compulsive features. There are also 4 subscales that can be calculated relating to impaired control over mental activities (i.e. uncertainty, rumination), contamination (i.e. preoccupation with cleanliness, fear of contamination), checking behaviours (i.e. repeated counting, checking doors locked) and urges and worries (i.e. violent impulses, fear or losing control over antisocial or sexual urges). Subscale scores can provide qualitative insight into the specific comorbid obsessive-compulsive features of TS.

Participants completed this questionnaire during their research session and the main outcome measure is their total Padua-L inventory score. Total and subscale raw scores were normalised to reflect discrepancies in the subscale item weightings (important to look at % of total possible score). A total disturbance raw score of 60 or more on the Padua-L inventory is indicative of OCD.

See Appendix 8 for the Padua-L.

The Obsessive Compulsive Inventory (OCI)

The OCI (Foa, Kozak, Salkovskis, Coles, & Amir, 1998) is a self-report questionnaire that was used to assess the severity of obsessive-compulsive symptoms. The OCI has 42 statements and the participant is asked to score how much the described experience has caused bother or distress to them during the last month. The possible ratings are not at all, a little, moderately, a lot and extremely; corresponding with a 0-4 scale of increasing distress. An overall mean OCI distress score can be calculated whereby a score of 42 or more is indicative of OCD. Additionally, there are

7 composite subscales that can be calculated: washing, checking, doubting, ordering, obsessing, hoarding and mental neutralising. Mean scores can be calculated for each subscale and a score of 2.5 or more in any subscale is indicative of OCD.

Participants completed this questionnaire during their research session and the main outcome measure is their total OCI distress score.

See Appendix 9 for the OCI.

The Yale Brown Obsessive Compulsive Scale (Y-BOCS)

The Y-BOCS (Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989) was used to measure OCD symptom severity and provides detailed information about the current nature of symptoms having occurred in the past week. This assessment is considered the standard tool for assessment of OCD symptoms in both clinical and research settings (Frost, Steketee, Krause, & Trepanier, 1995; Grabill et al., 2008).

The assessment consists of 10 interview items that measure the severity of obsessions (obsession subscale) and compulsions (compulsion subscale) with each item scored on a Likert scale (0-4) corresponding to increasing symptom severity. A total Y-BOCS score is calculated by adding all the items together and is out of a total of 40. The Y-BOCS provides an estimate of OCD severity which is independent from the type/content of obsessions and compulsions (Mataix-Cols, Fullana, Alonso, Menchón, & Vallejo, 2004).

Participants underwent assessment of this clinical interview during their research session and the main outcome measures is their total Y-BOCS score. Total scores on the Y-BOCS between 0–7 are considered nonclinical, 8-15 mild, 16-23 moderate, 24–31 severe and 32–40 are considered extreme.

See Appendix 10 for the Y-BOCS.

Other Neuropsychiatric conditions

HVs underwent screening with the MINI to help confirm the absence of physical or neurological injury known to affect brain function. Additionally, the MINI was used to screen participants with TS and to document the presence of other comorbid conditions that may be present.

Mini International Neuropsychiatric Interview (MINI)

The MINI (Sheehan et al., 1998) is a structured clinical interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. The interview is divided into modules that correspond to a diagnostic category and based upon the number of answers relating to the main criteria of the disorder, whether diagnostic criteria is met was calculated for each participant. For this research the following modules were assessed:

i. Major depressive episode; current (past 2 weeks) and recurrent
ii. Dysthymia; current (past 2 years)
iii. Manic episode; current and past
iv. Hypomanic episode; current and past
v. Panic disorder; current (past month) and lifetime
vi. Agoraphobia; current
vii. Social phobia; current (past month)
viii. Obsessive-compulsive disorder; current (past month)
ix. Alcohol dependence; past 12 months
x. Alcohol abuse; past 12 months
xi. Substance dependence; past 12 months
xii. Substance abuse; past 12 months
xiii. Psychotic disorders; lifetime and current
xiv. Mood disorders with psychotic features; lifetime and current
xv. Generalised anxiety disorder; current (past 6 months)

Participants underwent this clinical interview during their research session and the main outcome measures are whether they meet diagnostic criteria for each module or not.

See Appendix 11 for the MINI.

Medication

Participants with TS were asked whether they take medication and if so, the type and daily dosage was noted.

Attention distraction

Video observations

In order to investigate the effects of attention distraction on tic frequency participants were required to undergo baseline tic video recordings under no tic-related instructions (described previously). Furthermore, participants with TS were recorded before CPT task completion with the experimenter in the room for two minutes with instructions to allow their tics to happen, followed by another two-minute recording with instruction to inhibit their tics to the best of their ability. Recordings were done in this order to control for suppression mediated rebound in tic severity post suppression (Grados & Mathews, 2009; Verdellen, Hoogduin, & Keijsers, 2007).

From these recordings the frequency of tics occurring (motor and vocal) were recorded, producing a measure of an individual's capacity to inhibit their tics; the number of tics occurring when no attention distraction and active tic inhibition. Additionally, a measure of how many tics occur under instruction to allow their tics to happen in the absence of attentional distraction was recorded. Both baseline measures help us to establish the effects of both attention distraction and inhibitory control mechanisms on tic frequency; in doing so, whether reduction in tic severity occurs in a summative nature can be examined.

Participants were then video-recorded during the completion of the CPT task with instructions to inhibit tics for one-half of the experiment and to allow their tics to happen for the remaining half (order randomised and counterbalanced). Tic frequencies were then recorded from these videos at each level of attentional load (N targets: non-targets) under instruction to inhibit tics or when allowing tics to occur. Each block lasts for two-minutes.

Participants underwent tic frequency ratings at baseline and during CPT task performance during their research session and the main outcome measures is their individual tic frequencies.

To obtain a measure of how active tic management (suppress or allow) and attention distraction (baseline vs. CPT) influences an individual's capacity to tic, frequencies observed under tic management instruction (suppress or allow tics) were normalised to tic frequencies observed under no tic-related instructions. This degree of change (percentage) from tic frequencies observed under no active tic management or attention distraction will allow us to objectively measure the summative effects of tic management instruction and attention distraction on tic frequency.

2.3. Statistical approach

Statistical analysis

All variables were tested for normality using the Schapiro-Wilk statistic. Additionally, boxplots were evaluated to identify outliers, and participant *z*-score values that were beyond the ± 3.29 threshold were excluded from analysis. Where data was not normally distributed, log-transformation was applied to reduce skew and normalise data.

The distribution of categorical data across groups were analysed using Chi-Square analysis. Furthermore, specifically for the CANTAB IED task, Chi-square analysis was used to assess the number of participants passing or failing each stage, with likelihood ratio analysis (Robbins et al., 1998) used to analyse the pass rates for each IED stage.

Independent group comparisons (clinical status, HVs vs TS; comorbidity, Y/N) were made using independent *t*-tests on normal raw or log-transformed data, whilst Mann-Whitney *U* tests were conducted on raw data, where transformation failed to normalise.

Comparison of more than two independent groups, such as comorbidity subgroup, were made using one-way ANOVAs on normal raw or log-transformed data with Greenhouse-Geisser correction applied to correct for sphericity, where necessary. Following this, Gabriel's post-hoc procedure was applied, due to its suitability for use with uneven sample sizes. Where data was not normal, non-parametric Kruskall-Wallis analyses were applied to the raw data, followed by Mann-Whitney *U* to make targeted confirmatory post-hoc investigation.

Independent group comparisons (clinical status, HVs vs TS; comorbidity, Y/N) of repeated-measures variables were conducted using mixed-design ANOVAs. For these analyses, clinical status or comorbidity were entered as the between-subject variables. Furthermore, either task stage, task difficulty, attentional set-size, ISI duration, experimental block or condition and error or flanker type were entered as the within-subject variables. Analyses were conducted on normal raw or log-transformed data. Where transformation did not fully normalise the data, analysis of log-transformed data was deemed more appropriate to use than the raw data, especially considering that there is no non-parametric mixed-design alternative. Additionally, Greenhouse-Geisser correction was applied to correct for sphericity where necessary.

Within-group comparisons of repeated measure variables, such as the changes to MEPs or tic frequency under different tic-related instructions, were assessed using repeated measure ANOVAs, employed using normal raw or log-transformed data; no non-parametric alternative was needed. Greenhouse-Geisser correction was applied to correct for sphericity where necessary.

Where two or more independent variables were to be assessed within a repeated-measures design, such as the attention distraction CPT task, investigating different error types, attentional load and tic-instruction condition, a two-way repeated measures ANOVA was employed. Normal raw or log-transformed data was used as no non-parametric alternative was needed. Additionally, Greenhouse-Geisser correction was applied to correct for sphericity where necessary.

A 2x2 ANOVA was conducted to investigate the interaction between attention distraction and active tic suppression on tic frequencies.

In order to investigate the strength of relationships amongst variables, Pearson's correlation analyses were undertaken on normal raw or log-transformed variables and Spearman's Rho correlational analyses were conducted on raw, non-normal data. Furthermore, where appropriate, partial correlations were carried out, as detailed above.

To see whether medication with antipsychotics effected potential differences observed amongst clinical status (HVs or TS) or comorbidity (Y/N or subgroup), ANCOVAs were conducted on the log-transformed or raw normal variables, with

medication with antipsychotics (Y/N) entered as a covariate and clinical status or comorbidity entered as a fixed factor.

Throughout this thesis, only significant results (e.g. identified at the HV vs TS level) were followed up with further exploratory analyses, as described above.

Multiple testing correction

Multiple testing correction was made using the Benjamini-Hochberg False Discovery Rate (FDR) correction procedure (Benjamini, 1995) with FDR set to 0.1.

Compared to highly conservative methods that control for familywise error rate, such as the Bonferroni correction, Benjamini-Hochberg FDR correction controls for the proportion of falsely rejected hypotheses, known as the FDR. In doing so, this method, improves power for detection of genuine significant results and is therefore suitable for clinical studies, where sample sizes are smaller.

2.4. Participant characteristics

Total sample

Table 1. Participant characteristics of the total sample.

	Healthy volunteers	Tourette's participants	Statistics
N	22	33	
Age (***M, SD***)	34.05 ± 12.99	36.79 ± 13.77	U = 307.50, z = -.954, p = .340, r = -.13
Years Education (***M, SD***)	17.00 ± 2.60	16.24 ± 2.96	U = 297, z = -1.148, p = .251, r = -.16
Premorbid IQ (***M, SD***)	107.09 ± 8.32	107.39 ± 5.85	U = 33.5, z = -.508, p = .611, r = -.07
Sex (***N***)			χ^2 (1) = .657, p = .418
Female	9	10	
Male	13	23	
Ethnicity (***N***)			χ^2 (2) = .320, p = .852
White	18	28	
Asian (**Indian, Pakistani**)	3	3	
Other (**Mixed, Japanese, Iranian**)	1	2	

Our sample of HVs and those with TS did not differ on any key participant characteristics. It is therefore likely that any differences found in cognitive ability, neurophysiology, interoceptive awareness or clinical features are due to factors associated with the presence of TS.

Table 2. Participant characteristics of the Tourette's sample.

	Tics									Urges	Comorbidity						
	YGTSS			Rush-M						PUTS	OCD				ADHD		
Participant ID	Motor	Phonic	Total	N Body areas	Frequency		Severity		Total	Total	Padua-L	OCI	Y-BOCS	Likely OCD	ASRS	BAARS-IV	Likely ADHD
					Motor	Phonic	Motor	Phonic									
1	15	7	62	3	1	1	4	1	10	24	25	21	13	Y	45	98	Y
2	17	16	63	4	2	4	4	3	17	30	33	43	14	Y	49	97	Y
3	17	14	71	2	1	3	3	2	11	29	31	30	0	N	34	82	N
4	22	20	82	4	1	1	4	3	13	28	130	118	22.5	Y	34	79	N
5	6	6	42	2	1	1	1	1	6	17	44	38	8	N	37	93	Y
6	16	9	65	3	1	1	3	2	10	31	190	126	37	Y	58	97	Y
7	16	12	78	4	1	2	3	2	12	22	100	69	19	Y	47	93	Y
8	17	12	69	3	1	3	2	3	12	32	29	41	22	Y	40	75	Y
9	6	4	30	2	1	0	1	0	4	9	8	15	14	Y	23	91	N
10	17	0	47	3	1	0	4	0	8	24	73	39	4	Y	51	98	Y
11	21	11	62	4	1	1	4	2	12	25	44	39	17	Y	49	91	Y
12	20	19	69	4	1	3	4	3	15	32	139	-	22	Y	56	99	Y
13	23	24	87	3	2	4	4	4	17	26	54	56	19	Y	35	85	N
14	14	5	49	2	1	0	3	0	6	27	52	66	19	Y	43	99	N
15	20	5	55	3	2	1	4	1	11	18	35	16	0	N	54	85	Y
16	6	4	20	1	1	0	1	0	3	9	17	4	1	N	30	87	N
17	4	0	34	1	1	0	1	0	3	30	17	11	0	N	38	50	N
18	39	13	72	3	1	1	4	2	11	27	60	57	19	Y	55	98	Y
19	8	5	33	2	1	1	1	1	6	9	21	7	8	N	37	97	Y
20	19	10	59	4	1	0	3	0	8	32	108	73	19	Y	51	98	Y
21	16	11	57	2	1	1	3	1	8	26	24	26	21	Y	41	77	N
22	13	7	40	3	1	0	3	0	7	23	27	39	10	N	50	96	Y
23	17	8	55	4	1	1	4	1	11	26	14	28	6	N	39	97	Y
24	25	23	98	4	1	2	4	4	15	29	79	41	21	Y	50	97	Y
25	10	4	44	2	1	1	1	1	6	21	63	33	19	Y	47	96	Y
26	16	4	60	4	1	1	4	1	11	27	111	78	23	Y	57	99	Y
27	10	4	44	3	1	1	2	1	8	23	49	33	17	Y	30	90	Y
28	16	4	50	3	2	0	4	0	9	13	31	30	9	N	16	50	N
29	16	6	52	2	1	0	4	1	8	36	36	86	26	Y	68	99	Y
30	16	15	71	4	1	2	4	3	14	34	103	55	6	Y	49	92	Y
31	12	4	56	1	1	0	3	0	5	28	20	9	3	N	22	84	N
32	9	7	36	2	1	1	3	1	8	23	17	25	7	N	16	50	N
33	10	4	34	2	1	0	3	0	6	19	33	17	3	N	18	75	N

Changes in dataset

The majority of participants underwent all experiments; however, some did not undertake all experiments and outliers were excluded from analysis. Despite this, variation to participant numbers did not result in any significant differences in key participant characteristics.

General cognition

IED and SWM tests of the CANTAB

Table 3. Participant characteristics for the sample that underwent the IED and SWM subtests of the CANTAB

	Healthy volunteers	**Tourette's participants**	**Statistics**
N	20	33	
Age ***(M, SD)***	32.70 ± 12.64	36.79 ± 13.77	U = 255.5, z = -1.368, p = .171
Years Education ***(M, SD)***	17.15 ± 2.43	16.24 ± 2.96	U = 260.0, z = -1.302, p = .193
Premorbid IQ ***(M, SD)***	108.25 ± 6.66	107.39 ± 5.85	U = 284.5, z = - .838, p = .402
Sex ***(N)***			χ^2 (1) = .522, p = .470
Female	8	10	
Male	12	23	
Ethnicity ***(N)***			χ^2 (2) = 1.59, p = .450
White	17	28	
Asian **(Indian, Pakistani)**	3	3	
Other **(Mixed, Japanese, Iranian)**	0	2	

Excluding outliers, 20 HVs and 33 participants with TS took part in the IED and SWM tests of the CANTAB. There were no significant differences existing in participant characteristics.

SST test of the CANTAB

Table 4. Participant characteristics for the sample that underwent the SST subtest of the CANTAB.

	Healthy volunteers	Tourette's participants	Statistics
N	21	33	
Age (*M, SD*)	33.76 ± 13.25	36.79 ± 13.77	$U = 283.5$, $z = -1.119$, $p = .263$
Years Education (*M, SD*)	17.15 ± 2.63	16.24 ± 2.96	$U = 291$, $z = -.998$, $p = .318$
Premorbid IQ (*M, SD*)	108.25 ± 8.52	107.39 ± 5.85	$U = 317.5$, $z = -.516$, $p = .606$
Sex (*N*)			$\chi^2(1) = .351$, $p = .554$
Female	8	10	
Male	13	23	
Ethnicity (*N*)			$\chi^2(2) = 1.586$, $p = .453$
White	18	28	
Asian (Indian, Pakistani)	3	3	
Other (Mixed, Japanese, Iranian)	0	2	

One HV did not undertake the task, therefore 21 HVs and 33 participants with TS took part in the SST test of the CANTAB experiment. There were no significant differences existing in participant characteristics.

Attention and inhibition

Continuous Performance Task (CPT)

Table 5. Participant characteristics for the sample that underwent CPT task

	Healthy volunteers	Tourette's participants	Statistics
N	21	32	
Age (***M, SD***)	34.71 ± 12.92	37.25 ± 13.73	U = 285.5, z = - .919, p = .358
Years Education (***M, SD***)	17.05 ± 2.66	16.19 ± 2.99	U = 267, z = -1.27, p = .204
Premorbid IQ (***M, SD***)	106.81 ± 8.41	107.06 ± 5.62	U = 307, z = - .529, p = .597
Sex (***N***)			χ^2 (1) = .743, p = .389
Female	9	10	
Male	12	22	
Ethnicity (***N***)			χ^2 (2) = .053, p = .974
White	18	27	
Asian (**Indian, Pakistani**)	2	3	
Other (**Mixed, Japanese, Iranian**)	1	2	

One HV and one TS participant did not undertake this assessment. Therefore, 21 HVs and 32 participants with TS took part in the CPT experiment. There were no significant differences existing in participant characteristics.

Response Conflict Flanker (RCF)

Table 6. Participant characteristics of the sample that underwent the RCF

	Healthy volunteers	Tourette's participants	Statistics
N	21	33	
Age (*M, SD*)	34.71 ± 12.92	36.79 ± 13.77	U = 305.5, z = - .728, p = .467
Years Education (*M, SD*)	17.05 ± 2.66	16.24 ± 2.96	U = 280, z = -1.195, p = .232
Premorbid IQ (*M, SD*)	106.81 ± 8.41	107.39 ± 5.85	U = 328, z = - .329, p = .742
Sex (*N*)			χ^2 (1) = .887, p = .346
Female	9	10	
Male	12	23	
Ethnicity (*N*)			χ^2 (2) = .043, p = .979
White	18	28	
Asian (Indian, Pakistani)	2	3	
Other (Mixed, Japanese, Iranian)	1	2	

One HV did not complete these assessments. Therefore, 21 HVs and 33 participants with TS, took part in the RCF experiment. There were no significant differences existing in participant characteristics.

Neurophysiology

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

See Table 6 for the participant characteristics of the sample that underwent SICI/ICF assessment.

The same HV who did not undergo the RCF task also did not complete the SICI/ICF assessment. Therefore, 21 HVs and 33 participants with TS, took part in the SICI and ICF paired-pulse paradigms. There were no significant differences existing in participant characteristics.

Short-latency Afferent Inhibition (SAI)

Table 7. Participant characteristics for the sample that underwent the SAI paired-pulse paradigm.

	Healthy volunteers	Tourette's participants	Statistics
N	20	31	
Age (*M, SD*)	34.45 ± 13.20	37.29 ± 13.83	U = 256.6, z = -1.033, p = .302
Years Education (*M, SD*)	16.95 ± 2.69	16.19 ± 3.04	U = 257, z = -1.036, p = .300
Premorbid IQ (*M, SD*)	106.75 ± 8.63	106.97 ± 5.78	U = 280, z = - .581, p = .402
Sex (*N*)			χ^2 (1) = 1.138, p = .561
Female	8	8	
Male	12	23	
Ethnicity (*N*)			χ^2 (2) = .658, p = .720
White	18	27	
Asian (Indian, Pakistani)	2	3	
Other (Mixed, Japanese, Iranian)	0	1	

Two HVs and two participants with TS did not undertake the SAI experiment. Therefore, 20 HVs and 31 participants with TS took part in this experiment. There were no significant differences existing in participant characteristics.

Clinical symptoms

Psychopathologies

MINI

Table 8. Participant characteristics for those with TS that underwent screening with the MINI.

	Tourette's participants
N	30
Age (*M, SD*)	36.27 ± 13.49
Years Education (*M, SD*)	15.87 ± 2.80
Premorbid IQ (*M, SD*)	107 ± 5.92
Sex (*N*)	
Female	9
Male	21
Ethnicity (*N*)	
White	26
Asian (Indian, Pakistani)	2
Other (Mixed, Japanese, Iranian)	2

Three participants with TS did not complete the screening, therefore in total, 30 participants with TS underwent screening with the MINI.

Comorbidities

ADHD

Table 9. Participant characteristics for those with or without comorbid ADHD.

	ADHD	No ADHD	Statistics
N	21	12	
Age (*M, SD*)	33.81 ± 11.81	42 ± 15.86	$U = 89$, $z = -1.387$, $p = .165$, $r = -.24$
Years Education *(M, SD)*	16.19 ± 2.79	16.33 ± 3.37	$t(31) = .131$, $p = .896$, $d = .048$
Premorbid IQ (*M, SD*)	107.57 ± 5.19	107.08 ± 7.10	$t(31) = -.227$, $p = .822$, $d = -.085$
Sex (*N*)			$X_2(1) = 1.660$, $p = .198$
Female	8	2	
Male	13	10	
Ethnicity (*N*)			$X_2(2) = 1.567$, $p = .457$
White	19	9	
Asian (Indian, Pakistani)	1	2	
Other (Mixed, Japanese, Iranian)	1	1	

There were no significant differences in participant characteristics between those with and without comorbid ADHD.

OCD

Table 10. Participant characteristics for those with or without comorbid OCD.

	Comorbid OCD	**No OCD**	**Statistics**
N	21	12	
Age (*M, SD*)	35.14 ± 14.10	39.67 ± 13.27	U = 96, z = -1.125, p = .261, r = -.20
Years Education (*M, SD*)	16.14 ± 3.12	16.42 ± 2.78	t (31) = .252, p = .803, d = .096
Premorbid IQ (*M, SD*)	107.19 ± 5.85	107.75 ± 6.09	t (31) = .260, p = .796, d = .097
Sex (*N*)			X_2 (1) = 1.660, p = .198
Female	8	2	
Male	13	10	
Ethnicity (*N*)			X_2 (2) = 1.567, p = .457
White	19	9	
Asian (Indian, Pakistani)	1	2	
Other (Mixed, Japanese, Iranian)	1	1	

There were no significant differences in participant characteristics between those with and without comorbid OCD.

Comorbidity subgroups

Table 11. Participant characteristics of comorbidity subgroups.

	TS	TS+ ADHD	TS+ OCD	TS+ ADHD & OCD	Statistics
N	7	5	5	16	
Age (*M, SD*)	41.29 ± 14.04	37.40 ± 13.32	43.00 ± 19.84	32.69 ± 11.53	F (3, 29) = 1.07, p = .376
Years Education (*M, SD*)	16.29 ± 2.87	16.60 ± 2.97	16.40 ± 4.34	16.06 ± 2.82	F (3, 29) = .05, p = .987
Premorbid IQ (*M, SD*)	108.29 ± 7.25	107.00 ± 4.69	105.40 ± 7.34	107.75 ± 5.47	F (3, 29) = .26, p = .857
Sex (*N*)					X_2 (3) = 2.72, p = .436
Female	1	1	1	7	
Male	6	4	4	9	
Ethnicity (*N*)					X_2 (6) = 4.69, p = .585
White	5	4	4	15	
Asian (Indian, Pakistani)	1	1	1	0	
Other (Mixed, Japanese, Iranian)	1	0	0	1	

There were no significant differences in participant characteristics amongst different comorbidity subgroups.

Attention distraction

Comorbidity subgroups

Table 12. Participant characteristics of comorbidity subgroups who underwent the attention distraction CPT task.

	All	TS	TS + ADHD	TS + OCD	TS + ADHD & OCD	Statistics
N	32	7	5	5	15	
Age (*M, SD*)	37.25 ± 13.73	41.29 ± 14.04	37.40 ± 13.32	43.00 ± 19.84	33.40 ± 11.57	F (3, 28) = .877, p = .465
Years Education (*M, SD*)	16.19 ± 2.99	16.29 ± 2.87	16.60 ± 2.97	16.40 ± 4.34	15.93 ± 2.87	F (3, 28) = .072, p = .975
Premorbid IQ (*M, SD*)	107.06 ± 5.62	108.29 ± 7.25	107.00 ± 4.69	105.40 ± 7.34	107.07 ± 4.91	F (3, 28) = .237, p = .869
Sex *(N)*						X_2 (3) = 3.186, p = .364
Female	10	1	1	1	7	
Male	22	6	4	4	8	
Ethnicity *(N)*						X_2 (6) = 4.447, p = .616
White	27	5	4	4	14	
Asian (Indian, Pakistani)	3	1	1	1	0	
Other (Mixed, Japanese, Iranian)	2	1	0	0	1	

One participant with TS did not complete the CPT task. Therefore, 32 participants in total underwent the CPT attention distraction assessment. There were no significant differences in participant characteristics amongst the different comorbidity subgroups.

Chapter 3. General cognition

3.1. Introduction

The aim was to characterise the general cognitive profile of adults with TS using the CANTAB computerised testing battery.

Cognitive deficits associated with adult TS may underlie an individual's ability to suppress premonitory urges, to engage in successful tic inhibition or benefit from attention distraction. Thus, characterising the general cognitive profile of adult TS allowed the establishment of whether adult TS is associated with alteration to cognitive ability, such as deficits or enhancement, and identification of putative cognitive deficits to advance our understanding of what factors may influence tic generation, clinical severity and management.

3.2. Results

Premorbid IQ

Results

There were no significant differences in premorbid IQ, $U = 33.5$, $z = -.508$, $p = .611$, $r = -.07$, amongst HVs and those with TS.

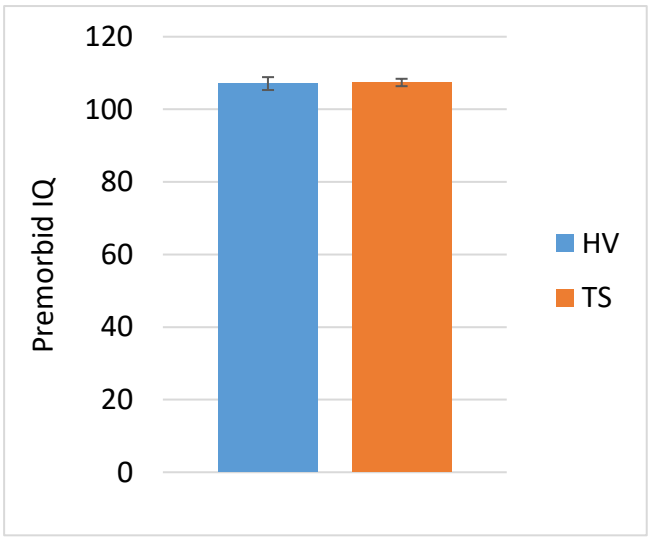


Figure 10. Mean premorbid IQ (WTAR) of HVs and those with TS . Error bars represent SEM.

Summary

Premorbid IQ as assessed using the WTAR was not found to be altered in adults with TS.

The Cambridge Automated Neuropsychological Test Battery (CANTAB) Intra-Extra Dimensional Set-shift (IED)

Results

Pass rates

All participants successfully completed IED stages requiring intra-dimensional discrimination acquisition and reversal stages (stages 1-7). There were no differences in pass rates amongst TS patients and HVs up to and including the IDR stage (all $p > .05$). At the EDS stage (stage 8), where participants are required to shift attention do a different stimulus dimension it was found that significantly more TS participants fail to complete this stage compared to HVs ($2i = 5.05$, $p = .025$). Additionally, significantly more TS participants failed the EDR stage (stage 9) than HVs ($2i = 6.14$, $p = .013$).

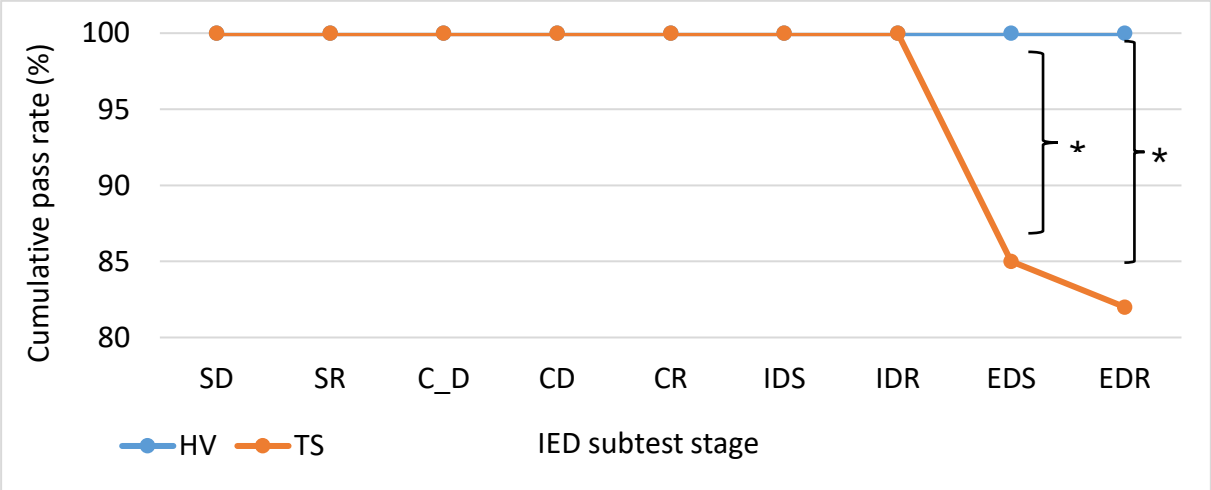


Figure 11. Cumulative pass rate (%) for each stage of the IED subtest for HVs and those with TS. Pass rates refer to the number of participants that have completed previous and current stages. *Significant following Benjamini-Hochberg FDR correction. *SD, simple discrimination; SR, simple reversal; C_D, compound discrimination; CD, compound discrimination; CR, compound reversal; IDS, intradimensional shift; IDR, intradimensional reversal; EDS, extradimensional shift; EDR, extradimensional reversal.*

Trials

Those with TS took significantly more trials to complete the overall task (*U* = 205.5, *z* = -2.29, *p* = .022, *r* = -.31) in comparison to HVs.

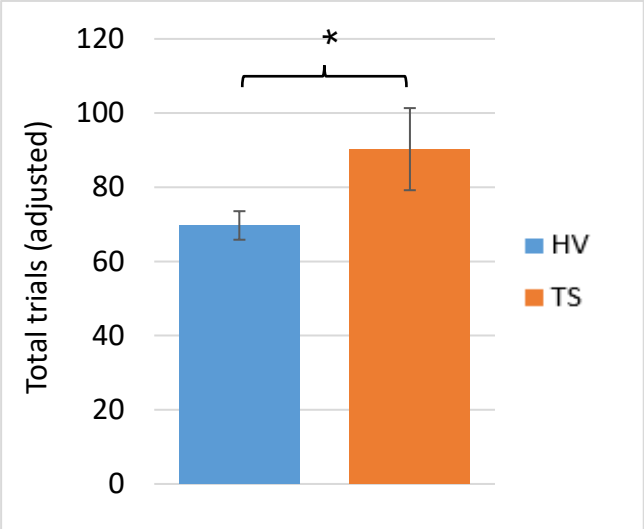


Figure 12. Mean number of total trials adjusted made for HVs and those with TS on the IED subtest. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

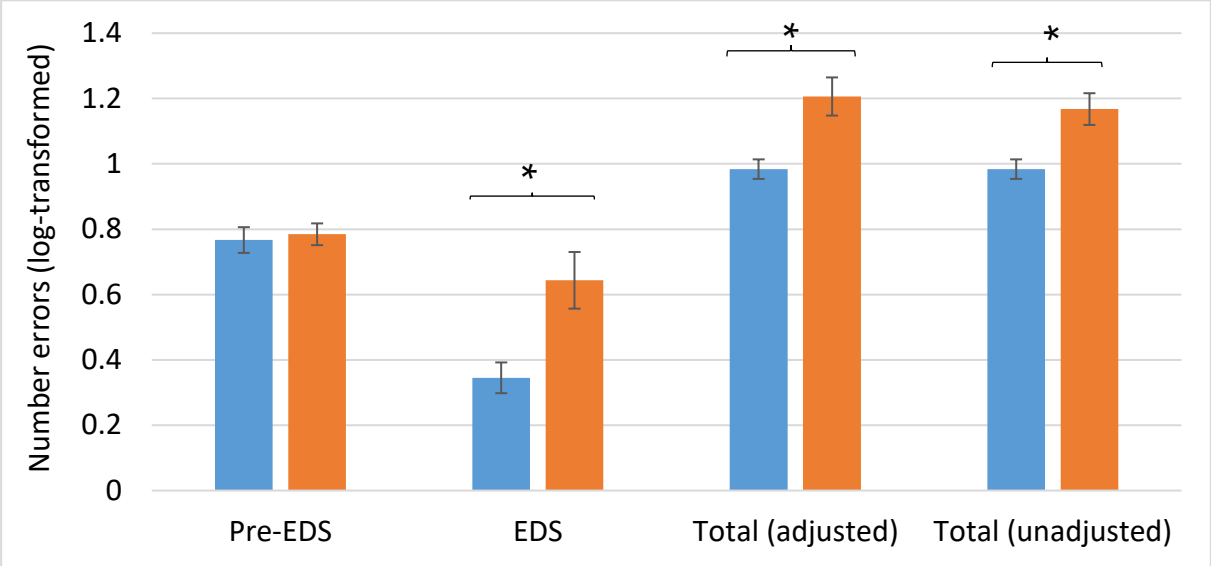
Errors

There was a significant main effect of IED stage on the number of errors made, *F* (4.193, 213.825) = 35.216, *p* = .000, *r* = .38. Planned contrasts (difference) comparing the number of errors made at the EDS stage to the mean effect of all previous IED stage errors, revealed significantly more errors at the EDS stage, *F* (1, 51) = 66.278, *p* = .000, *r* = .75.

There was a significant interaction effect between IED stage and clinical status of the participant, *F* (4.193, 213.825) = 2.441, *p* = .045, *r* = .11. To break down the interaction, planned contrasts (difference) revealed a significant difference when comparing the number of errors made by HVs and those with TS at the EDS stage to the mean effect of all previous stage errors, *F* (1, 51) = 6.373, *p* = .015, *r* = .33.

There was a trend towards a main effect of clinical status, *F* (1, 51) = 3.621, *p* = .063, *r* = .26.

A.



B.

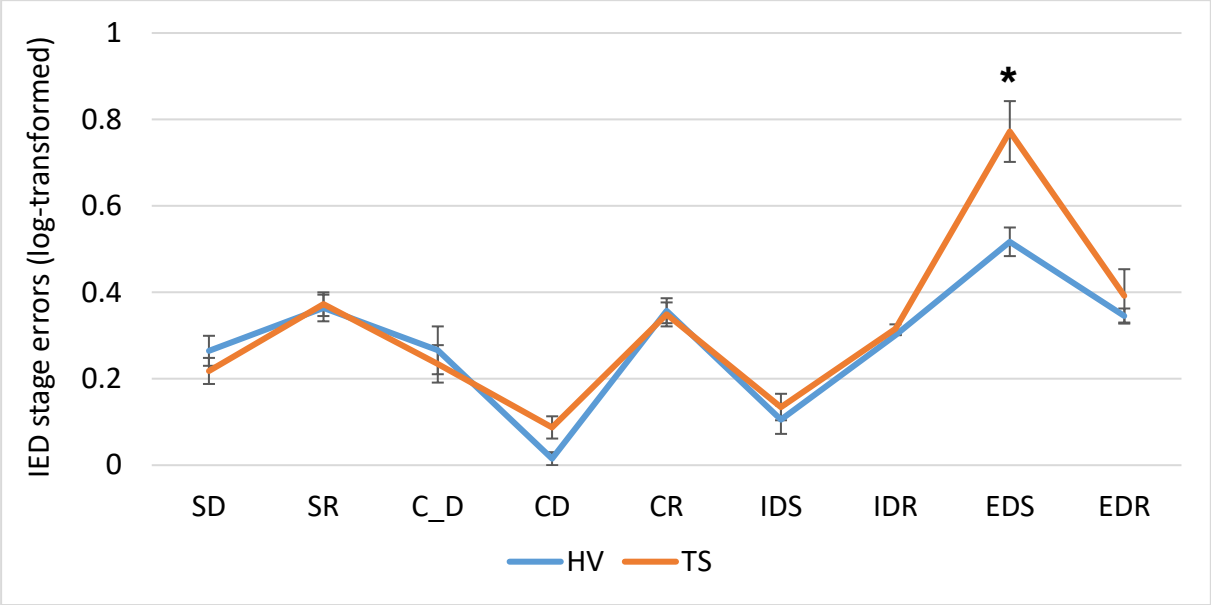


Figure 13. CANTAB IED attentional set shifting task performance. A) Mean number of pre-EDS errors (unadjusted), mean EDS errors (unadjusted) and mean total errors adjusted and unadjusted made by healthy volunteers (HV) and those with Tourette's (TS). B) Mean number of errors made for HVs and those with TS at each IED stage; data shown for the participants that attempted that particular stage, having passed the previous stage (unadjusted scores). Error bars represent SEM. *SD, simple discrimination; SR, simple reversal; C_D, compound discrimination; CD, compound discrimination; CR, compound reversal; IDS, intradimensional shift; IDR, intradimensional reversal; EDS, extradimensional shift; EDR, extradimensional reversal.* *Significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to EDS errors (log-transformed), F (1, 50) = 1.842, p = .181, r = .19. There remained a significant effect of clinical status on the number of EDS errors made, after controlling for the effect of medication with antipsychotics, F (1, 50) = 4.318, p = .043, η^2 = .079. The effect of clinical status on EDS errors, when controlling for antipsychotic medication also reaches significance following Benjamini-Hochberg FDR correction procedure (see Chapter 2).

Summary

During performance of the IED attentional set-shift task, there were no differences between HVs and those with TS in the number of errors across stages 1-7. This was indicative of an intact ability to learn, abstract and reverse rules. At stage 8, the extra-dimensional shift stage, all participants made significantly more errors compared to previous stages. The increase in errors made at the EDS stage was pronounced in those with TS, significantly so, when controlling for the effects of antipsychotic medication. Furthermore, those with TS underwent more trials overall in order to complete the task and 15% of TS participants failed to complete the EDS stage, whilst HVs completed all stages. These observations reflect impaired ability to shift attentional set, an index of cognitive inflexibility.

Stockings of Cambridge (SOC)

Results

Perfect solutions

There was a significant main effect of task difficulty (number of moves a problem required to complete the task) on the percentage of problems solved perfectly, F (2.117, 112.176) = 15.341, p = .000, r = .35.

Planned contrasts (simple) comparing the percentage of perfect solutions achieved at the highest level of difficulty (5 moves) found a significant increase in the percentage of perfect solutions achieved for 2 move, F (1, 53) = 31.525, p = .000, r =

.61 and 3 move solutions, *F* (1, 53) = 31.567, *p* = .000, *r* = .61, but no difference to 4 move solutions, *F* (1, 53) = 1.365, *p* = .248, *r* = .16.

There was no significant interaction between task difficulty (number of moves a problem required to complete the task) and the clinical status of the participant, *F* (2.117, 112.76) = .997, *p* = .376, *r* = .09. Additionally, there was no main effect of clinical status, *F* (1, 53) = .139, *p* = .771, *r* = .05.

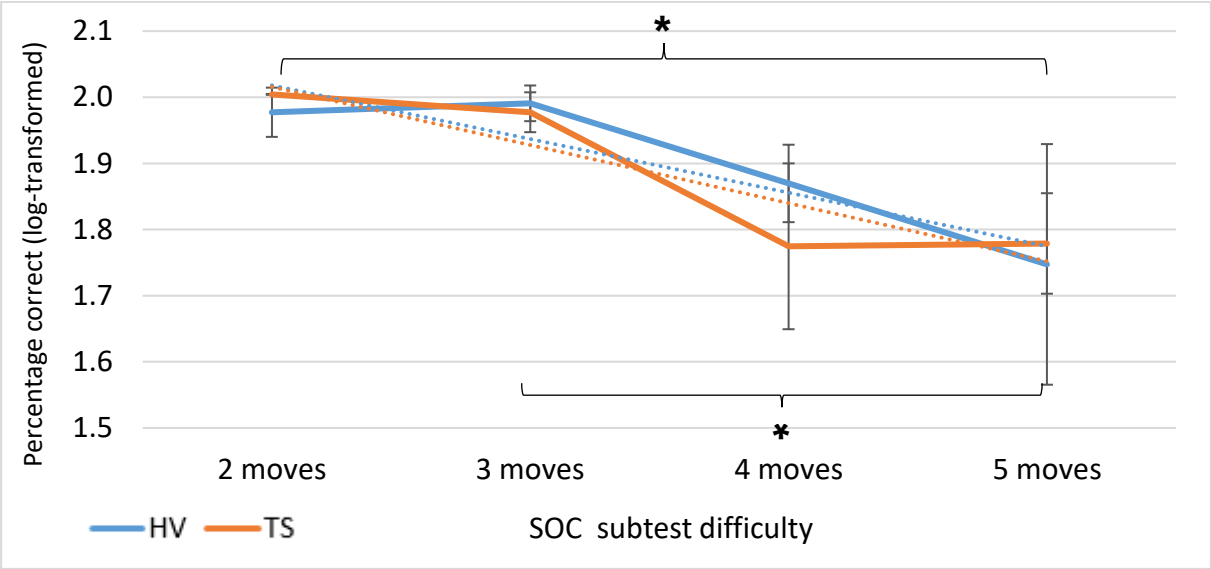


Figure 14. Percentage of perfect solutions across varying levels of difficulty on the SOC subtest in HVs and TS. Errors bars represent the SEM. *Significant following Benjamini-Hochberg FDR correction.

The number of perfect solutions made throughout the entire SOC task did not significantly differ amongst HVs and those with TS (*U* = 309.5, *z* = -.942, *p* = .346, *r* = -.13).

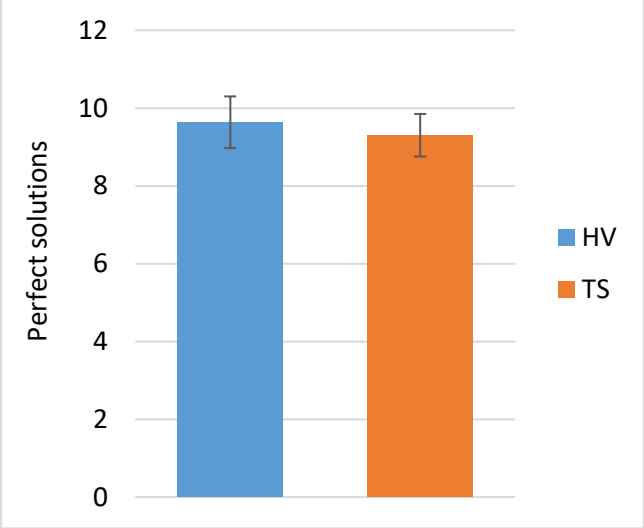


Figure 15. Mean perfect solutions made throughout the total SOC subtest in HVs and TS. Errors bars represent the SEM.

Mean ITT

The time spent thinking (planning) about the moves to make in order to solve the task prior to attempting the first move.

There was a significant main effect of task difficulty on mean initial thinking time, F (1.687, 89.404) = 62.061, p = .000, r = .53. Planned contrasts (simple) revealed that in comparison to 5 move solutions, participants took significantly less time to complete the first move of 2 move, F (1, 53) = 105.25, p = .000, r = .63, and 3 move solutions, F (1, 53) = 28.872, p = .000, r = .39, but not 4 move solutions, F (1, 53) = 3.647, p = .062, r = .15.

There was no significant interaction effect of task difficulty and clinical status of the participant on mean ITT, F (1.687, 89.404) = .936, p = .382, r = .08. Additionally, there was no main effect of clinical status on mean ITT, F (1, 53) = 2.085, p = .155, r = .11.

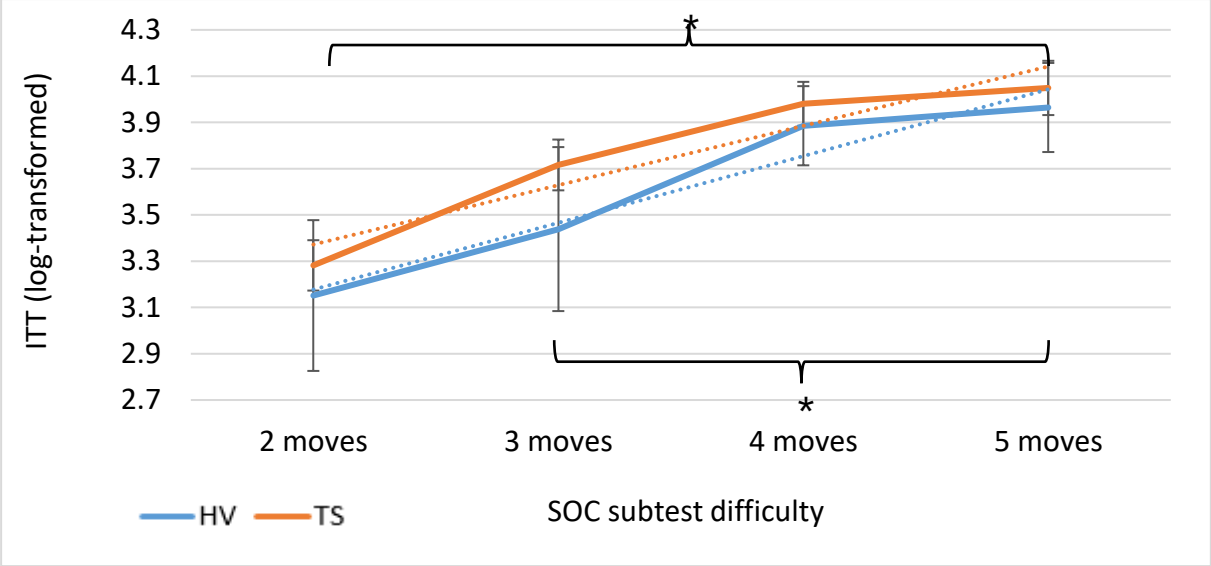


Figure 16. Mean initial thinking times at varying levels of difficulty on the SOC subtest in HVs and TS. Errors bars represent the SEM. *Significant following Benjamini-Hochberg FDR correction.

Mean STT

There was a significant main effect of task difficulty on the mean subsequent thinking time, F (3, 159) = 25.974, p = .000, r = .37.

Planned contrasts (simple) revealed that in comparison to 5 move solutions, participants took significantly less time to complete subsequent moves for 2 move, F (1, 53) = 32.857, p = .000, r = .62, and 3 move solutions, F (1, 53) = 28.303, p = .000, r = .59, but not for 4 move solutions, F (1, 53) = .074, p = .787, r = .12.

There was no significant interaction effect of task difficulty and clinical status of the participant on mean STT, F (3, 159) = .558, p = .644, r = .06. Additionally, there was no main effect of clinical status on mean STT, F (1, 53) = 1.859, p = .179, r = .18.

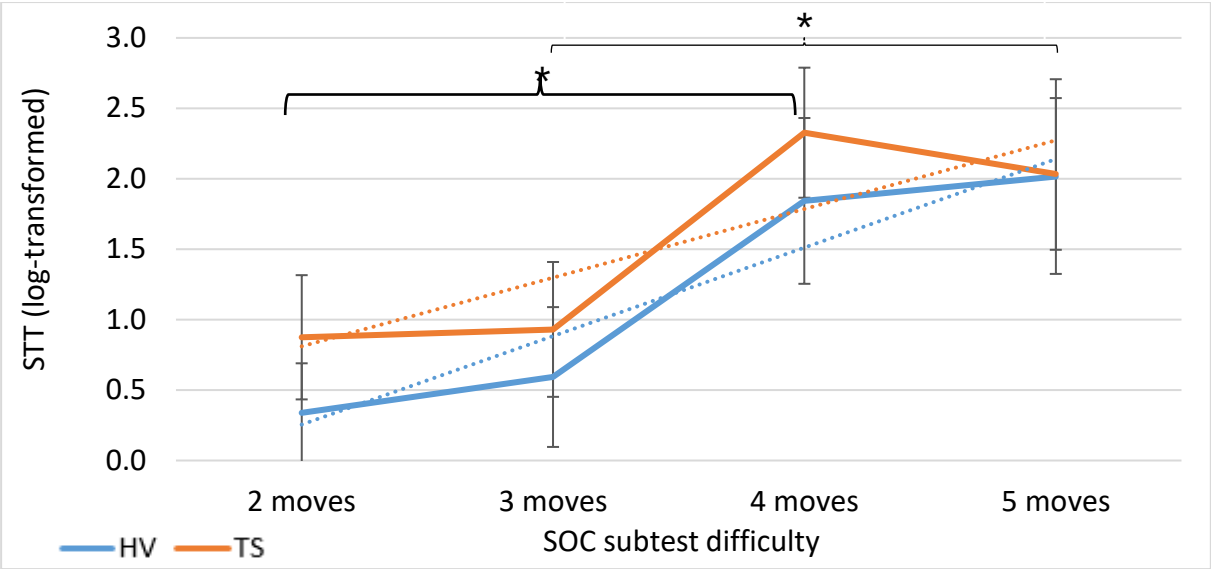


Figure 17. Mean subsequent thinking times across varying levels of difficulty on the SOC subtest in HVs and TS. Errors bars represent the SEM. *Significant following Benjamini-Hochberg FDR correction.

Summary

During performance of the SOC task, with increasing task difficulty participants made significantly fewer perfect solutions and displayed significantly longer initial and subsequent thinking times. The effect of task difficulty on task performance occurred independently of clinical status as there were no differences in planning ability (ITTs), completion of the solving plan (STTs) or problem solving accuracy between HVs and those with TS.

Spatial Working Memory (SWM)

Results

Total Errors

There was a significant main effect of task difficulty (number of boxes) on mean total errors, F (2, 102) = 59.192, p = .000, r = .61. Planned contrast (simple) revealed that in comparison to 8 box difficulty, participants made significantly fewer errors for 4 box, F (1, 51) = 104.014, p = .000, r = .82, and 6 box difficulty, F (1, 51) = 26.336, p = .000, r = .58.

There was no significant interaction effect of task difficulty and clinical status on total errors, F (2, 102) = .607, p = .547, r = .08. Additionally, there was no main effect of clinical status on total errors made, F (1, 51) = .003, p = .959, r = .01.

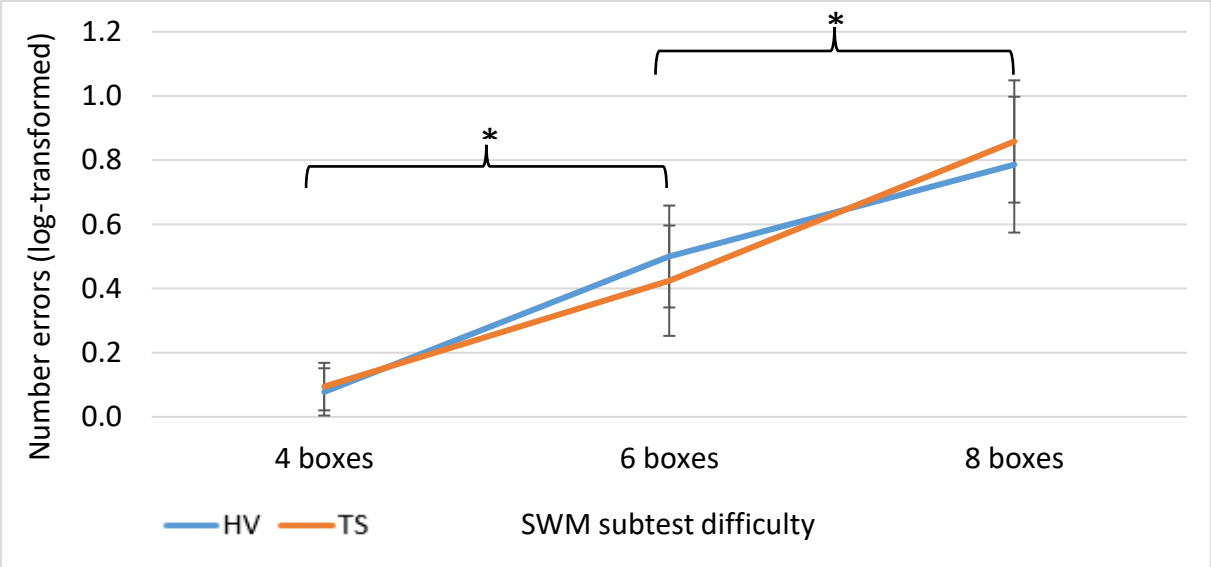


Figure 18. Mean number of total errors made at varying levels of task difficulty on the SWM subtest for HVs and TS. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

There was no significant difference amongst HVs and those with TS on the total number of errors made on the SWM task, U = 314.5, z = -.285 p = .776, r = -.04.

Between-errors

There was a significant main effect of task difficulty on the number of between-errors made, F (2, 102) = 61.966, p = .000, r = .61. Planned contrast (simple) revealed that participants made significantly more between-errors for problems with 8 boxes compared to 4 box, F (1, 51) = 114.352, p = .000, r = .83, and 6 box problems, F (1, 51) = 30.172, p = .000, r = .61.

There was no significant interaction effect of task difficulty and clinical status of the participant on between-errors made, F (2, 102) = .297 p = .744, r = .05. Additionally, there was no main effect of clinical status on between errors, F (1, 51) = .020, p = .888, r = .02.

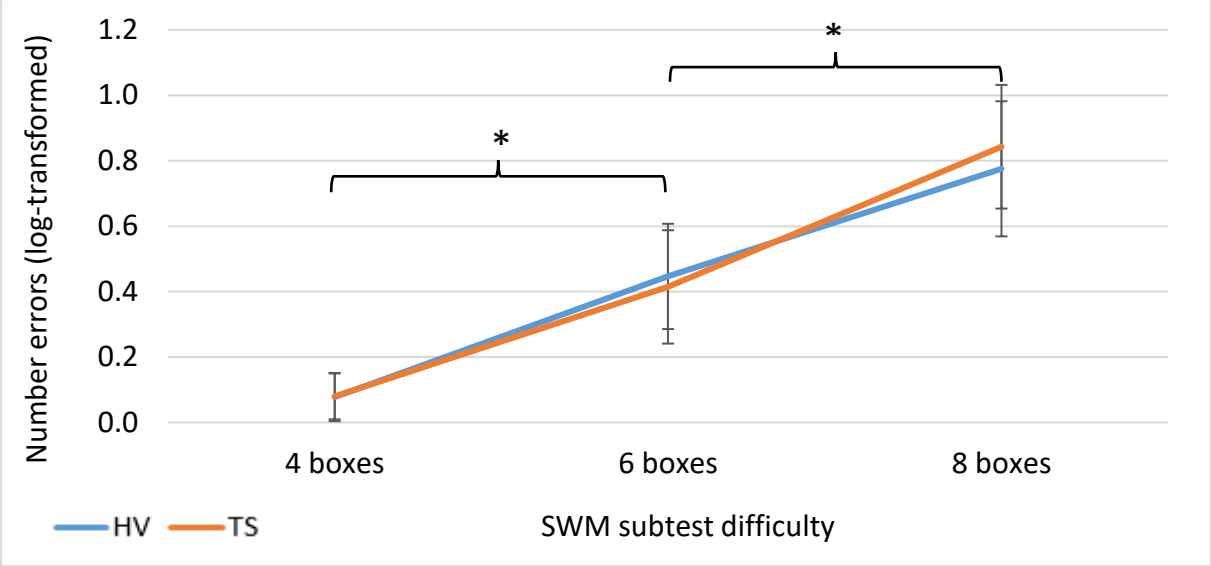


Figure 19. Mean number of between-errors made at varying levels of task difficulty on the SWM subtest for HVs and TS. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

There was no significant difference amongst HVs and those with TS on the between-errors made throughout the entire SWM task, $U = 315$, $z = -.276$ $p = .783$, $r = -.04$.

Within-errors

There was a significant main effect of task difficulty on the number of within-errors made, F (1.413, 72.054) = 4.781, $p = .01$, $r = .21$. Planned contrast (simple) revealed that participants made significantly more within-errors for problems with 8 boxes compared to 4 boxes, F (1, 51) = 8.882, $p = .004$, $r = .39$, but not 6 boxes, F (1, 51) = 1.178, $p = .283$, $r = .15$.

There was no significant interaction effect between task difficulty and clinical status of the participant on within-errors made, F (1.413, 72.054) = .868, $p = .390$, $r = .11$. Additionally, there was no main effect of clinical status on within-errors, F (1, 51) = .038, $p = .847$, $r = .03$.

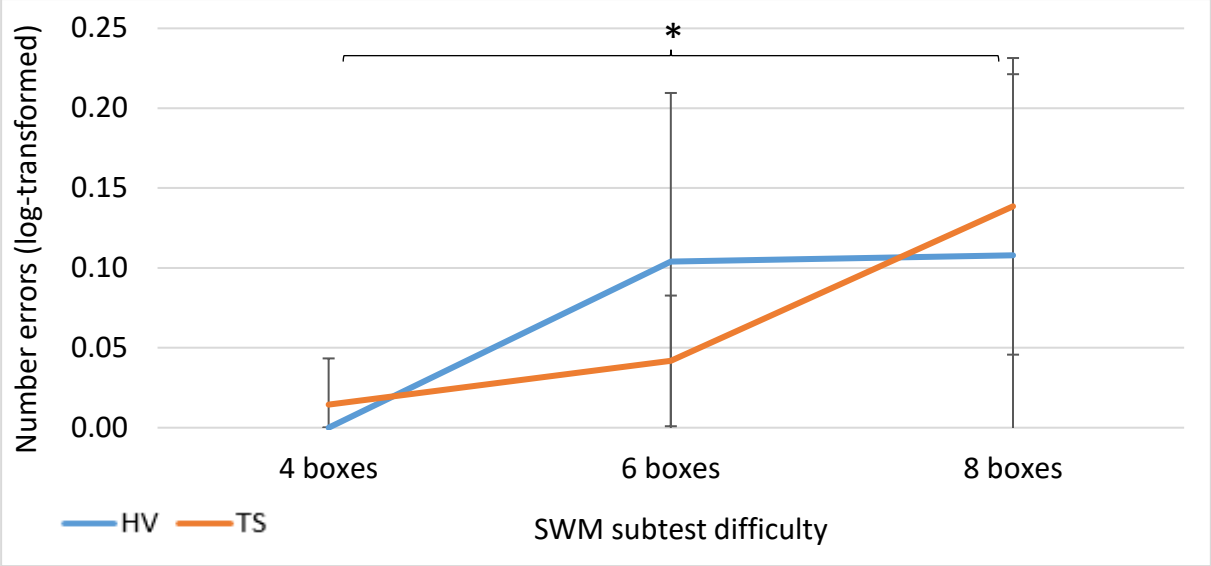


Figure 20. Mean number of within-errors made at varying levels of task difficulty on the SWM subtest for HVs and TS. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

There was no significant difference amongst HVs and those with TS on the within-errors made throughout the entire SWM task, $U = 326$, $z = -.085$ $p = .933$, $r = -.01$.

Double errors

There was no significant effect of task difficulty on the number of double errors made, F (1.33, 67.825) = 2.954, $p = .079$, $r = .20$. Further, there was no significant interaction effect of task difficulty and clinical status of the participant on double errors made, F (1.33, 67.825) = .366, $p = .608$, $r = .07$, and no main effect of clinical status on double errors, F (1, 51) = .100, $p = .753$, $r = .04$.

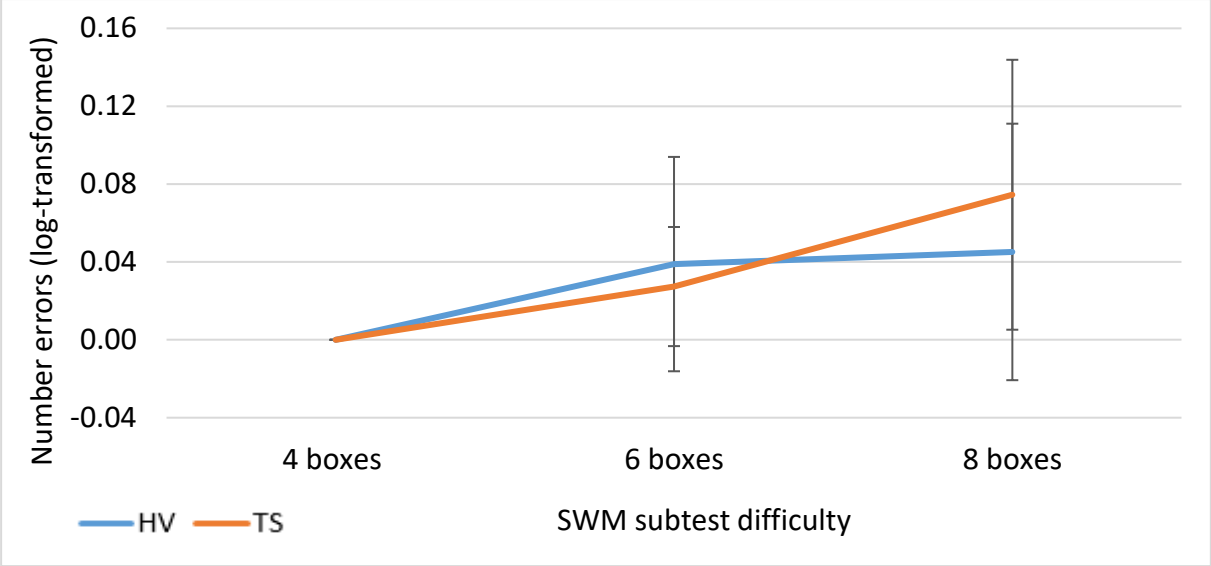


Figure 21. Mean number of double errors made at varying levels of task difficulty on the SWM subtest for HVs and TS. Error bars represent SEM.

There was no significant difference amongst HVs and those with TS on the double errors made throughout the entire SWM task, $U = 318$, $z = -.301$ $p = .763$, $r = -.04$.

Strategy

There was no significant difference in the mean strategy score of HVs and those with TS ($U = 311$, $z = -.350$ $p = .727$, $r = -.05$).

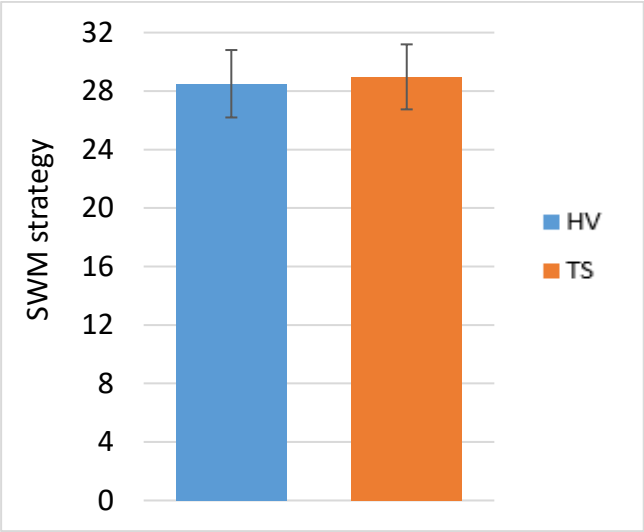


Figure 22. Mean total task strategy score on the SWM subtest for HVs and TS. Error bars represent SEM.

Summary

During performance of the SWM task, with increasing task difficulty participants made significantly more errors including opening boxes already found to be empty, revisiting boxes that had previously contained a token and repetition of these errors (within-errors, between-errors and double-errors, respectively). The effect of task difficulty on task performance occurred independently of clinical status and there is no evidence to suggest that those with TS have impairment to their ability their executive functioning and working memory, specifically in the ability to retain and manipulate visuospatial information and problem solving, as their performance (number of errors) and strategy employed did not differ from that of HVs.

Rapid Visual Information Processing (RVP)

Results

A'

There was no significant difference between HVs and participants with TS on the measure *A'*, t (53) = -.495, p = .622, d = -0.139.

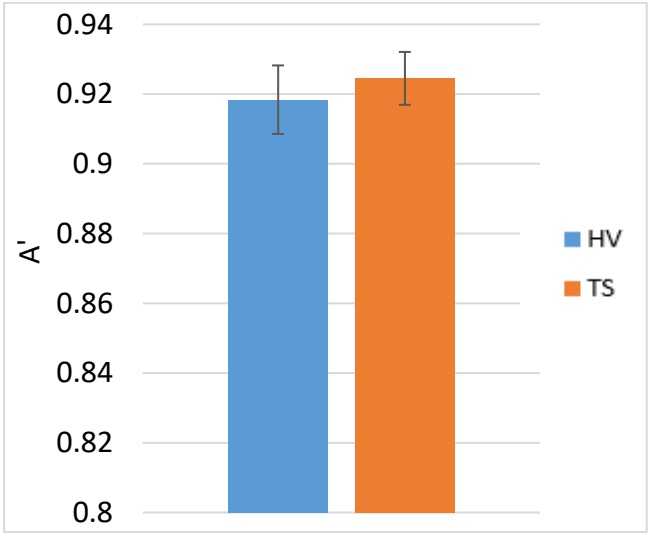


Figure 23. Mean *A'* score, a signal detection measure of sensitivity to the target, on the RVP subtest for HVs and TS. Error bars represent SEM.

B'

There was no significant difference between HVs and participants with TS on the measure *B'*, *U* = 341, *z* = -.383, *p* = .702, *r* = -.05

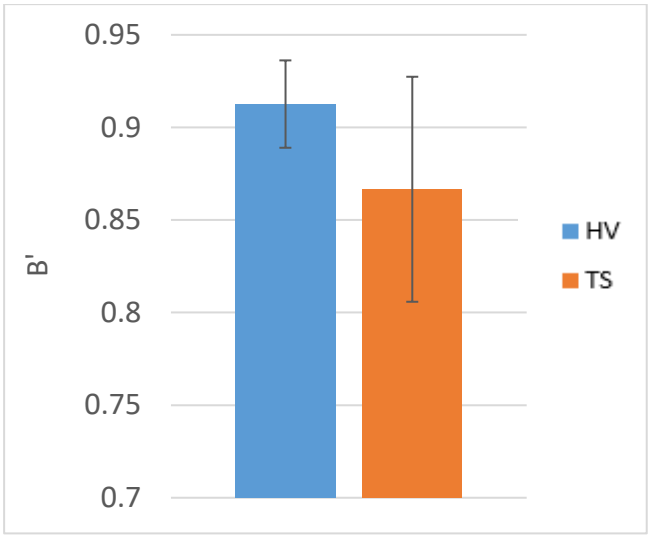


Figure 24. Mean *B'* score, a signal detection measure of the bias to respond i.e. false alarms, on the RVO subtest for HVs and TS. Error bars represent SEM.

Mean latency

There was no significant difference between HVs and participants with TS on mean latency, *t* (53) = 1.439, *p* = .156, *d* = 0.404.

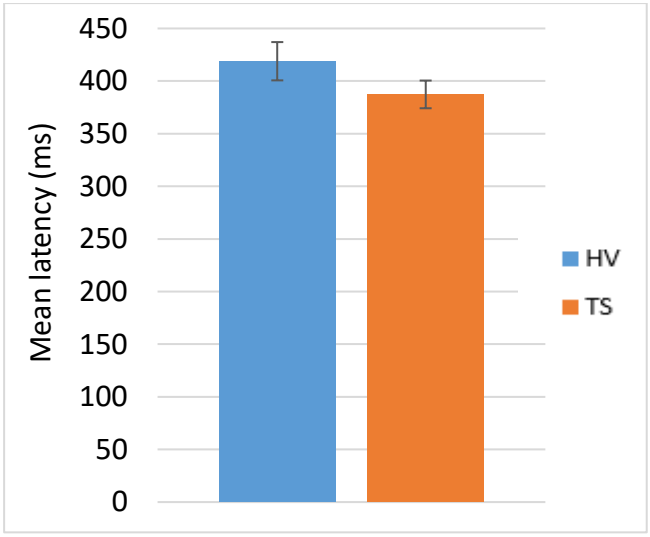


Figure 25. Mean latency (ms), on the RVP subtest for HVs and TS. Error bars represent SEM.

Total hits

There was no significant difference between HVs and participants with TS on total hits, t (53) = -.257, p = .798, d = -.073.

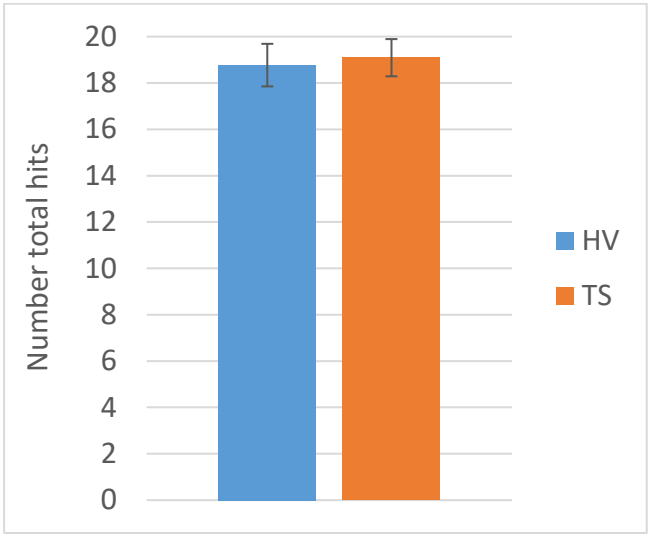


Figure 26. Mean number of total hits on the RVP subtest for HVs and TS. Error bars represent SEM.

Total misses

There was no significant difference between HVs and participants with TS on total misses, t (53) = -.305, p = .762, d = .086.

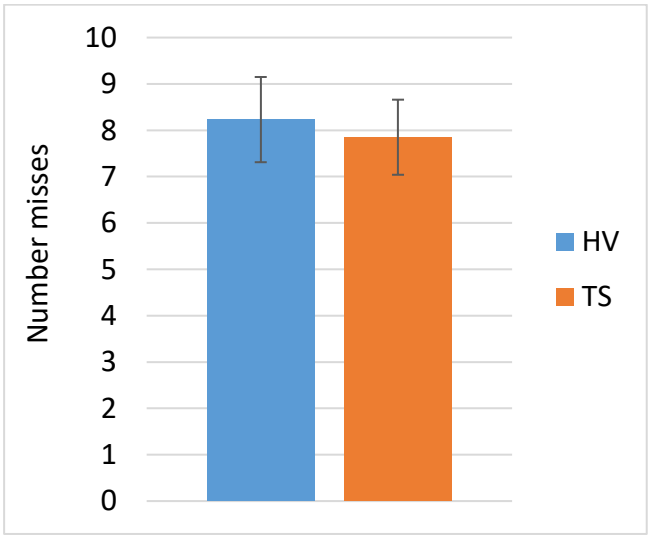


Figure 27. Mean number of total misses on the RVP subtest for HVs and TS. Error bars represent SEM.

Total false alarms

There was no significant difference between HVs and participants with TS on total false alarms, $U = 358.5$, $z = -.081$, $p = .936$, $r = -.01$.

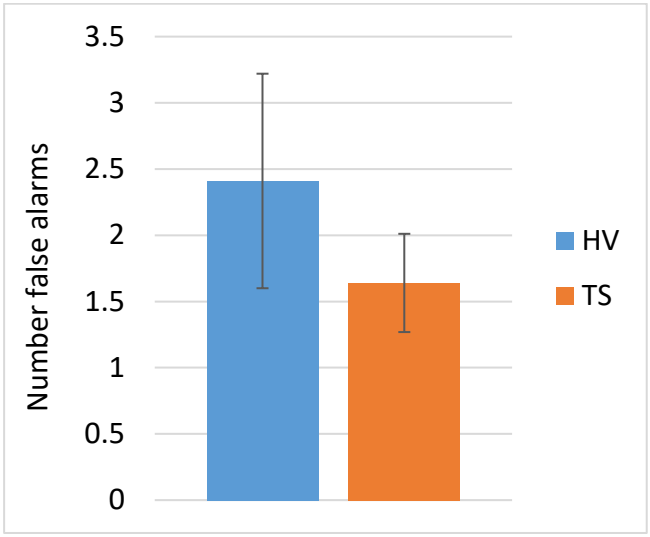


Figure 28. Mean number of false alarms on the RVP subtest for HVs and TS. Error bars represent SEM.

Total correct rejections

There was no significant difference between HVs and participants with TS on total correct rejections, t (53) = -.708, $p = .482$, $d = -.199$.

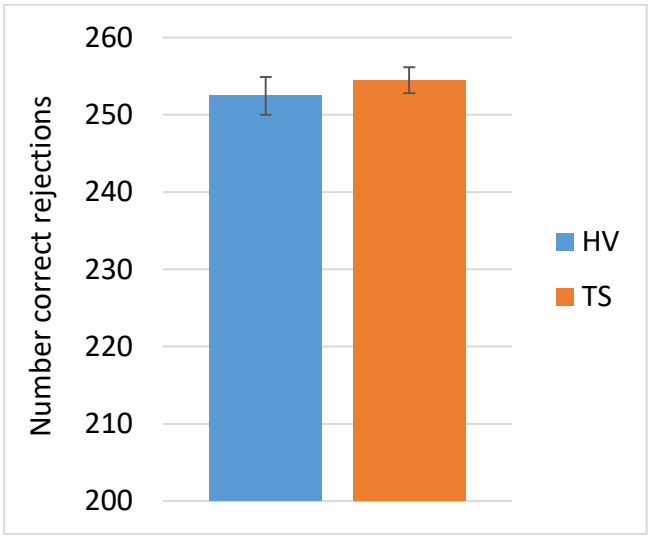


Figure 29. Mean number of correct rejections on the RVP subtest for HVs and TS. Error bars represent SEM.

Probability of a hit

There was no significant difference between HVs and participants with TS with probability of a hit, *t* (53) = -.296, *p* = .768, *d* = -.709.

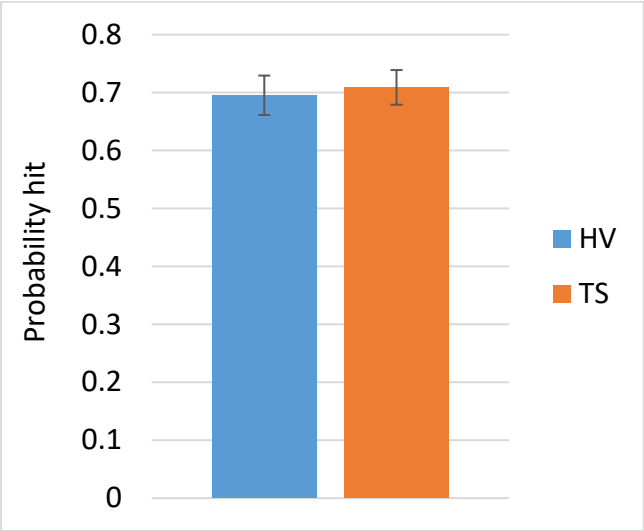


Figure 30. Mean probability of a hit on the RVP subtest for HVs and TS. Error bars represent SEM.

Probability of false alarm

There was no significant difference between HVs and participants with TS with probability of a false alarm, *U* = 360, *z* = -.052, *p* = .958, *r* = - .01.

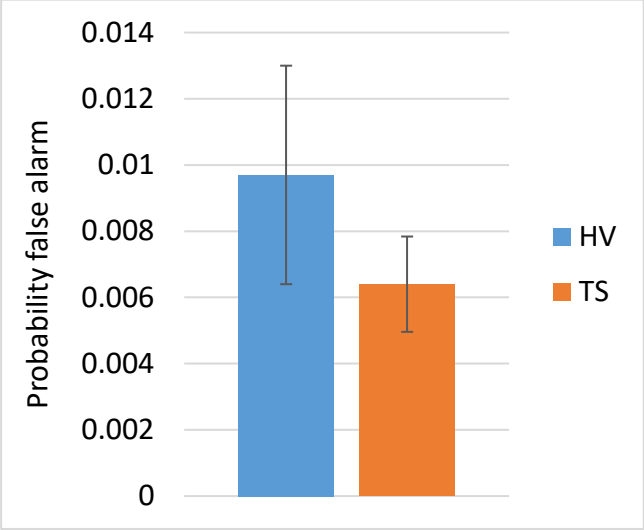


Figure 31. Mean probability of false alarms on the RVP subtest for HVs and TS. Error bars represent SEM.

Summary

During performance of the RVP task there were no differences existing amongst HVs and those with TS in sensitivity to the target regardless of response tendency (*A*'), the likelihood to respond i.e. false alarms (*B*"), or in measures relating to sequence detection and response accuracy (hits, misses, false alarms, correct rejections and mean latency). These findings support that there is no evidence of cognitive impairment related to rapid visual information processing in those with TS.

Stop-signal Task (SST)

Results

Reaction time

Mean

There was a significant difference in mean RT on GO trials, $U = 187$, $z = -2.83$, $p = .005$, $r = -.39$.

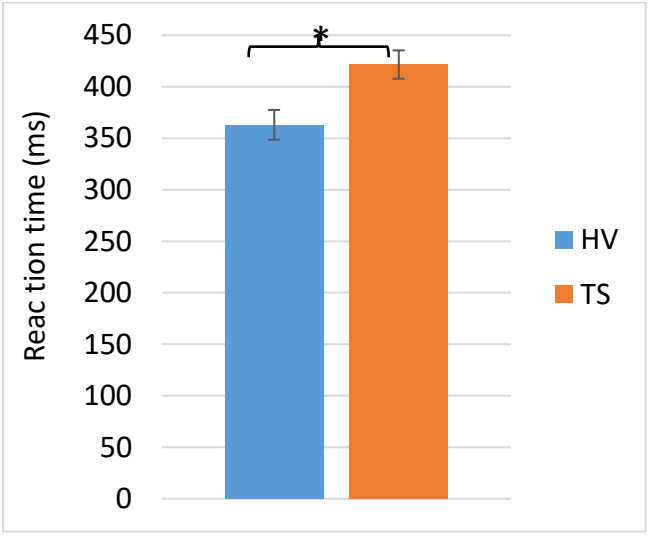


Figure 32. Mean reaction times (ms) on the SST subtest in HVs and TS. *Significant following Benjamini-Hochberg FDR correction. Error bars represent SEM.

Median

There was a significant difference in median RT for GO trials for HVs (range = 221) and participants with TS (range = 280.50), *U* = 191, *z* = -2.759, *p* = .006, *r* = -.38.

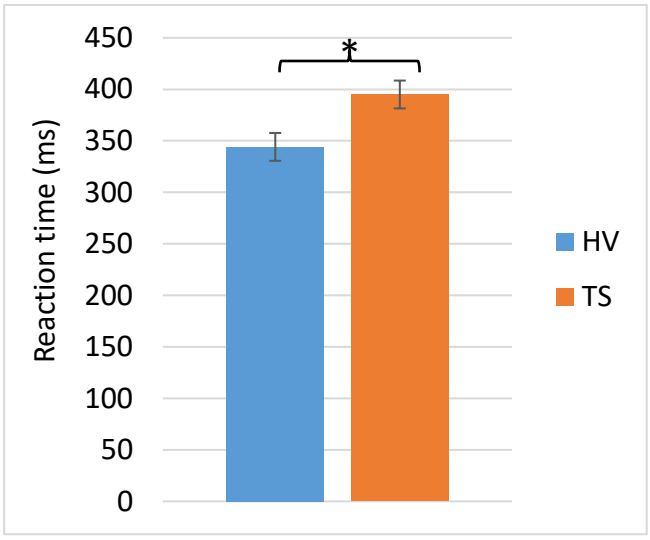


Figure 33. Median reaction times (ms) on the SST subtest for HVs and TS. *Significant following Benjamini-Hochberg FDR correction. Error bars represent SEM.

Minimum

There was no significant difference in minimum RT on go trials, *U* = 316.5, *z* = -.532, *p* = .594, *r* = -.07.

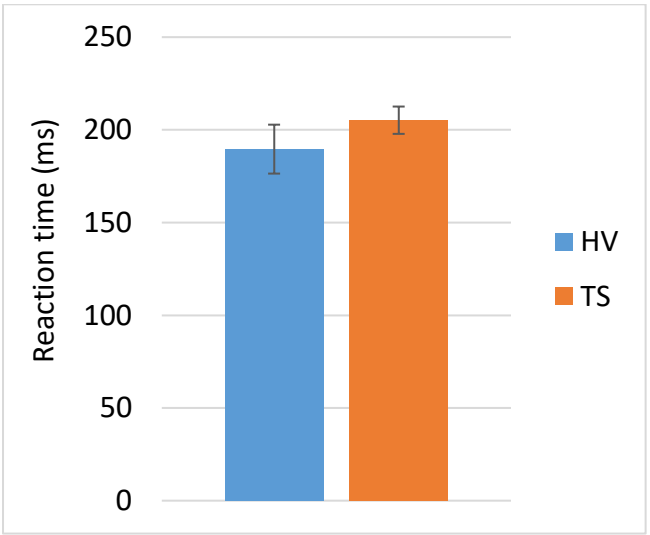


Figure 34. Minimum reaction times (ms) on the SST subtest for HVs and TS. Error bars represent SEM.

Maximum

There was a significant difference in the maximum RT on go trials, $U = 195.5$, $z = -2.679$, $p = .007$, $r = -.37$.

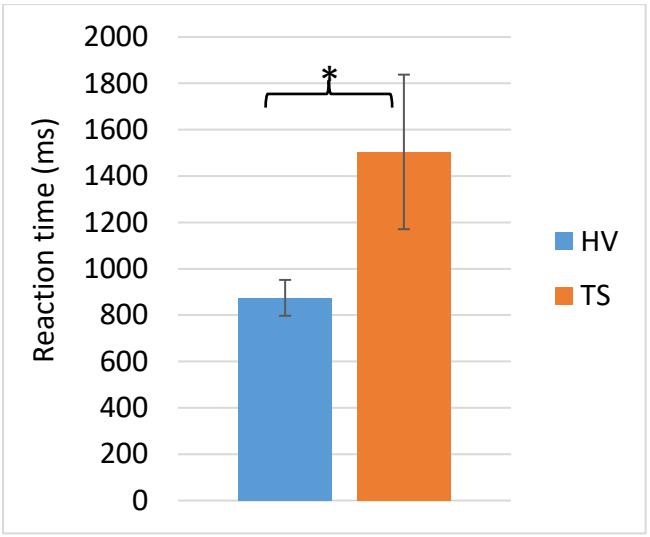


Figure 35. Maximum reaction times (ms) on the SST subtest for HVs and TS. *Significant following Benjamini-Hochberg FDR correction. Error bars represent SEM.

Standard deviation

There was significantly more variance in the standard deviation of RTs on go trials, $U = 170$, $z = -3.132$, $p = .002$, $r = -.43$.

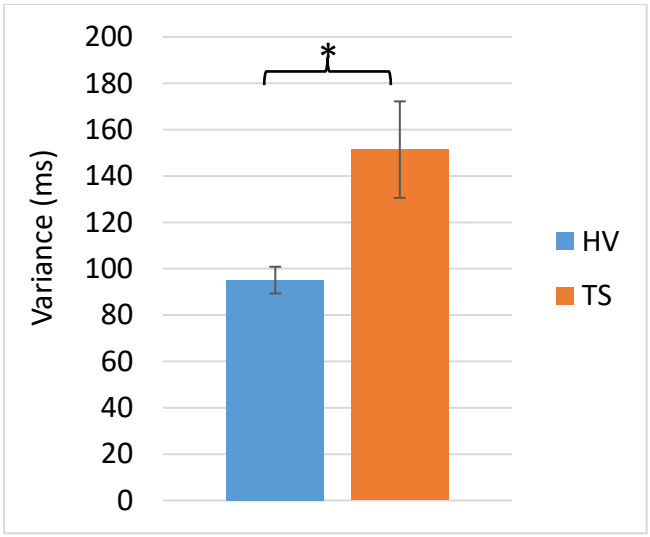


Figure 36. Standard deviation in reaction times (ms) on the SST subtest for HVs and TS. *Significant following Benjamini-Hochberg FDR correction. Error bars represent SEM.

Direction errors

There was no significant difference between HVs and adults with TS on the number of direction errors made, $U = 313$, $z = -.598$, $p = .550$, $r = -.08$.

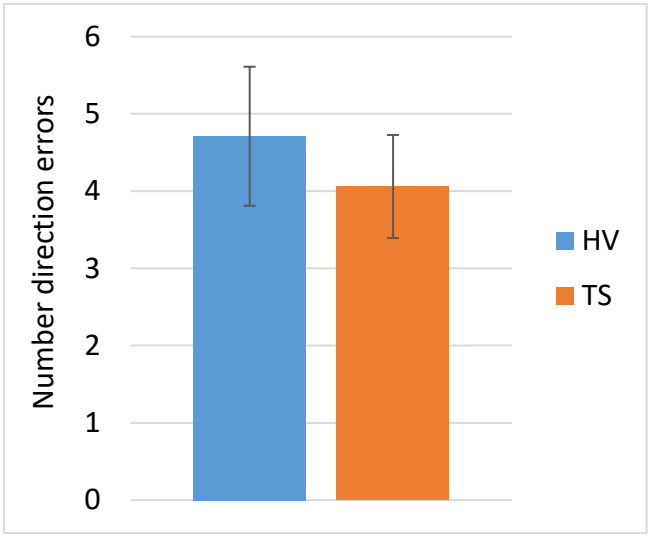


Figure 37. Mean number of direction errors on the SST subtest for HVs and TS. Error bars represent SEM.

Proportion successful stops

There was no significant difference between HVs and participants with TS on the proportion of successful stops, $U = 319$, $z = -.493$, $p = .622$, $r = -.07$.

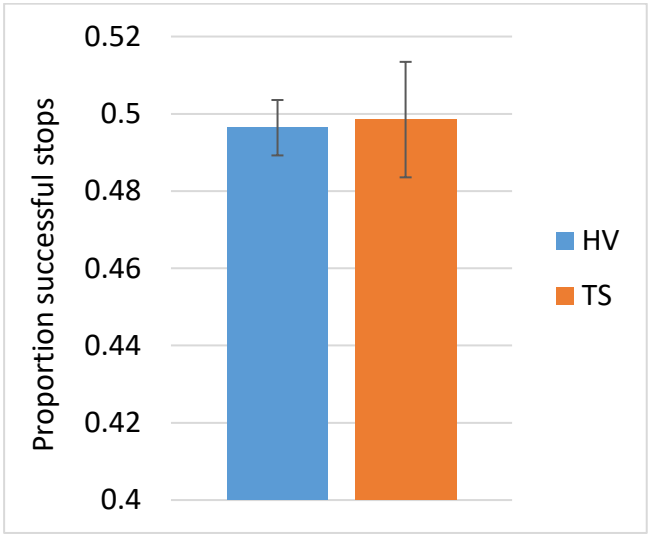


Figure 38. Mean proportion of successful stops made on the SST subtest by HVs and TS. Error bars represent SEM.

Stop signal delay (SSD)

There was no significant difference between HVs and those with TS on the stop signal delay, $U = 258$, $z = -1.570$, $p = .116$, $r = -.22$.

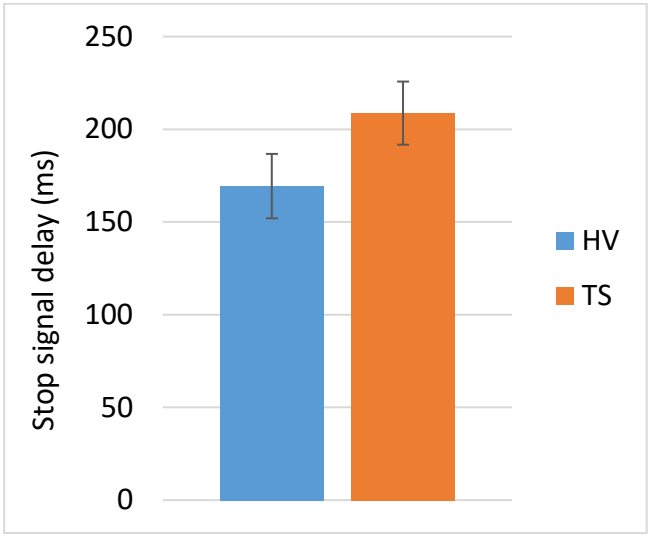


Figure 39. Mean stop signal delay (ms) on the SST subtest for HVs and TS. Error bars represent SEM.

Stop signal reaction time (SSRT)

There was no significant difference between HVs and those with TS on the stop signal reaction time, $U = 306$, $z = -.719$, $p = .472$, $r = -.10$.

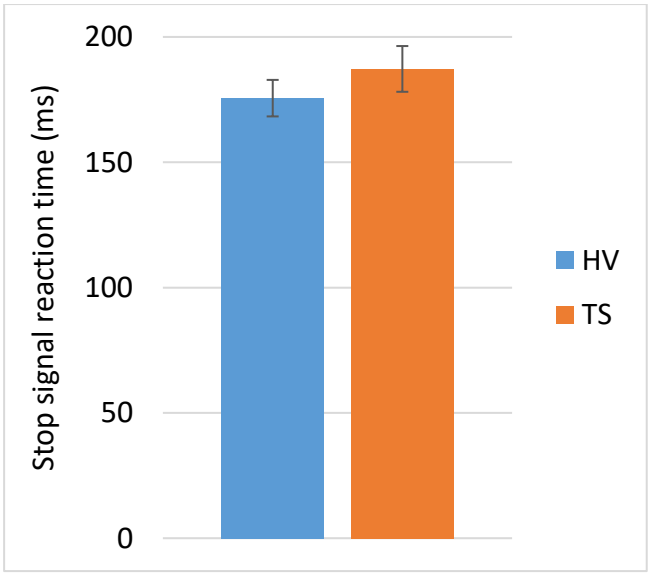


Figure 40. Mean stop signal reaction time (ms) on the SST subtest for HVs and TS. Error bars represent SEM.

Medication

Antipsychotic medication was significantly related to mean RTs on go trials, F (1, 51) = 4.573, p = .037, r = .29, and after controlling for the effect of antipsychotic medication, there was no longer a significant effect of clinical status on mean RTs, F (1, 51) = 3.822, p = .056, η^2 = .070.

Antipsychotic medication was significantly related to median RTs, F (1, 51) = 8.448, p = .005, r = .38. After controlling for the effect of antipsychotic medication, there was no longer a significant effect of clinical status on median RTs, F (1, 51) = 2.229, p = .142, η^2 = .042.

Antipsychotic medication was not significantly related to maximum RTs, F (1, 51) = .496, p = .484, r = .10; however when controlling for the effect of antipsychotic medication, there was no longer a significant effect of clinical status on maximum RTs, F (1, 51) = 2.665, p = .109, η^2 = .050.

Antipsychotic medication was not significantly related to SD RTs, F (1, 51) = .767, p = .385, r = .12; and there remained a significant effect of clinical status on SD RTs when controlling for the effect of antipsychotic medication, F (1, 51) = 5.224, p = .026, η^2 = .093.

Summary

During performance of the SST task, those with TS were found to have significantly slower mean, median and maximum reaction times on GO trials. Additionally, there were significantly more variance in the RTs of those with TS than HVs. After controlling for the effects of antipsychotic medication, the differences in RT were no longer significant; however, there remained significant variability in TS participant RTs (standard deviation) compared to HVs.

Furthermore, TS participants and HVs performed similarly on measures of task accuracy, such as direction errors and SSRT (time between start and stop signals in which the subject could successfully inhibit their response on 50% of trials). Additionally, performance was similar for measures of inhibitory control, including the proportion of successful stops made and the length of the SSD (delay between start and stop signals at which the subject was able to stop successfully 50% of the time).

Upon controlling for antipsychotic medication, significant differences in RT between HVs and those with TS no longer remained. These results suggest that antipsychotic medication may have made medicated participants RTs significantly slower than non-medicated TS participants, skewing the TS dataset. It is likely that medicated TS participants were responsible for the significantly longer (maximum) RTs. Despite controlling for medication there remained significantly, more variance in the RTs of TS participants compared to HVs. These results indicate that there may exist a slight motor slowing in RTs in TS that has no significant impact on task accuracy and subsequently no evidence of deficits to response inhibitory control in adults with TS.

Table 13. Summary of Chapter 3 General Cognition results

Chapter Section	Results	Main findings
WTAR *Premorbid IQ*	No difference between HVs and TS	No evidence of impairment to general intelligence in adults with TS
Intra-Extra Dimensional Set-shift (IED) *Rule learning and reversal, cognitive flexibility*	Significant difference between HVs and adults with TS on IED stage pass rates: - All HVs completed all 9 stages of the IED task - All adults with TS completed stages 1-7, however at stage 8, requiring discriminatory choices based off extra-dimensional stimuli (EDS) 15% failed to complete the stage and 18% failed the final EDR stage. Adults with TS took significantly more trials to complete the overall IED task More errors were made by all participants at the EDS stage, however adults with TS made significantly more errors than HVs No significant difference between HVs and adults with TS on pre-EDS stage errors (stages 1-7) Adults with TS make significantly more total errors	Adults with TS have intact ability to learn and reverse rules during stages (1-7) of task requiring intra-dimensional discriminatory choices. However, there appears to be a deficit with cognitive flexibility to habitually learned behaviours, as evidence by deficits specific to EDS stage (8) of IED task.
Stockings of Cambridge (SOC) *Spatial planning, working memory and problem solving*	No significant difference between HVs and adults with TS on mean number of perfect solutions, mean initial thinking times (ITT) or mean subsequent thinking times (STT)	No evidence of impairment to spatial planning, working memory and problem solving in adults with TS
Spatial Working Memory (SWM) *Working memory, manipulation of visuospatial information and strategy development*	No significant difference between HVs and adults with TS on mean number of errors made (total, between, within and double) or mean strategy score	No evidence of impairment to spatial working memory or ability to develop systematic search strategy in adults with TS
Rapid Visual Information Processing (RVP) *Sustained attention and impulsivity*	No significant difference between HVs and adults with TS in mean sensitivity to target regardless of response tendency (A'), mean likelihood to respond to false alarms (B'), mean latency, total hits, total misses, total false alarms, total correct rejections, probability of a hit, probability of false alarm	No evidence of impairment to sustained attention and impulsivity in adults with TS.
Stop Signal Test (SST) *Response inhibition*	No significant differences between HVs and adults with TS on reaction times (RTs), mean number of direction errors, proportion of successful stops, stop signal delay (SSD) or stop signal reaction time (SSRT). Adults with TS were seen to have significantly more variability in the range of RTs.	More variability amongst the reaction times of adults with TS but no evidence that TS impacts response inhibition performance.

3.3. Discussion

There is a significant impact of TS on an individual's QOL in both adults and children due to tic and urge severity and impairments associated with psychopathologies and comorbidities (Eapen, Snedden, Crncec, Pick, & Sachdev, 2016; Eddy, Cavanna, et al., 2012; Eddy et al., 2011; Elstner, Selai, Trimble, & Robertson, 2001; Robertson, 2015b; Storch et al., 2007). Areas impacted include psychosocial aspects such as self-esteem, social relationships, stigma and bullying (Bawden, Stokes, Camfield, Camfield, & Salisbury, 1998; Leckman, Peterson, King, Scahill, & Cohen, 2001; O'Hare et al., 2015; Swain, Scahill, Lombroso, King, & Leckman, 2007). Such burdens have lasting interference on an individual's experience of education (APA, 2013; Haddad, Umoh, Bhatia, & Robertson, 2009), resulting in higher rates of unemployment and classification within a lower social class than their parents (Debes, Hjalgrim, & Skov, 2008; Elstner et al., 2001; Lebowitz et al., 2012; Pappert et al., 2003; Specht et al., 2011).

Despite the barriers faced by children and adolescents with TS, there is evidence of above average academic performance (Wei, 2011) and low prevalence rates of learning difficulties and/or intellectual disability, with on average 3.4- 4% affected (Freeman et al., 2000; Freeman & Tourette Syndrome International Database, 2007). Whilst there is evidence that TS is associated with learning difficulty in children (Debes, Lange, Jessen, Hjalgrim, & Skov, 2011; Khalifa, Dalan, & Rydell, 2010) reports of impairment are more likely to be a consequence of comorbidity (Abwender et al., 1996; Freeman et al., 2000) and mental fatigue associated with urge and tic control (Dykens et al., 1990; Erenberg, 2005; Peterson, Pine, Cohen, & Brook, 2001). Furthermore, by adulthood, neuronal structural reorganisation is acquired to compensate for neurodevelopmental alteration to CSTC circuitry (Jackson, Parkinson, Jung, et al., 2011); such mechanisms may facilitate the acquisition and retention of general intelligence.

Premorbid IQ as assessed by the WTAR is an estimate of general intelligence based on reading ability, known to correlate with IQ. This reflects the observation that vocabulary remains intact following neurological injury. The adults with TS in this study did not differ on premorbid estimates of intelligence from HVs, both of which were in the normal range. Although a small sample, this suggests that general intelligence is not impaired in adult TS. Our results are consistent with reports that

intelligence is unlikely to be impacted in TS (Como, 2001) and robust observations of intact verbal fluency in adult TS (Eddy & Cavanna, 2017; Schoenberg et al., 2015; Stebbins, 1995; Watkins et al., 2005; Zapparoli et al., 2016).

Our results reiterate that in adult TS there is no evidence of impaired general intelligence, as estimated by premorbid IQ. Thus, our results therefore support the existence of specific, as opposed to global cognitive impairment in adult TS (Morand-Beaulieu, Leclerc, et al., 2017). Furthermore, more educational support is warranted in those with TS, especially so, for those with comorbidity that further impact access and benefit from education (Debes, Hjalgrim, & Skov, 2010).

Executive functioning encompasses skills that allow us to adapt to novel situations. Such abilities allow us to navigate uncertain situations and involve planning, reasoning, problem solving, cognitive flexibility and response inhibition (Chan, Shum, Toulopoulou, & Chen, 2008). Coordination of these complex processes requires extensive cross-talk across CSTC networks and circuits involving PFC and associative areas (Godefroy, 2003). Cognitive flexibility represents executive functions that together moderate the ability to be flexible and shift attention (Gilbert & Burgess, 2008) and overcome novel or unexpected situations (Chudasama et al., 2003; Eagle et al., 2008; Moore & Malinowski, 2009).

Typically, assessments of cognitive flexibility require the participant to make discrimination among stimuli dimensions and to learn, abstract and reverse rules based on task feedback received. During intra-dimensional stages, new stimuli are presented and the correct choice, remains within the same stimulus dimension. Conversely, during extra-dimensional stages, new stimuli are presented but the correct choice shifts to a new stimulus dimension. Task performance requires participants to learn rules via positive feedback and to identify rule changes via negative feedback. Following a rule change, participants need to inhibit prior responses to extinguish the reinforced intra-dimensional stimulus rule governing previous responding and shift attention towards the extra-dimensional stimulus dimension that was earlier irrelevant. Successful performance therefore requires intact rule learning, abstraction and reversal in response to feedback, response inhibition of an already acquired attentional bias and the subsequent ability to shift attention to novel stimulus dimensions (Berg, 1948; Morand-Beaulieu, Leclerc, et al.,

2017; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Robbins, 2007; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000).

Neuroimaging and lesion studies have identified that different aspects of cognitive flexibility are mediated by overlapping, reciprocal projections. Frontostriatal projections from the PFC to striatum and thalamus are involved in modulating cognitive flexibility (Castane, Theobald, & Robbins, 2010; Clarke, Robbins, & Roberts, 2008; Floresco, Ghods-Sharifi, Vexelman, & Magyar, 2006; Ragozzino, 2007; Rogers et al., 2000). Specifically, fronto-striatal circuits involving the DLPFC and striatum have been implicated in both set-shifting and task-switching (Birrell & Brown, 2000; Dias, Robbins, & Roberts, 1996a, 1996b; Graham et al., 2009; Manes et al., 2002; Owen et al., 1991; Ragozzino, 2007; Sohn, Ursu, Anderson, Stenger, & Carter, 2000), whereas fronto-striatal circuits involving the OFC and dorsomedial striatum have been implicated in reversal learning (Bellebaum, Koch, Schwarz, & Daum, 2008; Castane et al., 2010; Clarke et al., 2008; Dias et al., 1996a; Divac, 1971; Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010; Hampshire & Owen, 2006; Leeson et al., 2009; McAlonan & Brown, 2003; Rogers et al., 2000).

This double dissociation of frontostriatal function in cognitive flexibility has been demonstrated during Wisconsin Card Sorting Task (WCST) performance in a PET study of HVs. During stages requiring new rule learning, the DLPFC was activated. This was especially prominent during extra-dimensional shifts which reflected the requirement of a shift of attentional set. However, reversal stages were associated with activations of the left caudate nucleus, an efferent of the OFC (Rogers et al., 2000). Additionally, the impact of damage of the LPFC is specific to shifting of attentional set but not reversal learning (Birrell & Brown, 2000; Bissonette et al., 2008; Dias et al., 1996a; Dias, Robbins, & Roberts, 1997; Owen et al., 1991). Furthermore, an fMRI study, where participants were required to shift attention between stimulus dimensions, found a further dissociation of the PFC in cognitive flexibility. The VLPFC was found to be more active during the attentional shift aspects (EDS) of the task and the DLPFC during the working memory and strategy demands of the EDS problem, such as formulating the need to switch between dimensions (Hampshire & Owen, 2006).

Dopamine is a key neuromodulator within fronto-striatal circuits and facilitates PFC-driven attentional shift and prediction error coding via phasic dopamine in response

to feedback (Montague, Dayan, & Sejnowski, 1996; Schultz, 2013; Schultz, Dayan, & Montague, 1997; Steinberg et al., 2013). Increased release of dopamine in the striatum and PFC during tasks of cognitive flexibility occurs in response to novel situations (Ko et al., 2009; Monchi, Ko, & Strafella, 2006; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). This results in PFC-mediated shift and stabilisation of attention and prediction error coding in response to task feedback, allowing utilisation of rule learning (Crofts et al., 2001; Hampshire, Duncan, & Owen, 2007; Klanker, Feenstra, & Denys, 2013; Roberts et al., 1994; Schultz, 1997). The role of DA in cognitive flexibility, in extra-dimensional set-shift in particular, has been illustrated by the administration of sulpiride, a D2 receptor antagonist. Whilst D1 receptors are primarily associated with the PFC and set-shifting, D2 receptors are most abundant within the dorsal striatum, with increased dopamine being beneficial to flexibility regulation (Owen et al., 1991; Sohn et al., 2000). Sulpiride specifically impaired EDS performance without affecting IDS performance (Mehta, Manes, Magnolfi, Sahakian, & Robbins, 2004; Mehta, Sahakian, McKenna, & Robbins, 1999).

PFC dopamine-dependent attentional set-shift and learning are crucial to cognitive flexibility. Additionally a role of the orbito-frontal cortex has been shown to mediate cognitive flexibility in response to uncertainty, involving reward and punishment feedback (Chudasama et al., 2003; Cools, Clark, Owen, & Robbins, 2002; Eagle et al., 2008; Hampton & O'Doherty J, 2007; Kringelbach & Rolls, 2003; Moore & Malinowski, 2009). Specifically, the OFC does not establish the valence of feedback, but rather mediates shifts in attention in response to feedback (Hampshire & Owen, 2006). The role of the OFC in reversal learning has been demonstrated as OFC damage has been shown to lead to an impairment specific to reversal learning, with no impact on the ability to shift attention (Boulougouris, Dalley, & Robbins, 2007; Dias et al., 1997; Hornak et al., 2004; McAlonan & Brown, 2003; Remijnse et al., 2006). It has further been established that impaired reversal learning occurs following alteration in the communication between prefrontal areas and the caudate (basal ganglia), as opposed to localised OFC impairment (Rudebeck, Saunders, Prescott, Chau, & Murray, 2013; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009).

Another crucial facet of cognitive flexibility is the successful inhibition of former task responses and top-down control of attentional set; both of these cognitive functions

are localised to the right inferior and left middle frontal gyrus (Aron, Monsell, Sahakian, & Robbins, 2004). Following lesions of the left hemisphere, during task-switching tests participants have greater temporal switching ability and RTs, whilst lesions to the right hemisphere results in switch and accuracy costs. These results highlight the requirement of inhibitory control in cognitive flexibility and raise a crucial issue that deficits may be either attention-based or inhibition-based (Yaniv et al., 2017). During performance of the WCST, a meta-analysis found a trend for bilateral activation of the inferior frontal gyrus (Buchsbaum, Greer, Chang, & Berman, 2005) implicating inhibitory control as essential for cognitive flexibility. Additionally, the pre-SMA/SMA has been identified to play an important role in the inhibitory control of novel actions (Hoffstaedter, Grefkes, Zilles, & Eickhoff, 2013; Nachev, Wydell, O'Neill, Husain, & Kennard, 2007; Swick, Ashley, & Turken, 2011) and has been identified to be beneficial in particular for cognitive flexibility performance on the WCST (Konishi et al., 2011; Obeso, Robles, Marron, & Redolar-Ripoll, 2013).

Altered reward processing and impairment in cognitive flexibility have been observed in schizophrenia, autism spectrum disorder, OCD, Parkinson's and addiction (Ceaser et al., 2008; Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Cools, Barker, Sahakian, & Robbins, 2001; Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006; Yerys et al., 2009). All of these conditions have disrupted frontostriatal circuits and altered dopamine signalling implicated in their pathology (Klanker et al., 2013; Miyake & Friedman, 2012). Furthermore, participants with schizophrenia, noted to have both OFC and dopaminergic abnormalities, are found to make significantly more errors at EDS stages of the CANTAB IED task, where performance requires an attentional set-shift in response to feedback (Leeson et al., 2009).

Alterations in the structural and functional integrity of CSTC circuitry, involved in the complex co-ordination of executive functions has been observed in those with TS (Godefroy, 2003; Muller-Vahl et al., 2009; Wittfoth et al., 2012; Worbe, Gerardin, et al., 2010). Furthermore, reduced white matter within the inferior frontal gyrus (Jacobson, Javitt, & Lavidor, 2011; Muller-Vahl et al., 2009) and reduced structural connectivity between the pre-SMA, basal ganglia and wider fronto-striatal networks have been observed in adult TS (Cheng et al., 2014), structures and networks crucial to aspects of inhibitory control. In addition, dysfunction of dopaminergic signalling within frontostriatal regions in TS (Conceicao, Dias, Farinha, & Maia, 2017; Fraint &

Pal, 2015; Graybiel, 2008; Maia & Conceicao, 2017, 2018; McNaught & Mink, 2011; Novotny et al., 2018) provides mounting evidence to implicate dysfunction of cognitive flexibility in adults with TS (Morand-Beaulieu, Leclerc, et al., 2017).

The WCST (Berg, 1948) is the most extensively used measure to evaluate cognitive flexibility (Morand-Beaulieu, Leclerc, et al., 2017). In adults with TS the most evidence indicates normal performance (Bornstein, 1991b; Channon, Crawford, Vakili, & Robertson, 2003; Channon, Sinclair, Waller, Healey, & Robertson, 2004; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2005; Lavoie, Thibault, Stip, & O'Connor, 2007; Muller et al., 2003; O'Connor, Lavoie, Stip, Borgeat, & Laverdure, 2008; Yaniv et al., 2017). There is however, evidence of impairment in WCST performance in adult TS (Eddy & Cavanna, 2017; Gruner, & McKay, 2013; Ji, 2010; Matsuda et al., 2012). In a recent study, no differences in performance on a brief computerised WCST variant were found in 12 remitted adults with TS, 19 non-remitted adults with TS or 19 HVs (Yaniv et al., 2018). Aside from the WCST, alternative set-shifting tasks have been used to investigate cognitive flexibility, with adults with TS found to make significantly more extra-dimensional set-shift errors (Watkins et al., 2005) and have reduced accuracy on number ordering tasks, governed by different rule categories (Yaniv et al., 2017). Interestingly, studies that find typical WCST performance in adult TS, nevertheless report moderate effect sizes (Bornstein, 1991b; Muller et al., 2003; Yaniv et al., 2017). Deficits may therefore exist within cognitive flexibility of adult TS but are yet to be elucidated due to a lack of statistical power; an issue inherent in adult TS research, characterised by small sample sizes, comorbidity and medication confounds and task choice discrepancy (Morand-Beaulieu, Leclerc, et al., 2017).

Our results have identified an impairment in attentional set-shift in adults with TS, specifically at the EDS stage of the CANTAB IED task. Prior to the EDS stage, adults with TS demonstrate typical ability to learn, abstract and reverse rules when intra-dimensional stimuli are used. This indicates a specific deficit in the ability to set-shift, as evidenced by more trials and errors at this stage and a 15% failure rate. As described above, D2 receptor antagonists have been demonstrated to specifically affect EDS performance on the IED task (Mehta et al., 2004; Mehta et al., 1999). Of our sample of thirty three adults with TS, nine were medicated with antipsychotics, compounds known to influence dopaminergic functioning (see Chapter 8 for details).

Medication with antipsychotics was not found to be significantly related to EDS errors and there remained a significant effect of clinical status on the number of EDS errors made after controlling for the effects of antipsychotic medication. We can therefore conclude that EDS errors represents a genuine cognitive deficit inherent to those with TS and is not an artefact of medication effects.

Our findings are consistent with intact cognitive flexibility during intra-dimensional stages of WCST variants (Bornstein, 1991; Channon, Crawford, Vakili, & Robertson, 2003; Channon, Sinclair, Waller, Healey, & Robertson, 2004; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2005; Lavoie, Thibault, Stip, & O'Connor, 2007; Muller et al., 2003; O'Connor, Lavoie, Stip, Borgeat, & Laverdure, 2008; Yaniv et al., 2017). Our results are also consistent with impairment during extra-dimensional stages of cognitive flexibility tasks in adult TS (Eddy & Cavanna, 2017; Gruner, & McKay, 2013; Ji, 2010; Matsuda et al., 2012; Watkins et al., 2005). Discrepancies exist between our results and the results of extra-dimensional stages of WCST variants; this inconsistency is unlikely due to issues of statistical power, but rather task demands.

The duration of WCST variants is either completion of six rule change categories (min 60 trials) or when all 128 cards have been used (Berg, 1948; Piper et al., 2012). Similarly, the IED task involves the completion of nine rule changes (min 54 trials) or a maximum of 495 trials. Furthermore, each rule switch occurs as soon as every 6th trial (correct consecutive trials) on the IED task and as soon as every 10th trial on WCST variants (Piper et al., 2012). Whilst both tasks can switch rules often, the number of trials that intra-dimensional stimuli are reinforced across these tasks differs significantly. For instance, WCST variants reinforce intra-dimensional stimuli rules for at least 10 trials with optimum performance. On the other hand, the IED task reinforces intra-dimensional stimuli rules for at least 47 trials following optimum performance (stages 1-7). Rules based on intra-dimensional stimuli are reinforced for significantly longer during the IED task meaning WCST variants are less likely to evoke habitual learning of rules. Based on this information, WCST variants are suitable measures of cognitive flexibility (Rogers et al., 2000), however, the CANTAB IED task is suitable for probing cognitive flexibility with regards to habitually learned behaviour.

In TS, there appears to be intact rule learning, reversal, and the ability to shift attention. Our results do not dispute that adult TS has intact cognitive flexibility, as assessed previously (majority using WCST), rather we argue that there is a specific deficit to be flexible with cognition, following habitual learning. Our results are consistent with the observations that TS, due to alteration to the striatal habit learning systems, may be associated with enhanced formation of habits (Delorme et al., 2016; Kim et al., 2018). For example, Delorme and colleagues found evidence that individuals with TS would favour over goal-directed actions, habit learning during reward-based learning (Delorme et al., 2016). Furthermore, Kim and colleagues discovered in adolescents with TS during learning of motor behaviour patterns, that the more severe an individual's tics, the longer the duration of unlearning (Kim et al., 2018). However, even studies of habitual learning in adults with TS is under-explored and remains largely inconclusive. There is evidence for adult TS to be associated with increased rates of implicit learning when reward-based (Palmenteri et al, 2009; Palmenteri et al., 2011). There is also evidence implicating impaired habit learning (Marsh et al., 2004) relative to normal controls for both children and adults with TS and difficulty transitioning from sequenced to non-sequenced habit learning in children and adolescents with TS (Shephard et al., 2019). Our results support in adult TS, there is dysfunction shifting cognition away from learnt habit behaviours (Delorme et al., 2016; Kim et al., 2018).

It is difficult to establish whether cognitive inflexibility at the EDS stage is due to a deficit in inhibiting a habitually learned attentional-bias, to reversal learning of habitual behaviours, in shifting attention away from habitually learned stimuli or a combination of these. Further investigation of cognitive flexibility of habitually learned behaviours in adult TS is warranted. These findings extend the proposal that deficits in cognitive flexibility on the WCST is an endophenotype of TS (Eddy & Cavanna, 2017) and argue further that EDS errors on the IED task, representing difficulty with attentional set-shift of habitually learned behaviours is an endophenotype of TS.

Planning is an executive function that requires the appropriate organisation of behaviour and cognitions in a particular sequence that results in the timely achievement of an objective (Owen, 1997). Tasks that assess planning ability typically require a participant to use reasoning and decision making to solve problems. Planning is usually an index of the time taken before a participant initiates

their responding (Owen, Downes, Sahakian, Polkey, & Robbins, 1990); therefore motor initiation and execution can influence estimations.

Decision making appears relatively intact in adult TS on performance of the Iowa Gambling Task (Crawford, Channon, & Robertson, 2005; Eichele et al., 2016), Cognitive Bias Task (Gruner, 2009) and counterfactual thinking tasks (Zago et al., 2014). There is evidence however for slight impairment on the Roger's Decision-Making Task (Watkins et al., 2005). Some decision making tasks have motivational or affective components; tasks assessing planning with affective decision-making components may find deficits in adult TS, due to their associated comorbidities. Assessment of planning should therefore occur with decision-making components devoid of motivational and affective components to ensure indices of planning are not compromised by deficits to affective decision-making.

As TS impacts the motor system, it is difficult to make strong conclusions around the degree to which fine motor skills are affected (Kalsi et al., 2015). There is evidence for impaired (Abramovitch et al., 2017; Bornstein, 1991b; Margolis, Donkervoort, Kinsbourne, & Peterson, 2006; O'Connor et al., 2008) and intact motor skills assessed with variants of the Purdue Pegboard Task (Lavoie et al., 2007; Morand-Beaulieu, O'Connor, Sauve, Blanchet, & Lavoie, 2015). There is evidence of deficits to motor dexterity (Neuner et al., 2012; Stebbins, 1995) and intact dexterity (Marsh, Alexander, Packard, Zhu, & Peterson, 2005) on rotor, mirror tracing and hand steadiness tasks. Furthermore typical motor performance is seen on simple reaction time (Margolis et al., 2006) and finger tapping tasks (Bornstein, 1991b; Lavoie et al., 2007; Margolis et al., 2006; Neuner et al., 2012). In the largest sample to date, adult TS has been identified to have fine and gross motor impairment to one standard deviation lower than HVs (Abramovitch et al., 2017). Tasks assessing planning should therefore consider putative motor skill impairment.

The CANTAB SOC task is suited to assessment of planning in individuals where motor-skill impairment may exist. The touch-screen technology ensures that calculations of initial and subsequent thinking times takes into account an individual's fine motor dexterity and speed. During the task, there is a phase where participants follow on-screen movements of their responses to the previous problem solving task phase. Subsequently, the problem solving and 'follow' phases are yoked together, accounting for an individual's motor speed. Estimates of planning on the SOC task

are therefore reflective of the time taken to plan responses and not reflective of fine motor-skill impairment. Furthermore, the SOC task is devoid of motivational and affective decision-making and problem solving tasks and is therefore suitable for the assessment of planning in individuals with TS, as performance is unlikely to be influenced by deficits to affective decision-making.

Our research found no evidence to suggest that adult TS is associated with impaired planning ability, completion of the solving plan or problem solving accuracy, as evaluated by the CANTAB SOC task. Normal planning ability has also been found in adults with TS on the Tower of London Task (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006; Lavoie et al., 2007; Watkins et al., 2005) and the Six-Elements Test (Channon et al., 2004). Thus, our results, alongside previous and studies undertaken during the duration of this research, supports that planning and problem solving ability are not impaired in adult TS (Morand-Beaulieu, Leclerc, et al., 2017). Despite evidence of alteration in CSTC circuitry the intact performance observed in adult TS in problem solving and planning could be a consequence of different organisational planning techniques seen to be employed in TS (Laverdure, O'Connor, & Lavoie, 2013; O'Connor, Audet, Julien, Aardema, Laverdure, & Lavoie, 2015) that develop to overcome neurocognitive limitations.

Performance on tasks of working memory requires the ability to problem-solve alongside encoding and manipulation of information across modalities and holding this in short-term memory until required later in the task. Previously, adult TS has been associated with intact multitasking, learning, memory encoding and retrieval, visuo-motor integration and visuo-spatial manipulation (Channon, Crawford, et al., 2003; Channon et al., 2006; Channon, Pratt, & Robertson, 2003; Lavoie et al., 2007; Morand-Beaulieu, Leclerc, et al., 2017). However, evidence for deficits specific to working memory in adult TS remains inconclusive (Morand-Beaulieu, Leclerc, et al., 2017).

Exploration of working memory in those with TS has occurred primarily in children and adolescents. Intact working memory ability has been found during performance on forwards and backwards digit span and N-back tasks (Chang, McCracken, & Piacentini, 2007; Church, Wenger, et al., 2009; Crawford et al., 2005; Termine et al., 2016). Conversely, the majority of evidence indicates the existence of deficits in verbal working memory, forward digit-span (De Monte, 2007) and visuo-spatial

working memory tasks (Chang et al., 2007; Lin, Lai, & Gau, 2012; Rasmussen, Soleimani, Carroll, & Hodlevskyy, 2009; Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005). Importantly, investigation into executive functioning, especially working memory in children and adolescents occurs during vital stages of neurodevelopment; consequently conclusions of functioning occur during an under-developed state (Yaniv et al., 2017).

Exploration of working memory function in adult TS has revealed evidence of typical performance on verbal working memory, forward and backward digit span, N-back and letter and digit ordering tasks (Bornstein, 1991b; Channon et al., 2006; Crowe, 2000; Eddy, Mitchell, Beck, Cavanna, & Rickards, 2010; Eddy, Rickards, & Cavanna, 2014; Goudriaan et al., 2006; Stebbins, 1995). Impairment in adult TS has been observed during tasks of digit ordering (Eddy & Cavanna, 2015; Eddy, Rickards, & Cavanna, 2012) on the forward Corsi Span (Channon, Flynn, & Robertson, 1992) and on 2-N-back tasks (Muller et al., 2003). Heterogeneity in both TS severity and comorbidity can account for a proportion of the discrepancies in the literature (Yeates, 1994) as can variations in task complexity, where deficits are revealed, the more demanding the task (Channon et al., 2009; Eddy, Rickards, et al., 2012).

Our results support the growing body of evidence that adult TS is not associated with global impairment in executive functioning and working memory deficits. Specifically, our results found no evidence to suggest that adults with TS have impairment in executive functioning or working memory that corresponds to the retention and ability to manipulate visuospatial information as assessed by the CANTAB SWM task. Furthermore, our adult TS strategy scores were similar to HVs, further reinforcing intact problem solving abilities.

Sustained attention requires the maintenance of prolonged attention overtime and is assessed by the capacity of an individual to accurately detect signals that occur infrequently (Howells, Georgiou-Karistianis, & Bradshaw, 1998). Children and adolescents with TS have been shown during CPT tasks to make omission errors, where targets that are frequently presented are not attended to, indicative of impaired attention (Huckeba, Chapieski, Hiscock, & Glaze, 2008; Oades, 2000; Rasmussen et al., 2009; Shin, Chung, & Hong, 2001; Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, & Schultz, 2010). Furthermore, they have also

been show to display longer RTs to all signals, which indicates global inattentiveness (Greimel et al., 2011; Lin et al., 2012).

Whether sustained attention remains altered in adult TS however has been so far inconclusive; there is evidence for no impairment as tested with CPT tasks (Matsuda et al., 2012) and D2 cancellation tasks (Muller et al., 2003) as well as evidence for impairment in sustained attention observed during vibrotactile tasks (Georgiou, Bradshaw, & Phillips, 1998) and highly demanding letter cancellation tasks (Channon, Flynn, & Robertson, 1992). Unfortunately, there are few studies assessing sustained attention in adults with TS. There are discrepancies existing in those that do, and on the more demanding tasks, deficits are more apparent (Morand-Beaulieu, Leclerc, et al., 2017). Furthermore, aspects of attention will be difficult to dissociate from the effects that urge and tic control mechanisms have on attentional resource capacity (Erenberg, 2005).

The present results provide evidence that adult TS is not associated with impairments in sustained attention, relating to rapid visual information processing, as explored by the CANTAB RVP task. We further extend the knowledge base of sustained attention in adult TS, and coincide with reports of intact sustained attention (Matsuda et al., 2012; Muller et al., 2003). Whilst evidence for deficits occur only on demanding tasks, it is important to take into consideration reports of deficits in sustained attention secondary to deficits in working memory, whereby efforts to ensure task complexity are overly taxing (Morand-Beaulieu, Grot, et al., 2017; Yaniv et al., 2017).

Response inhibition is an executive function paramount to a range of cognitions. The ability to inhibit attentional biases, distractions and interference is vital to ensure utilisation of cognitive resources (Diamond, 2002; Elliott, 2003). As inhibitory control is a crucial pre-requisite to optimise cognition, often deficits are mistakenly attributed to other executive functions, when inhibitory deficit is the primary concern (Morand-Beaulieu, Grot, et al., 2017; Yaniv et al., 2017). Inhibitory control is not a unitary construct, with multiple facets mediated by dorsolateral and orbitofrontal cortices (Aron, Robbins, & Poldrack, 2004; Berlin, Rolls, & Kischka, 2004; Braver, Barch, Gray, Molfese, & Snyder, 2001; Konishi et al., 1999; Metzler & Parkin, 2000).

Response inhibition is relevant to understanding involuntary movements and impulsivity and is therefore the most explored cognitive ability in TS research (Bari & Robbins, 2013; Chamberlain & Sahakian, 2007; Deckersbach, Rauch, Buhlmann, & Wilhelm, 2006; Torregrossa, Quinn, & Taylor, 2008; D. W. Woods et al., 2005). Inhibition of urges, thoughts, emotions and behaviours are complex and difficult to objectively measure. Therefore, tasks that assess inhibitory control typically focus on inhibition of an initiated and poised-for-execution motor action (Jahanshahi & Rothwell, 2017). Other assessments include stimulus-response paradigms, whereby successful performance requires inhibition of inappropriate automatic responses or attentional biases (Ridderinkhof, 2004; Salthouse, 2010). Tasks that investigate prepotent motor responses are however, considered a 'pure' measure of response inhibition (Jahanshahi & Rothwell, 2017; Kalsi et al., 2015; Miyake et al., 2000), with observed deficits corresponding to impulsive behaviour and impulse control deficits (Castro-Meneses, Johnson, & Sowman, 2015; Logan, 1997; Oosterlaan, Logan, & Sergeant, 1998).

In children and adolescents with TS, there is evidence during the Simon and go-nogo tasks for impaired (Channon et al., 2004; Wylie, Claassen, Kanoff, Ridderinkhof, & van den Wildenberg, 2013) and normal response inhibition (Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008). In addition, normal accuracy on go-nogo tasks have been observed alongside slower RTs (Eichele et al., 2010; Shephard, Jackson, & Groom, 2016). Authors propose these results are representative of the need to slow motor output in order to be able to facilitate task performance and tic control. Alternatively, this could represent a compensatory trade-off between speed and accuracy. Delayed RTs and more frequent omission errors on the go-nogo task were associated with decreased sensorimotor activation in adolescents (Thomalla et al., 2014). These associations, demonstrated to be induced by fronto-parietal network reorganisation, are likely an adaptive response to CSTC circuitry hyperactivity. Therefore, during stages of neural reorganisation, children and adolescents with TS may be more susceptible to errors in attention and inhibition, reflective of increased effort to achieve dual control of tics and task performance. Interestingly, on a demanding oculomotor task, enhanced cognitive and inhibitory control was observed in adolescents with TS (Mueller, Jackson, Dhalla, Datsopoulos,

& Hollis, 2006), indicative that reorganisation can be compensatory and result in superior performance compared to HVs.

Structural and functional brain changes occur overtime in those with TS, coinciding with better clinical and cognitive outcomes in adulthood (Laverdure et al., 2013; O'Connor, Audet, Julien, Aardema, Laverdure, & Lavoie, 2015). Interestingly, adolescents with TS demonstrating inhibitory deficits, were noted to have worse tic severity than individuals without impairment (Jung, Jackson, Nam, Hollis, & Jackson, 2015). These results imply that compensatory reorganisation, beneficial to response inhibition (Jackson, Parkinson, Jung, et al., 2011), may correspond to better tic control. Typically, the majority of TS cases reduce in severity overtime, with a large proportion of cases remitting in adulthood. A recent longitudinal study found that adults with TS, who display worse response inhibition as assessed by stop-signal tasks, acquire better clinical outcomes overtime, alongside better response inhibition performance (Yaniv et al., 2018). Furthermore, it was found that where TS had remitted in adulthood, response inhibition was similar or superior to HVs; implying that in some instances, TS does not have a lasting negative impact on all aspects of neuropsychology.

In adults with TS, there is evidence for impaired inhibitory performance on Stroop tasks (Eddy, Rickards, et al., 2012; Eddy et al., 2014; Goudriaan et al., 2006; Muller et al., 2003; Schoenberg et al., 2015), Simon tasks (Georgiou, Bradshaw, Phillips, Bradshaw, & Chiu, 1995), go-nogo tasks (Goudriaan et al., 2005) and Part B of the Trail Making Task (Channon, Flynn, & Robertson, 1992; Eddy & Cavanna, 2015, 2017; Schoenberg et al., 2015). Conversely, normal performance has been found on flanker tasks (Channon et al., 2009; Channon et al., 2006), Stroop tasks (Channon, Flynn, & Robertson, 1992; Crowe, 2000; Eddy & Cavanna, 2017; Lavoie et al., 2007; Matsuda et al., 2012; Silverstein, 1995; Thibault, O'Connor, Stip, & Lavoie, 2009), Simon tasks (Morand-Beaulieu et al., 2015; Thibault et al., 2009), Part B of the Trial Making Test (Bornstein, 1991b; Lavoie et al., 2007; Silverstein, 1995) and go-nogo tasks (Draper, Jude, Jackson, & Jackson, 2015; Hershey et al., 2004; Morand-Beaulieu, Grot, et al., 2017; Muller et al., 2003; Serrien, Orth, Evans, Lees, & Brown, 2005; Watkins et al., 2005).

Literature investigating neurocognitive function in adult TS is complex and largely inconclusive due to discrepancies. It is important to observe that, where no

significant deficits are identified in adult TS, there are moderate effect sizes implying a lack of statistical power to detect a genuine effect (Bornstein & Yang, 1991; Channon, Pratt, et al., 2003). Intriguingly, evidence of impairment is also most apparent during performance of complex, demanding tasks (Eddy, Rickards, et al., 2012; Eddy et al., 2014; Murphy, & Eddy, 2013). One interpretation is that inhibitory deficits in adult TS are subtle and therefore only evident on tasks of appropriate sensitivity. Conversely, impairment following complex tasks may be reflective of secondary impairment in inhibition, due to taxing of other reciprocal cognitive processes (Morand-Beaulieu, Grot, et al., 2017; Yaniv et al., 2017). Methodological issues including lack of statistical power due to small sample sizes, lack of control or exploration of severity, comorbidity and medication, alongside task selection, need to be considered when evaluating inhibitory function in adult TS (Morand-Beaulieu, Leclerc, et al., 2017). Furthermore, a recent meta-analysis concluded that there is likely a moderate but significant alteration in inhibitory control in adult TS (Morand-Beaulieu, Grot, et al., 2017).

Our results found no evidence to suggest that adult TS is associated with impaired response inhibition of prepotent motor responses, as evaluated by the CANTAB SST task. Our results are therefore consistent with reports of intact inhibitory performance in adult TS (Bornstein, 1991b; Channon et al., 2009; Channon, Flynn, & Robertson, 1992; Channon et al., 2006; Crowe, 2000; Draper et al., 2015; Eddy & Cavanna, 2017; Hershey et al., 2004; Lavoie et al., 2007; Matsuda et al., 2012; Morand-Beaulieu, Grot, et al., 2017; Morand-Beaulieu et al., 2015; Muller et al., 2003; Ozonoff, Strayer, McMahon, & Filloux, 1998; Roessner et al., 2008; Serrien et al., 2005; Silverstein, 1995; Thibault et al., 2009; Thibeault et al., 2016; Watkins et al., 2005).

The CANTAB SST task is presented in a staircase design, adapting task parameters to an individual's performance, within their capabilities. It is therefore likely that the SST demonstrates specificity and sensitivity to inhibitory function (Jahanshahi & Rothwell, 2017; Kalsi et al., 2015; Miyake et al., 2000) without encroaching on other cognitive domains. Interestingly, our adult TS participants displayed slower RTs; this observation however, was attributable to medication with antipsychotics and not reflective of compensatory speed for accuracy trade off, often noted to be employed in those with TS (Eichele et al., 2010; Mueller et al., 2006; Shephard et al., 2016).

Intact response inhibition was observed in our adult TS sample and suggestive of remission of childhood inhibitory deficits. However, we cannot conclusively rule out the existence of impairment, for compensatory mechanisms that do not jeopardise speed for accuracy may be employed. Despite this, our results provide evidence that aspects of executive functioning, remains intact in a sample of adults. Whether due to remission or compensatory mechanisms, our results support claims that TS does not have a lasting negative impact on response inhibition (Yaniv et al., 2018).

Because alterations of CSTC circuitry is implicated in TS pathology, abnormalities of executive functions have been proposed to exist in TS (Eddy et al., 2009; Morand-Beaulieu, Leclerc, et al., 2017). How executive function is impacted in adult TS is relatively unknown (Morand-Beaulieu, Leclerc, et al., 2017). However, the most frequent and robust reports of deficits are associated with specific impairments in inhibitory control and cognitive flexibility (Morand-Beaulieu, Leclerc, et al., 2017). This contrasts with proposed global deficits in a range of general cognitions (Eddy, Rickards, et al., 2012).

Discrepancies in the literature investigating cognition in adult TS have been largely due to methodological issues. Firstly, lack of statistical power (Bornstein & Yang, 1991; Channon, Pratt, et al., 2003), due to small samples sizes, inherent to the low prevalence of adult TS (Bloch et al., 2011; Bloch et al., 2006; Yaniv et al., 2017) has reduced the degree to which subtle deficits can be detected. Furthermore, a variation of tasks, ranging in difficulty and sensitivity have been used, all assessing different aspects of executive functioning (Channon et al., 2009; Eddy, Rickards, et al., 2012; Eddy et al., 2014; Kalsi et al., 2015; Murphy, & Eddy, 2013). Similarly, deficits in specific cognitions have often been reported as global dysfunction (Yaniv et al., 2017). Finally, a lack of control or consideration for tic and urge severity, comorbidity and medication (Morand-Beaulieu, Leclerc, et al., 2017; Yeates, 1994) further complicates the investigation of cognition in adult TS.

Our results have found impairment in cognitive flexibility specific to habitually learned behaviours that is independent of antipsychotic medication use. All other aspects of general cognition assessed were found to be intact in adult TS. Later, in Chapters 7 and 8, we investigate the influence of clinical features and the role of comorbidity on general cognition in adult TS.

Chapter 4. Attention and inhibition

4.1. Introduction

The aim was to explore in detail whether adult TS is associated with specific cognitive deficits to attention and/or inhibitory control. New tasks were developed that were complex and sensitive to attention and inhibition in parallel, with minimal dependence on working memory, and used to evaluate the degree of impairment existing in adult TS. This allowed the determination of whether deficits to attention and/or inhibitory control exist in adult TS and whether action and inhibition are separate entities.

4.2. Continuous Performance Task (CPT)

Task design

There is evidence to suggest that cognitive dysfunction is implicated in adult TS (Channon et al., 2009; Channon et al., 2006; Eddy et al., 2009). However, the literature is at large inconsistent (Channon et al., 2009; Eddy et al., 2009; Kalsi et al., 2015; Robertson, 2015a). Discrepancies in the literature can be attributed to a failure to characterise and control for tic and urge severity, comorbidity and medication effects; culminating in concerns regarding causality (Morand-Beaulieu, Leclerc, et al., 2017; Yeates, 1994). Furthermore, questionable task suitability, sensitivity and lack of consensus on the tasks chosen to investigate aspects of cognition is problematic. These affect the degree to which conclusions can be drawn, and correctly attributed to neurocognitive domains. (Channon et al., 2009; Eddy, Rickards, et al., 2012; Eddy et al., 2014; Kalsi et al., 2015; Murphy, & Eddy, 2013).

Impairments in aspects of executive functioning, specifically in attention and inhibitory control, have been reported in adult TS (Channon et al., 2009; Robertson, 2015a). However, tasks sensitive to detect such impairments appear to commonly encompass higher degrees of inhibitory demands and task complexity (Channon et al., 2009). Caution is warranted with task complexity as it is difficult to manipulate task demands without placing demands on working memory, which might restrict the extent to which findings can be attributed to the specific domains of attention and inhibition (Eddy et al., 2009).

To overcome the methodological issues of previous neuropsychological assessment in TS, a variant of a CPT was created that:

1. Was complex, moderating task difficulty with minimal constraints on working memory. CPT tasks used previously (Channon et al., 2009), for example, increase task complexity by using words and associated meaning that tax working memory and therefore make it difficult to dissociate the source of performance differences. In our CPT, task difficulty was manipulated by varying the attentional load throughout the task by increasing the target-to-non-target set-size from one target up to a total of four targets. Furthermore, our chosen visual stimuli were individual letters that are easy to discriminate. Thus, it was anticipated that attentional load manipulation would enhance task complexity with minimal working memory constraints. The use of attentional load manipulation to increase CPT task complexity has not been studied previously.
2. Had strong inhibitory demands. Tasks used previously, have been associated with high hit rates and low false alarm rates, with over 95% accuracy (Channon et al., 2009). Thus, floor effects are a likely explanation of the previous inability to establish the existence of attention or inhibition deficits in adult TS. To overcome this, increasing task demands are needed. Again, a key consideration is to avoid placing large constraints on working memory so that performance can be attributed to genuine inhibitory demands. To increase task complexity inhibitory demands were manipulated by:

a. Presenting targets 70% of the time and non-targets 30% of the time; these parameters are known to establish a strong prepotent motor response (Channon et al., 2009; Lucke et al., 2015; Roessner et al., 2008).
b. Presenting stimuli briefly and vary ISI durations to reduce working memory demands and less attentional processing.

During pilot studies (*n*= 4), stimuli were presented for 500ms with ISIs of 500, 750 and 1000ms. Hit-rate accuracy of 95-81% and false-alarm accuracy of 93-89% were seen with increasing target set size. Further, piloting (*n*= 4) this task with flankers that were either compatible (also targets), incompatible (non-targets) or neutral (non-letters) to the target letter, hit-rate accuracy became 96-90% and false-alarm accuracy 84-88% with increasing target set size. In comparison, pilot studies (*n*= 3) where stimuli were presented for 250ms with ISIs of 250, 500, 750, 1000 and

1500ms led to hit-rate accuracy of 83-95% and false-alarm accuracy of 76-77%, with increasing target set-size. Therefore, alterations of the speed of presentation and ISIs resulted in the enhanced need for vigilance during task performance that appears to have increased both task attentional demands (hit-rate accuracy) and inhibitory demands (false-alarm accuracy). Coincidently this method appeared more effective than manipulating working memory demands by using distracting flankers.

Another important feature of CPT tasks is that attention and inhibition can be investigated in parallel; this is important because:

1. Action and inhibition can be examined to establish whether they are separate entities. This will allow the inference as to whether the capacity to inhibit remains constant when attention is varied; this has important implications for the development of attentional distraction therapies.
2. The task structure gives the unique opportunity to examine the effects of varying levels of attentional load on tic frequency. Furthermore, it enables the examination of attentional and inhibitory mechanisms during free ticcing and tic inhibition and the dissociation of the effects of tic suppression mechanisms from task performance. This is examined later, in Chapter 9.

To summarise, the CPT variant was developed to increase target to non-target set-size so that attentional load can be varied. It is anticipated that moderating attentional load alongside brief, varied presentation of stimuli, when responses to targets are required 70% of the time, will induce a strong prepotent motor tendency that is difficult to inhibit upon infrequent occurrence of non-target signals. It is anticipated that errors of commission (responding to non-targets), an index of altered inhibition, will increase with attentional load. Additionally, the proportion of commission errors made with increasing attentional demand will allow us the inference as to whether the capacity to inhibit remains constant when attention is variable. In this chapter, CPT scores for adults with TS are an average of performance achieved under both free to tic and tic suppression conditions. Furthermore, in Chapter 9, this CPT variant will allow insight into tic management where task performance is analysed for conditions under instruction to tic freely and instruction to actively suppress tics.

Results

Hit reaction time (HRT)

Total task

Independent *t*-tests revealed that those with TS had significantly slower HRTs for the total CPT task compared to HVs, *t* (51) = -3.703, *p* = .001, *d* = -1.058.

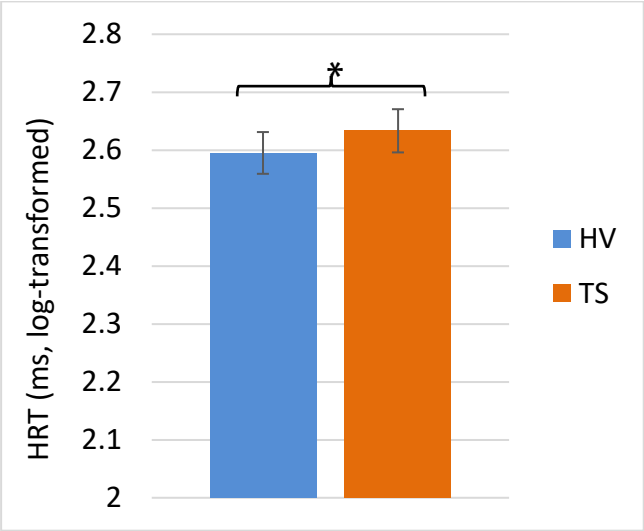


Figure 41. Total task mean hit reaction times (ms, log-transformed) on the CPT task for HVs and TS. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Target set-size

Correct trials

There was a significant main effect of target set-size on HRT for correct trials, *F* (2.464, 125.650) = 124.964, *p* = .000, *r* = .71. Planned contrast (Helmert) comparing HRTs when only one target occurred, to the mean effect on HRT of all subsequent set sizes, revealed significantly quicker HRTs for fewer targets, *F* (1, 51) = 366.949, *p* = .000, *r* = .94.

There was no significant interaction effect between target set-size and clinical status of the participant on HRT, *F* (2.464, 125.650) = .832, *p* = .459, *r* = .08.

There was a significant main effect of clinical status, F (1, 51) = 13.662, p = .001, r = .46, whereby those with TS were significantly slower than HVs regardless of target set-size.

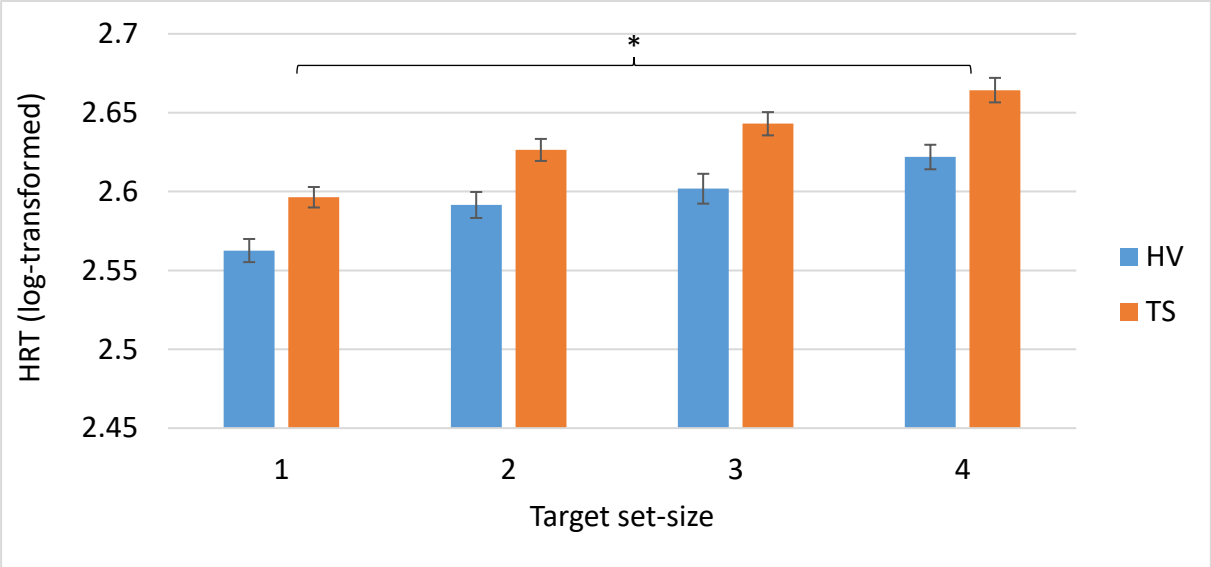


Figure 42. Mean hit reaction times (ms, log-transformed) on the CPT task at different target set-sizes, varying task difficulty with increasing attentional load, for HVs and TS. Error bars represent SEM. *Differences in target set-sizes significant following Benjamini-Hochberg FDR correction.

Incorrect trials

There was no significant effect of target set-size on RT for incorrect trials, F (1.504, 76.713) = .634, p = .490, r = .09. Further, there was no significant interaction effect between target set-size and participant clinical status, F (1.504, 76.713) = 1.284, p = .276, r = .13, and no significant main effect of clinical status on incorrect trial RT, F (1, 51) = .093, p = .762, r = .04.

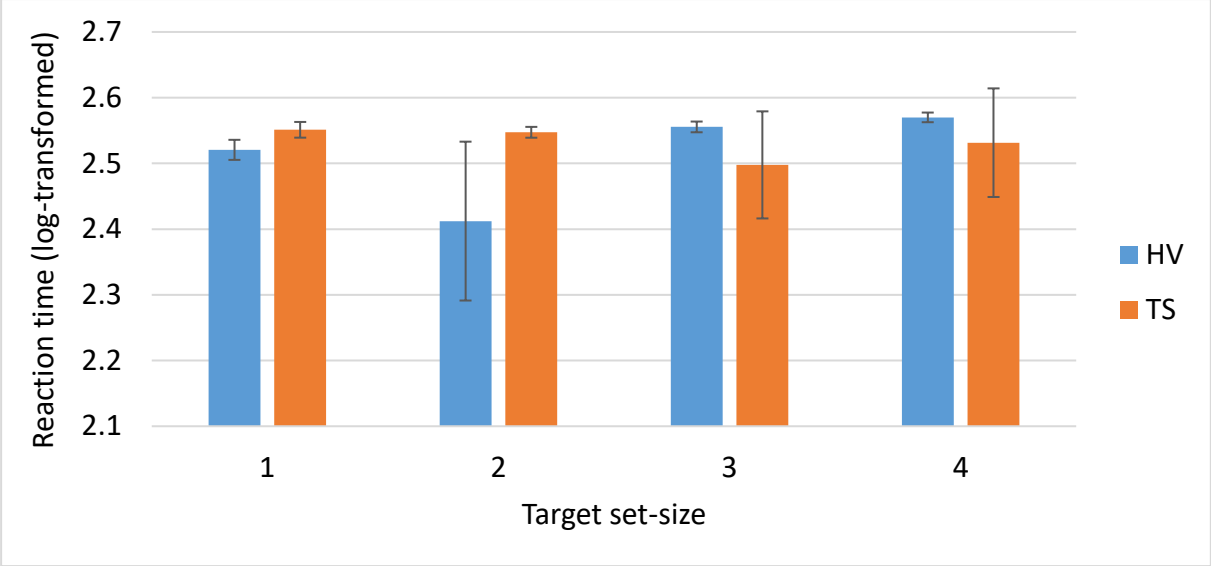


Figure 43. Mean reaction times (ms, log-transformed) of incorrect trial responses on the CPT task at different target set-sizes, varying task difficulty with increasing attentional load, for HVs and TS. Error bars represent SEM.

Inter-stimulus intervals (ISIs)

There was a significant main effect of ISI duration on participant HRTs, F (2.214, 112.895) = 138.912, p = .000, r = .74. Planned contrasts (Helmert) comparing the mean effect of the slowest ISI on HRT to the mean effect of all subsequent ISI durations, shows that with increasing ISIs HRTs become significantly quicker, F (1, 51) = 248.469, p = .000, r = .91.

There was a significant main interaction between ISI duration and participant clinical status, F (2.214, 112.895) = 3.837, p = .021, r = .18. To break down the interaction, planned contrasts (Helmert) confirmed that HRTs were significantly slower, the shorter the ISI duration, F (1, 51) = 4.816, p = .033, r = .29, and identified the largest magnitude of differences between HVs and those with TS (significantly slower) to be most prominent at the slowest ISI duration of 250ms.

There was a significant main effect of clinical status, F (1, 51) = 13.250, p = .001, r = .45, with those with TS having slower HRT, irrespective of ISI duration.

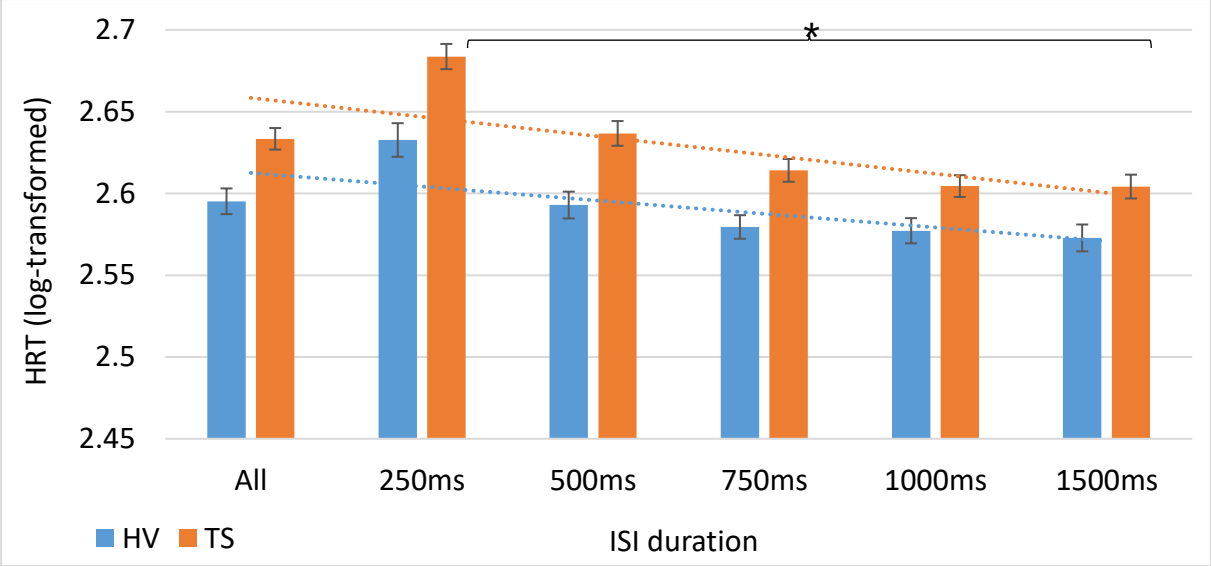


Figure 44. Mean hit reaction times (ms, log-transformed) on the CPT task at different inter-stimulus intervals (ISIs) for HVs and TS. Error bars represent SEM. *Differences in ISIs significant following Benjamini-Hochberg FDR correction.

Experimental block

There was a significant main effect of experimental block on participant HRTs, F (4.681, 238.721) = 16.187, p = .000, r = .25.

Planned contrasts (Helmert) comparing the mean effect of the first block on HRT to the mean effect of all subsequent blocks, showed that overtime HRTs become significantly slower, F (1, 51) = 88.077, p = .000, r = .80.

There was no significant main interaction between experimental block and participant clinical status, F (4.681, 238.721) = 1.501, p = .194, r = .08.

There was a significant main effect of clinical status, F (1, 51) = 13.315, p = .001, r = .46, with those with TS having slower HRT irrespective of experimental block.

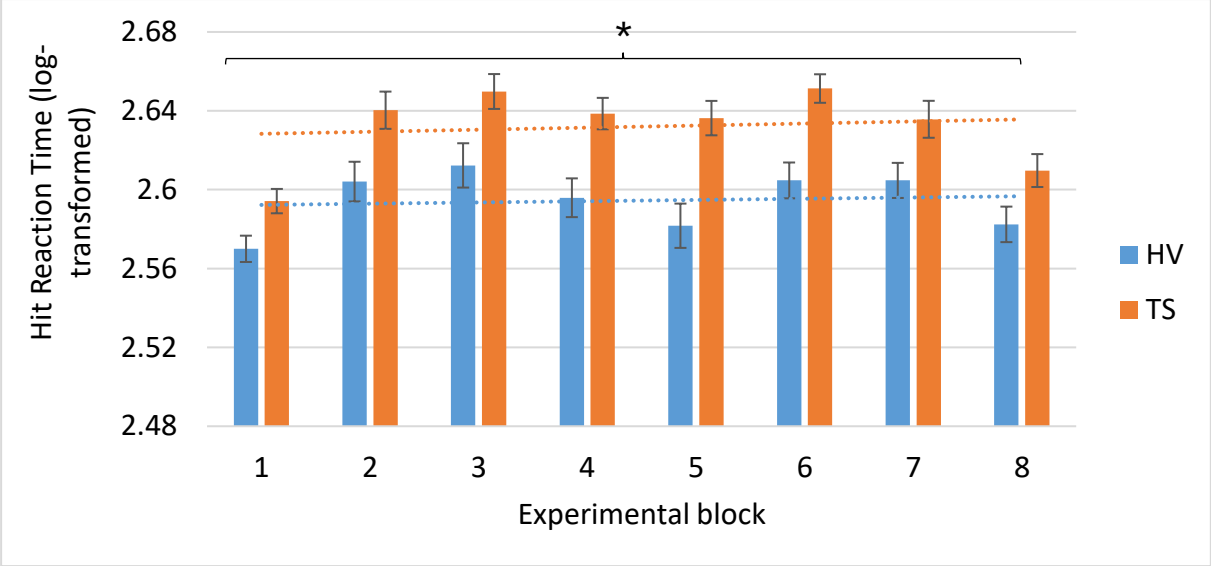


Figure 45. Mean hit reaction times (ms, log-transformed) on the CPT task at each experimental block for HVs and TS. Error bars represent SEM. *All differences in HRT at experimental blocks and by clinical status significant following Benjamini-Hochberg FDR correction.

Errors

Target set-size

There was no significant main effect of the type of error on the number of errors made on the CPT task, F (1, 51) = 1.498, p = .227, r = .17.

There was a significant interaction effect between error type and clinical status of the participant, F (1, 51) = 5.078, p = .029, r = .30, whereby those with TS made significantly more omission errors than HVs.

There was no significant main effect of target set-size on the number of errors made on the CPT task, F (3, 153) = 1.334, p = .267, r = .09 and no interaction between target set-size and clinical status on CPT task errors, F (3, 153) = 2.280, p = .090, r = .12.

There was a significant interaction effect between the type of error and target set-size on the number of errors made on the CPT task, F (2.453, 125.107) = 37.603, p = .000, r = .48.

To break down the interaction, planned contrasts (Helmert) comparing the mean number of errors made at target set-size 1 to the mean number of errors occurring

for all subsequent target set-sizes revealed significantly fewer commission errors and significantly more omission errors when 1 target compared to all other set-sizes, F (1, 51) = 88.029, p = .000, r = .80.

There was no significant interaction effect between the type of error made, target set-size or clinical status of the participant on the number of errors made on the CPT task, F (2.453, 125.107) = .781, p = .484, r = .08.

There was no significant main effect of clinical status, F (1, 51) = .849, p = .361, r = .13.

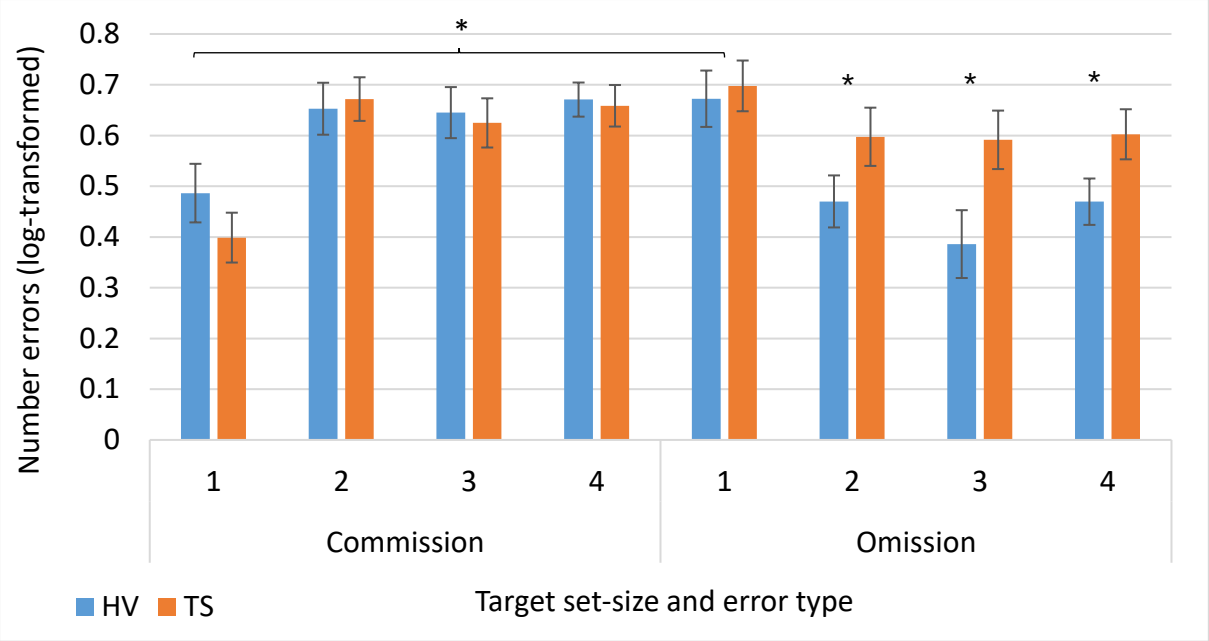


Figure 46. Mean number of commission (left) and omission (right) errors (log-transformed) on the CPT task at different target set-sizes for HVs and TS. Error bars represent SEM. *Interaction effect between error type and target set-size and difference in the number of omission errors made by HVs and TS significant following Benjamini-Hochberg FDR correction.

Experimental block

There was a significant main effect of error type on the number of errors made on the CPT task, F (1, 51) = 7.234, p = .010, r = .35, with more commission errors being made overall.

There was a significant interaction effect between error type and clinical status of the participant, F (1, 51) = 4.748, p = .034, r = .29, indicating that whilst fewer omission errors are made overall, those with TS made significantly more omission errors than HVs. HVs and those with TS make similar numbers of commission errors.

There was a significant main effect of block number on the amount of errors made on the CPT task, F (5.693, 290.364) = 3.202, p = .005, r = .10.

Planned contrasts (difference) comparing the mean errors made in the final block to the mean effect of all previous categories, revealed that significantly more errors were made overtime, F (1, 51) = 9.947, p = .003, r = .40.

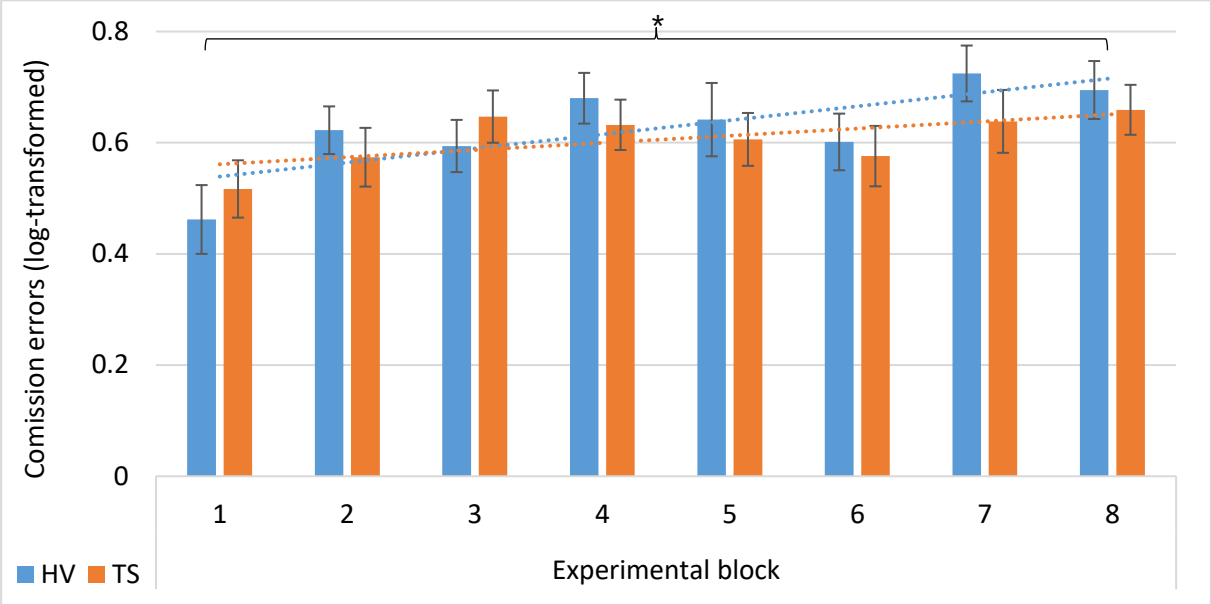
There was no significant block x clinical status interaction, F (5.693, 290.364) = .121, p = .992, r = .02, indicating that the increase in errors made in the final block of the task occurred irrespective of clinical status.

There was a significant interaction between error type and block, F (7, 357) = 3.345, p = .002, r = .10, but no significant error type x block x clinical status interaction, F (7, 357) = 1.595, p = .136, r = .07.

Planned contrasts (Helmert) revealed that participants made significantly fewer commission errors in the first block of the experiment in comparison to the remaining blocks, F (1, 51) = 17.470, p = .000, r = .51. The number of omission errors were constant overtime.

There was no significant effect of clinical status on the number of errors made, F (1, 51) = .827, p = .367, r = .13.

A.



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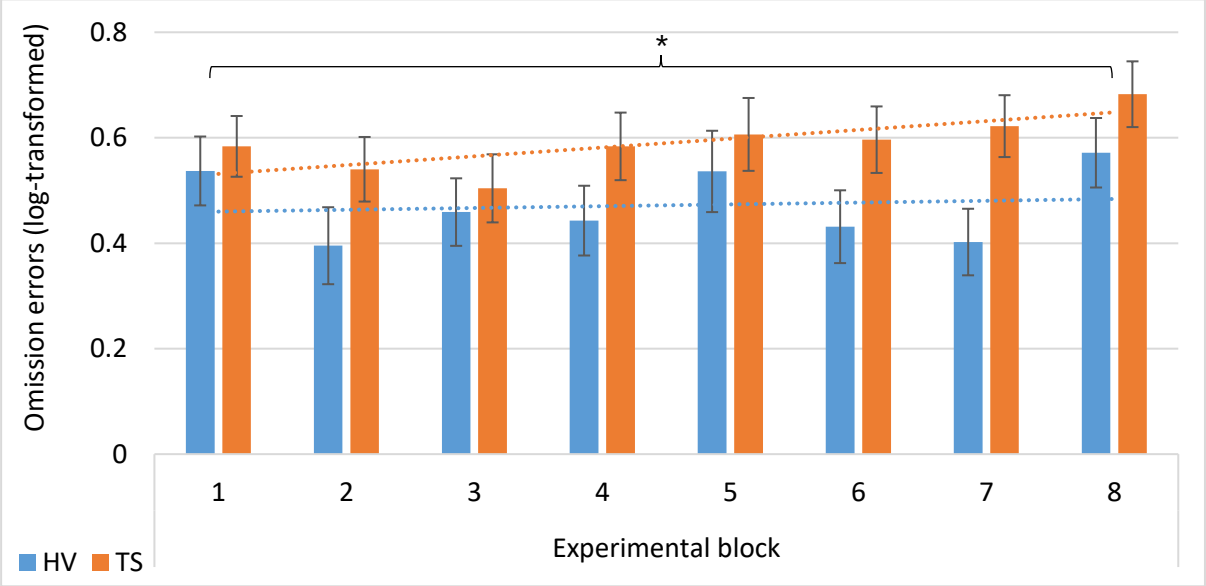


Figure 47. Mean number of A) commission errors; and B) omission errors (log-transformed) on the CPT task at each experimental block for HVs and TS. Error bars represent SEM. *More commission errors made overall, more omission errors made by TS and effects of experimental blocks significant following Benjamini-Hochberg FDR correction.

Total task

Independent *t*-tests revealed that those with TS made significantly more omission errors compared to HVs on the total CPT task, t (51) = -1.887, p = .037, d = -0.54.

There was no difference in the number of commission errors made between those with TS and HVs on the total CPT task, t (51) = .049, p = .961, d = .014.

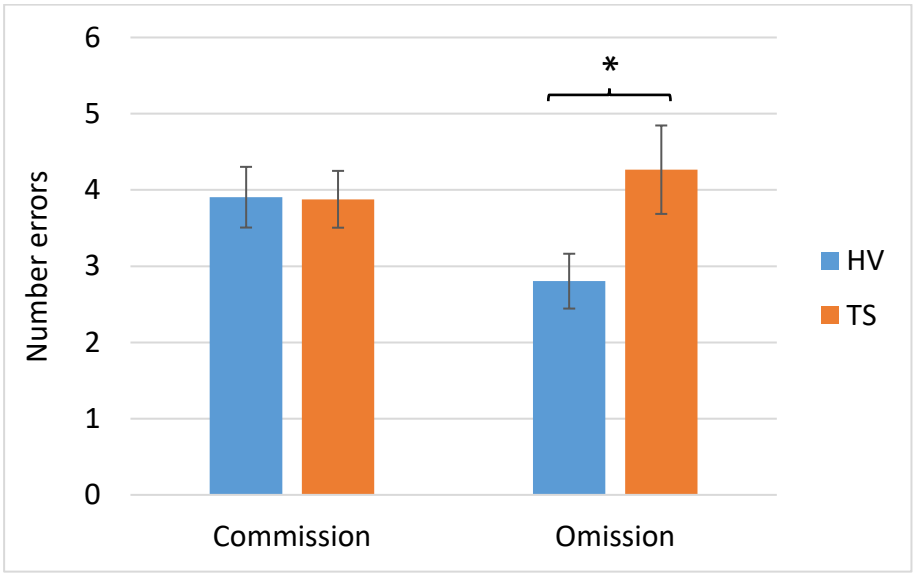


Figure 48. Mean number of total task commission (left) and omission (right) errors made on the CPT task by HVs and TS. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Perseverative Errors and Multiple Responding

Participants with TS made more perseverative errors and more multiple responses than HVs, however these did not reach significance, U = 272.500, z = -1.459, p = .145, r = -.20 and U = 242.500, z = -1.724, p = .085, r = -.24 respectively.

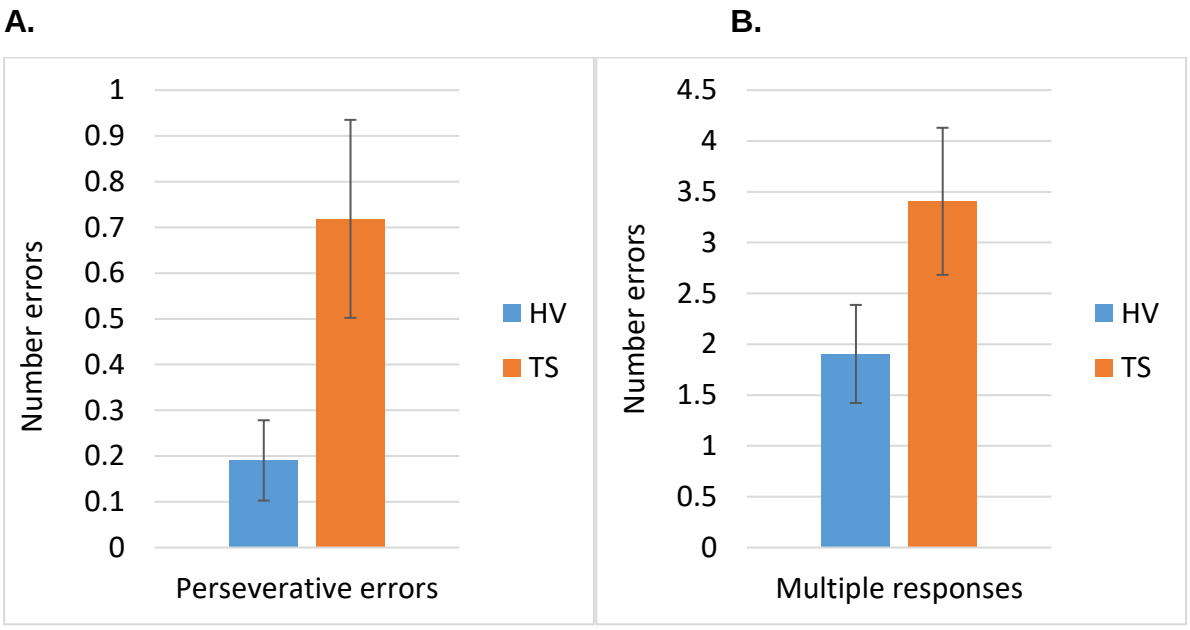


Figure 49. Mean number of A) perseverative errors and B) multiple responses made on the CPT task by HVs and TS. Error bars represent SEM.

Accuracy

Target set-size

There was a significant main effect of the type of error on CPT task accuracy, *F* (1, 51) = 63.977, *p* = .000, *r* = .75, where participants were more accurate for omission than commission errors.

There was no significant interaction effect between error type and clinical status of the participant, *F* (1, 51) = .175, *p* = 677, *r* = .06. There was no significant main effect of target set-size on CPT task accuracy, *F* (3, 153) = 1.808, *p* = .148, *r* = .11 and no interaction between target set-size and clinical status on CPT task accuracy, *F* (3, 153) = .287, *p* = .834, *r* = .04.

There was a significant interaction effect between the type of error and the target set-size on task accuracy, *F* (3, 153) = 11.830, *p* = .000, *r* = .27. To break down the interaction, planned contrasts (Helmert) comparing the mean accuracy for one target to the mean effect on accuracy of all subsequent target set-sizes revealed that there was significantly better accuracy for commission errors at target set-size 1 compared to other set-sizes, *F* (1, 51) = 29.432, *p* = .000, *r* = .60.

There was no significant interaction effect between the type of error made, the target set-size or clinical status of the participant on task accuracy, F (3, 153) = .248, p = .863, r = .04. Further, there was no significant main effect of clinical status, F (1, 51) = .073, p = .788, r = .04.

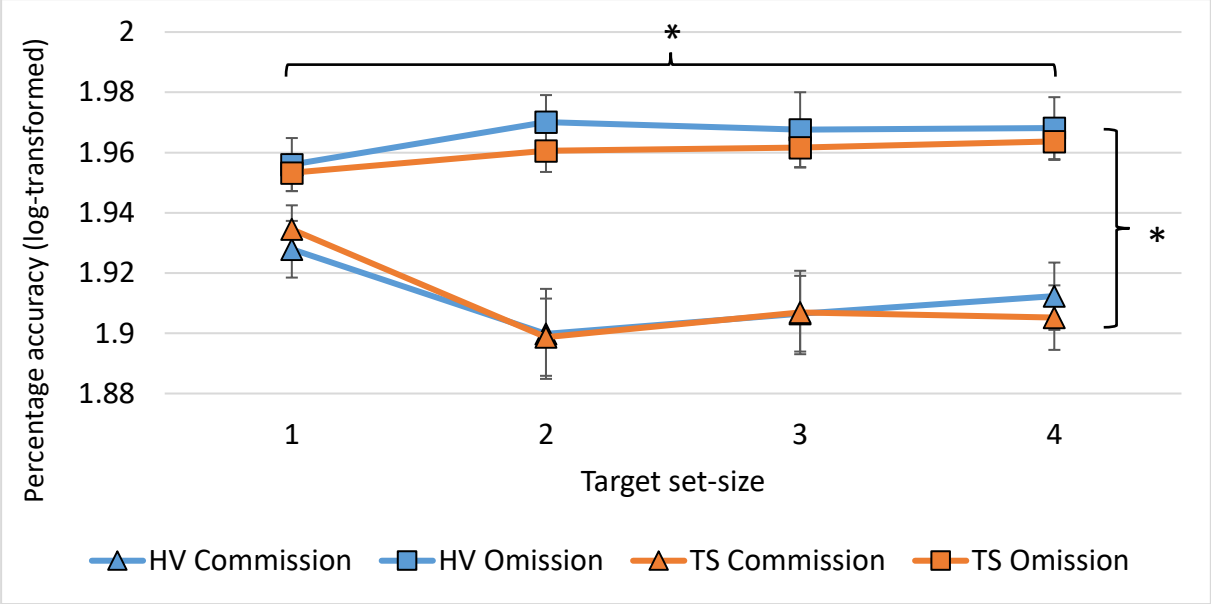


Figure 50. Mean percentage accuracy of commission (triangle) and omission (square) errors (log-transformed) made on the CPT task at different target set-sizes by HVs and TS. Error bars represent SEM. *Better accuracy for omission errors and all error types at target set-size 1 compared to all others significant following Benjamini-Hochberg FDR correction.

Experimental block

There was a significant main effect of the type of error on CPT task accuracy, F (1, 51) = 70.575, p = .000, r = .76, with all participants being more accurate for omission type errors. There was no significant interaction effect between error type and clinical status of the participant, F (1, 51) = 1.047, p = .311, r = .14.

There was a significant main effect of block number on CPT task accuracy, F (4.879, 248.837) = 3.198, p = .009, r = .11. Planned contrasts (difference) comparing the mean accuracy of the last block to the mean effect of accuracy of all previous blocks, revealed that significantly reduced accuracy occurs overtime, F (1, 51) = 6.493, p = .014, r = .34.

There was no significant block x clinical status interaction, F (4.879, 248.837) = .603, p = .694, r = .05, indicating that the decrease in task accuracy overtime occurs irrespective of clinical status.

There was a significant interaction between error type and block, F (5.206, 265.517) = 2.249, p = .047, r = .09, but no significant error type x block x clinical status interaction, F (5.206, 265.517) = 1.248, p = .286, r = .07.

Planned contrasts (difference) comparing task accuracy in the first block to the mean effect of accuracy in the remaining blocks revealed that overtime there was a significant reduction in commission error accuracy, F (1, 51) = 11.302, p = .001, r = .43. Omission error accuracy does not appear to significantly reduce overtime.

There was no significant main effect of clinical status, F (1, 51) = .650, p = .424, r = .11.

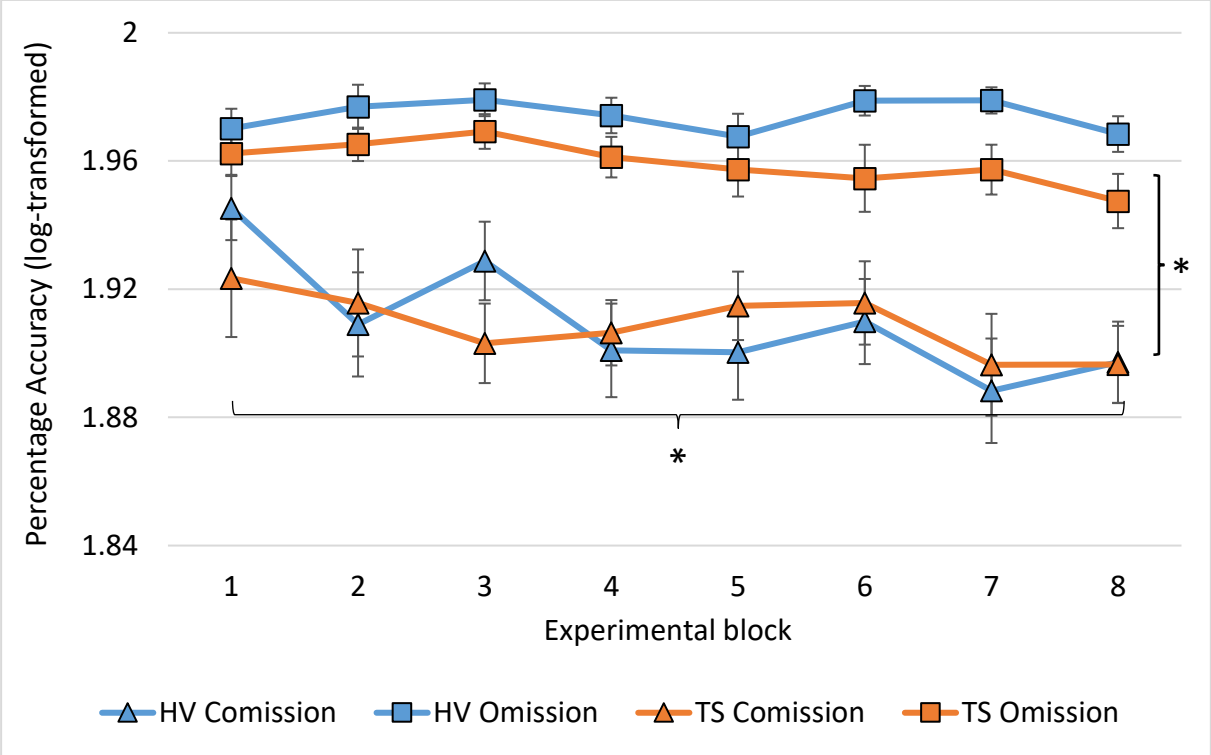


Figure 51. Mean percentage accuracy of commission (triangle) and omission (square) errors (log-transformed) made on the CPT task at each experimental block for HV and TS. Error bars represent SEM. *Better accuracy for omission errors and interaction between block and error type significant following Benjamini-Hochberg FDR correction.

Detectability *d*

There was a significant main effect of target set-size on detectability *d*, F (3, 153) = 4.593, p = .004, r = .17, but no set-size x clinical status interaction, F (3, 153) = 1.126, p = .340, r = .09.

Planned contrasts (deviation) for comparisons of the mean overall experimental effect revealed that participants were significantly better at discriminating between non-targets and targets when the task had 3 targets, F (1, 51) = 10.135, p = .002, r = .41. There was no significant main effect of clinical status on detectability *d*, F (1, 51) = .023, p = .890, r = .02.

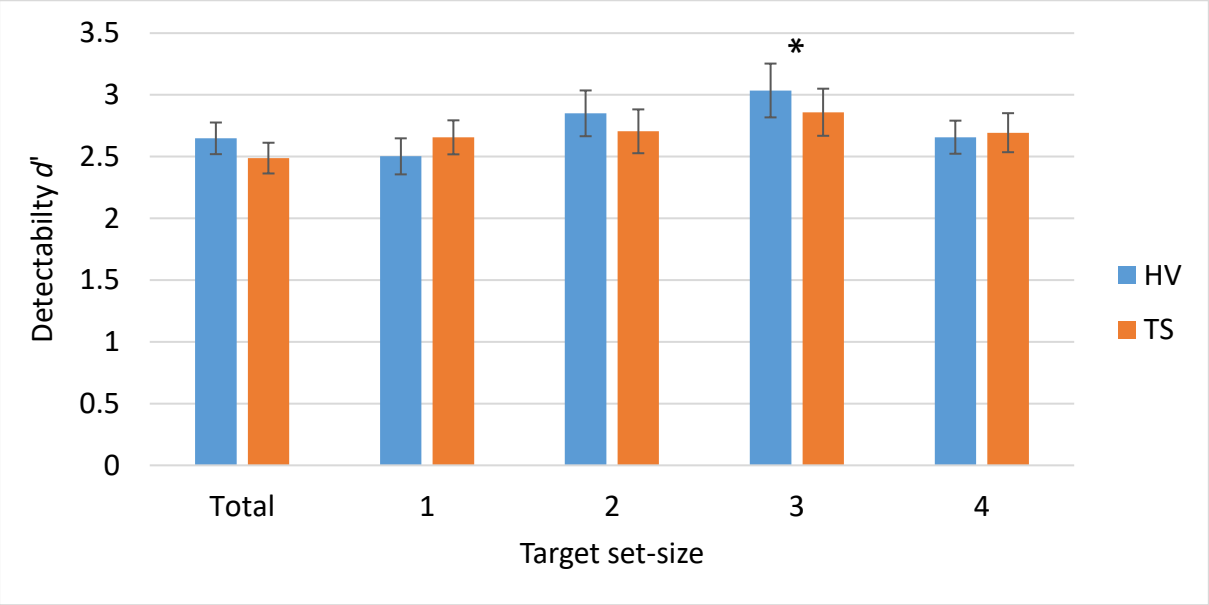


Figure 52. Mean detectability *d*' on the CPT task at different target set-sizes and total task performance for HVs and TS. Error bars represent SEM. *Better *d* at set-size 3 significant following Benjamini-Hochberg FDR correction.

Response style *c*

There was a significant main effect of target set-size on participant response style *c*, F (2.549, 129.988) = 11.353, p = .000, r = .28. Planned contrasts (Helmert) comparing the response style of participant to one target to the mean effect on response style of all subsequent set-sizes, revealed that participants were more conservative in their response style, emphasising accuracy for smaller set-sizes, F

(1, 51) = 36.702, *p* = .000, *r* = .65, and were comparatively more liberal emphasising speed over accuracy for larger target set-sizes.

There was a significant set-size x clinical status interaction, *F* (2.549, 129.988) = 2.836, *p* = .049, *r* = .15. Planned comparisons (deviation) that makes comparisons to the mean overall experimental effect revealed that HVs and those with TS differed significantly in response style when target set-size was 3, *F* (1, 51) = 6.094, *p* = .017, *r* = .33. Those with TS behave more conservatively, and HVs more liberally.

There was a significant main effect of clinical status on participant response style *c*, *F* (1, 51) = 5.031, *p* = .029, *r* = .30, whereby those with TS were more conservative in their responding, emphasizing accuracy over speed and HVs more liberal, emphasising speed over accuracy.

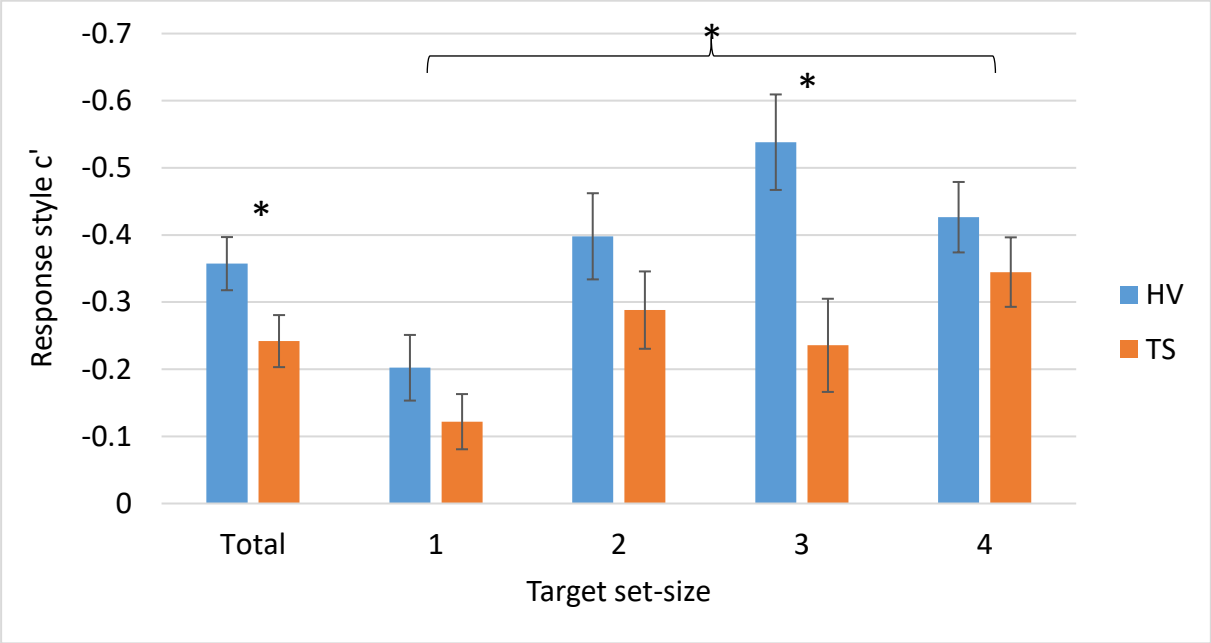


Figure 53. Mean response style *c*' on the CPT task at different target set-sizes and total task performance for HVs and TS. Error bars represent SEM. *More conservative responding in those with TS and at smaller set-sizes was significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to HRT (total task, log-transformed), *F* (1, 50) = .112, *p* = .739, *r* = .05. There was a significant effect of

participant clinical status on HRT after controlling for the effect of medication with antipsychotics, F (1, 50) = 10.230, p = .002, η^2 = .170. The effect of clinical status on HRT, when controlling for antipsychotic medication also reaches significance following Benjamini-Hochberg FDR correction procedure (see Chapter 2).

Medication with antipsychotics was significantly related to participant response style c, F (1, 50) = 21.274, p = .000, r = .55. When controlling for the effect of antipsychotic medication, there was no longer a significant effect of clinical status on participant response style c, F (1, 50) = .263, p = .610, η^2 = .005.

Medication with antipsychotics was not significantly related to total omission errors, F (1, 50) = .920, p = .342, r = .13. When controlling for the effect of antipsychotic medication, there was no longer a significant effect of clinical status on total omission errors, F (1, 50) = 1.969, p = .167, r = .19.

Summary

During performance of the CPT variant, participants displayed increased HRTs in response to increasing attentional demands, shorter ISI durations and length of the experiment. These results occurred irrespective of clinical status, representing the demand on information processing with an increased need for sustained vigilance overtime. Whilst there were no differences in RTs on incorrect trials, adults with TS were significantly slower on correct trials compared to HVs. Adults with TS were slower, irrespective of target set-size or length of ISI duration but HRTs were proportional to attention load and ISI duration. Additionally, the rate of slowing occurring to HRTs overtime were similar for both HVs and adults with TS. Medication with antipsychotics was not able to account for the significant slowing in HRTs of adults with TS.

Participants made significantly more errors of omission and significantly fewer errors of commission at the smallest attentional load compared to all other loads, where the number of errors was comparable. Furthermore, this pattern for each type of error was observed in adults with TS and HVs. All participants, irrespective of clinical status, were observed to display more errors overtime, consistent with the effects of fatigue relating to sustaining attention. In particular, commission errors were time-

sensitive, decreasing significantly with experimental block; omission errors, however, remained constant overtime.

Participants made more commission than omission errors overall during performance of the CPT task. Despite observations of fewer commission errors at the lowest attentional load, adults with TS made the same amount of commission errors as HVs on the CPT task. However, adults with TS made significantly more omission errors than HVs; this overall task effect was attributable to attentional demand of more than one target. Furthermore, adults with TS made more perseverative errors and multiple responses than HVs, but these observations did not reach significance. Medication with antipsychotics were found to be accountable for the significant difference in the number of omission errors made by adults with TS. Thus, controlling for the effects of medication with antipsychotics abolished this effect and there was no difference in the number of omission errors made on the CPT task between adults with TS and HVs.

The ability to discriminate between targets and non-targets was the same for adults with TS and HVs, as indicated by detectability *d* scores. Additionally, all participants displayed a conservative response style at smaller target set-sizes, favouring accuracy over speed. With larger target set-sizes, participants become more liberal, prioritising speed over accuracy. Intriguingly, despite similar signal detection, adults with TS had a significantly more conservative responding style, favouring accuracy over speed. HVs on the other hand were liberal in their responding. The significantly more conservative response style might be attributable to the use of antipsychotic mediation as there was no significant difference in response style in adult TS compared to HVs after controlling for this. However, after controlling for antipsychotic medication effects the finding that adults with TS had slower HRTs compared to HVs during performance of the CPT variant remained significant.

4.3. Response Conflict Flanker (RCF)

Task design

There is evidence to suggest that TS is associated with disruption of attentional and inhibitory mechanisms. Such alterations may impact action selection and conflict detection mechanisms. RCF tasks can examine selective attention and inhibitory

control alongside basal ganglia-dependent action selection and ACC dependent conflict detection (Beste et al., 2008; Botvinick et al., 1999; Eriksen & Eriksen, 1974; Mink, 1996).

In our RCF variant targets are presented alongside neutral, compatible or incompatible flankers. Such parameters have been illustrated to create strong inhibitory interference (Stahl et al., 2014). The directional response of the target is anticipated to be facilitated by compatible flankers and unaffected by neutral flankers. In response to incompatible flankers, conflict is anticipated to be created due to the contrasting directional responses generated by stimuli (Eriksen & Eriksen, 1974). Task performance requires selection of the correct action, in accordance with the target, and inhibition of incorrect responses evoked by incompatible flankers (Cagigas, Filoteo, Stricker, Rilling, & Friedrich, 2007). Flanker compatibility effects can be observed in changes to RTs and accuracy (*n* errors) across trial types.

Furthermore, RCF tasks can assess a phenomenon known as the Gratton effect, attributed to the ACC (Botvinick et al., 1999; Gratton, Coles, & Donchin, 1992). Following conflict, cognitive control can be enhanced, resulting in a bias towards processing of task-relevant information, reducing interference from task irrelevant stimuli. Effects of conflict detection can be observed in the change to RTs on current trials compared to previous trials. It is predicted adults with TS may display alterations in compatibility effects and conflict detection, with the degree of impairment related to OCD comorbidity because abnormal ACC circuitry is implicated in this disorder; this will be explored in Chapter 8.

Results

Errors

There was a significant main effect of flanker type on the number of errors made on the RCF task, F (2, 104) = 137.158, p = .000, r = .75. Planned contrasts (simple) making comparisons to neutral flankers, found significantly more errors were made for incongruent flankers, F (1, 52) = 143.305, p = .000, r = .86, and significantly fewer errors for congruent flankers, F (1, 52) = 13.919, p = .000, r = .46. There was no significant interaction effect of flanker type and clinical status on the number of errors made, F (2, 104) = 1.101, p = .336, r = .10.

There was a significant main effect of error type on RCF task performance, *F* (1, 52) = 1095.486, *p* = .000, *r* = .98, with significantly more correct responses being made than incorrect.

There was no significant error type x clinical status interaction, *F* (1, 52) = .319, *p* = .574, *r* = .08.

There was a significant interaction between flanker type and error type on RCF task performance, *F* (1.352, 70.322) = 123.240, *p* = .000, *r* = .80.

Planned contrasts (simple) making comparisons to neutral flankers, revealed significantly more incorrect and fewer correct responses for incongruent flankers, *F* (1, 52) = 142.731, *p* = .000, *r* = .86, and significantly more correct responses and fewer incorrect responses for congruent flankers, *F* (1, 52) = 13.446, *p* = .001, *r* = .45.

There was no significant interaction effect of flanker type, error type and participant clinical status, *F* (1.352, 70.322) = .577, *p* = .499, *r* = .09, and no significant main effect of clinical status on RCF task performance, *F* (1, 52) = .565, *p* = .456, *r* = .10.

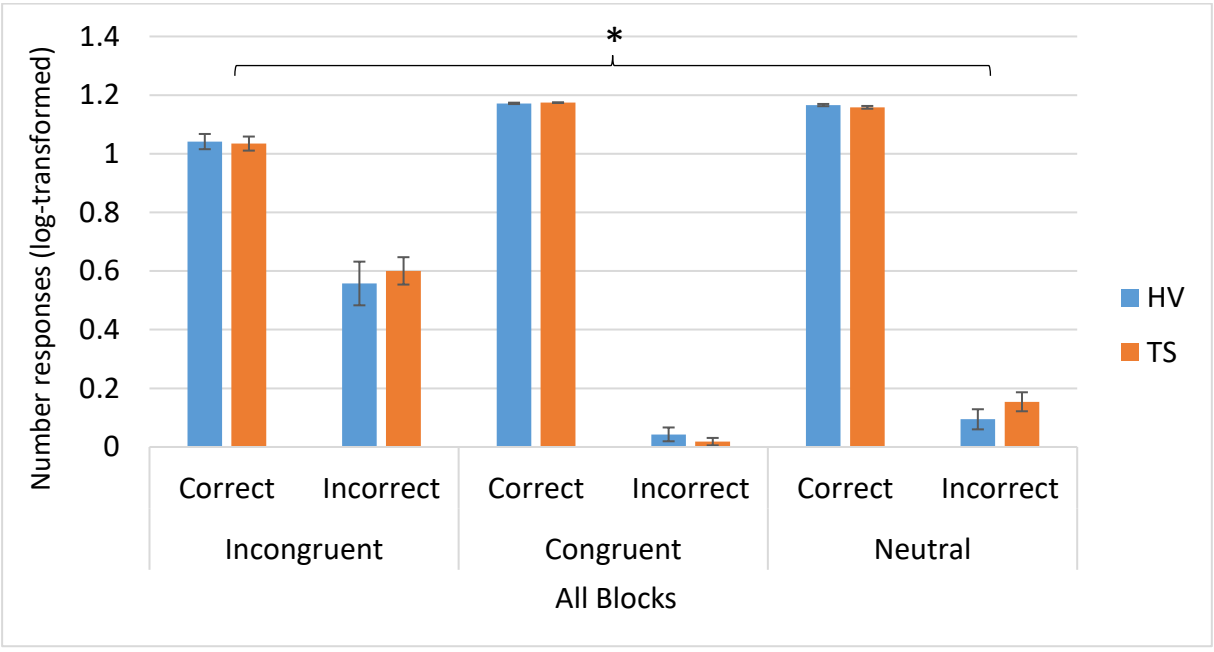


Figure 54. Mean number of correct or incorrect responses (log-transformed) for each flanker type (incongruent, congruent or neutral) on the RCF task for HVs and TS. Error bars represent SEM. *Flanker type effects remained significant following Benjamini-Hochberg FDR correction.

Reaction times

There was a significant main effect of flanker type on the RTs made on the RCF task, F (1.704, 88.610) = 384.208, p = .000, r = .90. Planned contrasts (simple), making comparisons to neutral flankers, found significantly slower RTs in response to incongruent flankers, F (1, 52) = 438.421, p = .000, r = .95, and significantly quicker RTs in response to congruent flankers, F (1, 52) = 62.350 p = .000, r = .74.

There was a significant interaction effect of flanker type and clinical status on the RTs made on the RCF task, F (1.704, 88.610) = 3.862, p = .031, r = .20. Planned contrast (repeated) revealed that participants were significantly slower to respond for incongruent flankers compared to congruent, with this being more exaggerated in those with TS, F (1, 52) = 5.454, p = .023, r = .31.

There was no significant main effect of clinical status on RTs, F (1, 52) = 3.204, p = .079, r = 24.

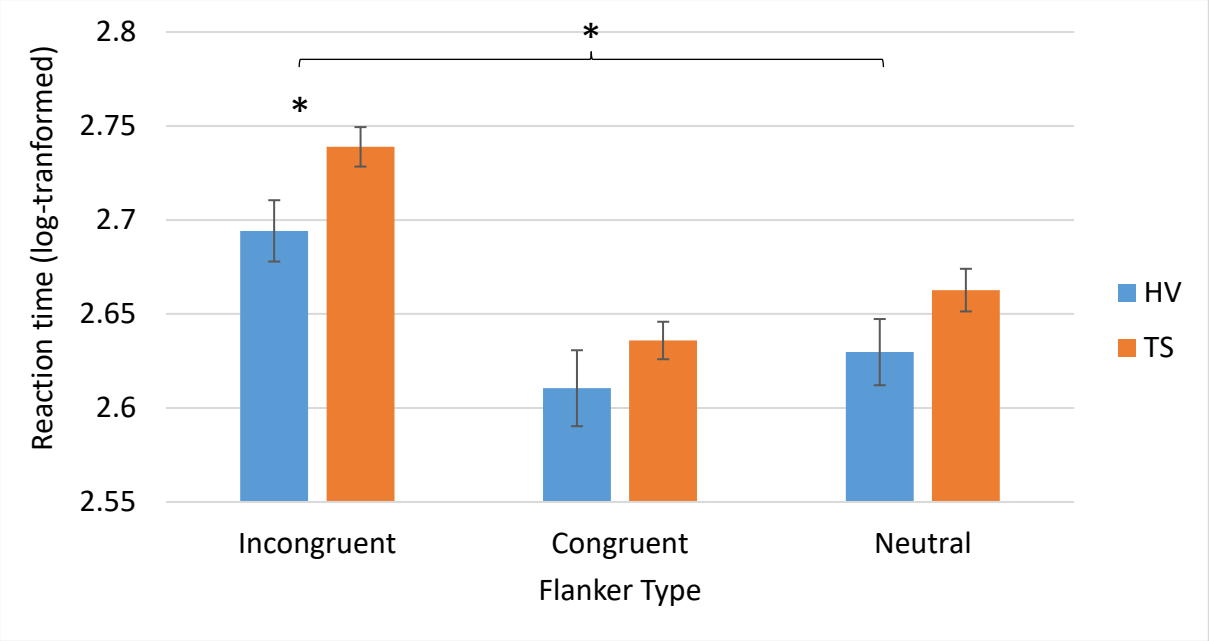


Figure 55. Mean reaction time (log-transformed) for each flanker type (incongruent, congruent or neutral) for HVs and TS. Error bars represent SEM. *Incongruent flanker and clinical status effects on reaction time remained significant following Benjamini-Hochberg FDR correction.

Flanker effects

There was a significant main effect of previous trial flanker type on current trial RTs, *F* (1, 52) = 7.773, *p* = .007, *r* = .36, whereby RTs were significantly quicker when previous trial flankers were congruent compared to incongruent. There was no significant interaction effect of previous trial flanker type and participant clinical status, *F* (1, 52) =.016, *p* = .900, *r* = .02.

There was a significant main effect of current trial flanker type on RTs, *F* (1, 52) = 403.877, *p* = .000, *r* = .94, where similarly, RTs were significantly quicker for congruent than incongruent trials.

There was a significant current trial flanker type and clinical status interaction, *F* (1, 52) = 8.341, *p* = .006, *r* = .37, whereby participants with TS had significantly slower RTs, especially in response to current trial incongruent flankers.

There was no interaction effect between previous and current flankers on RTs, *F* (1, 52) = 2.472, *p* = .122, *r* = .21, and no previous x current x clinical status interaction, *F* (1, 52) = .064, *p* = .802, *r* = .04.

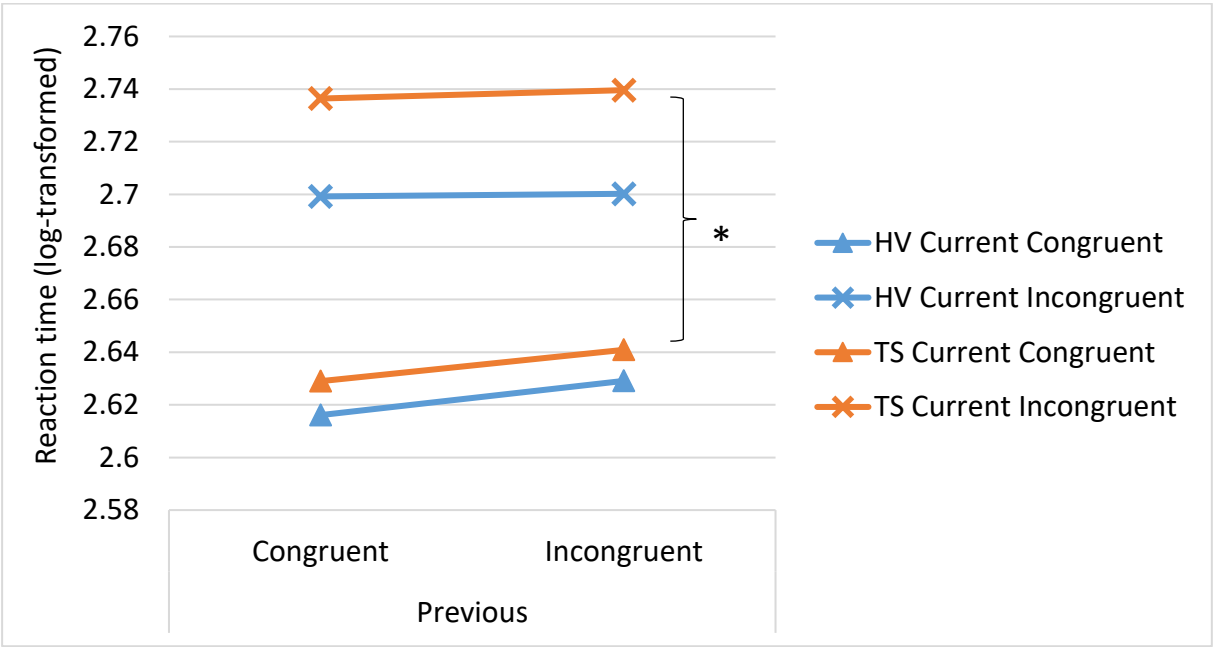


Figure 56. Effects of previous trial flanker type on the mean reaction time (log-transformed) of current trials on the RCF task for HVs and TS. Flankers were either congruent (left, triangle) or incongruent (right, cross).

Medication

Medication with antipsychotics was not significantly related to RTs in response to incongruent flankers (log-transformed), F (1, 51) = .180, p = .674, r = .06. After controlling for the effects of antipsychotic medication, the significant effect of clinical status on incongruent flanker RTs remained, F (1, 51) = 5.723, p = .020, η^2 = .101. The effect of clinical status on incongruent flanker RTs, when controlling for antipsychotic medication also reaches significance following Benjamini-Hochberg FDR correction procedure (see Chapter 2).

Summary

During performance on the RCF task, compared to neutral trials, participants were slower and less accurate on incongruent trials. These results are in accordance with task generated target-flanker conflict, increasing information processing demands. Conversely, compared to neutral trials, participants were quicker and more accurate on congruent trials due to facilitation of information processing. In addition to trial-type effects common to both groups, adults with TS were significantly slower, specifically on incongruent trials compared to HVs, an effect that was independent of antipsychotic medication. Furthermore, there were no differences in the number of errors made, across trial types, between adults with TS and HVs. Additionally, there were no observed effect of previous trial type on the RTs of current trials.

4.4. Discussion

Attention is an executive function covering several different, yet inter-related, cognitive phenomenon (Gray, 2016). Attentional resources can be allocated amongst multiple task requirements (Hahn et al., 2008) or focused specifically on information of interest (Tsal, Shalev, & Mevorach, 2005). Furthermore, attention needs to be flexible, orientated and shifted in line with changing task demands (Gilbert & Burgess, 2008) and able to be sustained overtime, maintaining vigilance (Howells et al., 1998).

Inhibition is another multifaceted executive function that controls attentional biases, distractions and interference (Aron, Robbins, et al., 2004; Berlin et al., 2004; Braver et al., 2001; Konishi et al., 1999; Metzler & Parkin, 2000), ensuring efficient utilisation

of cognitive resources (Diamond, 2002; Elliott, 2003). Furthermore, inhibition of former task responses and control of attentional set is essential to cognitive flexibility (Aron, Monsell, et al., 2004; Buchsbaum et al., 2005; Hoffstaedter et al., 2013; Nachev et al., 2007; Swick et al., 2011). Crucially, inhibitory control is essential to regulation of movement and behaviours (Riva et al., 2018; Yaniv et al., 2018).

Investigation into the neurocognitive aspects of TS has typically explored attention and inhibition separately, despite their functional overlap. As discussed previously in Chapter 3, in adults with TS, there is evidence both for impaired and intact inhibitory performance. Impairments were most apparent following complex, demanding tasks (Eddy, Rickards, et al., 2012; Eddy et al., 2014; Murphy, & Eddy, 2013) suggesting deficits may actually be secondary to impaired attention (Morand-Beaulieu, Grot, et al., 2017; Yaniv et al., 2017). Furthermore, in the absence of attentional demands, we found no evidence that adult TS was associated with impaired response inhibition of prepotent motor responses on the SST.

The evidence suggesting that attention is altered in TS is mixed (Morand-Beaulieu, Leclerc, et al., 2017). For example, in children and adolescents, disrupted performance on the dichotic listening tasks (Tsal et al., 2005) but intact selective attention during D2 cancellation tasks have been reported (Oades, 2000). Furthermore, adolescents have been observed to displayed enhanced selective attention, alongside slower responses (Muller et al., 2003). Poor divided attention on auditory-consonant-trigram tasks (Chang et al., 2007) as well as intact dual-task performance (De Monte, 2007) has also been observed. In adults with TS, there is evidence of intact ability to orientate attention, despite being slow to shift attention (Georgiou et al., 1998; Georgiou, Bradshaw, Phillips, & Chiu, 1996; Howells et al., 1998) and evidence for altered selective attention during difficult letter cancellation tasks (Channon, Flynn, & Robertson, 1992). There are observations of intact selective attention in adult TS during an attentional blink paradigm, despite making more post-target intrusion errors (Georgiou-Karistianis, 2006). Divided attention is also found to be both intact in adult TS (Aukrust et al., 2003) and impaired (Johannes, Wieringa, Nager, et al., 2001) during dual-tasks when auditory stimuli conflicts with visual stimuli. Sustained attention in adults TS is found to be intact on simple CPT (Matsuda et al., 2012) and D2 cancellation tasks (Muller et al., 2003) or impaired during vibrotactile tasks (Georgiou et al., 1998) and highly demanding letter

cancellation tasks (Channon, Flynn, & Robertson, 1992). Furthermore, attentional aspects of cognitive flexibility in adult TS appear mixed, with evidence for and against impairments (see Chapter 3). In our sample of adults with TS, we found a specific deficit in attentional set-shifting of habitually learned behaviours.

In adult TS, few studies have investigated attention and results are again mixed with evidence of impairment arising from tasks that are demanding (Morand-Beaulieu, Leclerc, et al., 2017). Furthermore, it is difficult to dissociate alterations in attention from inhibitory dysfunction. Reports of intact performance often coincides with evidence of impact on other executive functions (Morand-Beaulieu, Grot, et al., 2017; Yaniv et al., 2017). Participants may employ strategies to acquire typical attentional performance; occurring at the expense of optimum inhibition, and vice versa (Mueller et al., 2006; Plessen et al., 2009; Plessen et al., 2004; Roessner et al., 2008). For example, during maintenance of inhibitory control, TS participants show slower RTs and more attentional errors (Thomalla et al., 2014).

Inhibitory control is a crucial pre-requisite for optimised cognition. Several aspects of attention require inhibitory control. Selecting, dividing, orientating and shifting of attention requires inhibition of prior attentional biases and responding to distractors. Inhibition of distractors is also essential for sustaining attention. During tasks requiring attention or inhibition, different areas of the brain are activated. However, these regions are implicated in inhibitory processing (Aron, Monsell, et al., 2004). During task switching activities, magnetoencephalography has revealed activation of the inferior gyrus; a structure known for its role in inhibition (Aron, Monsell, et al., 2004; Jacobson et al., 2011). This functional overlap between attention and inhibition has structural brain parallels. For example, inhibition of task responses and top-down control of attention are both localised to right inferior gyrus and left middle frontal gyrus (Aron, Monsell, et al., 2004). The orbitofrontal cortex has also been shown to be involved in both inhibitory and attentional aspects of cognitive flexibility (Chudasama et al., 2003; Eagle et al., 2008; Moore & Malinowski, 2009). To further complicate the distinction, whilst correlations exist amongst measures of response inhibition and set-shifting ability, it has been argued that attention and inhibition are separate entities, despite being highly inter-related (Miyake et al., 2000).

It is therefore important to be able to dissociate attentional deficits from those of inhibition. This, however, becomes more complex in the case of TS, because of

possible compensatory mechanisms that may compromise each function. It is therefore of relevance to examine these executive functions in parallel within the same task. Doing so will help establish whether they are separate entities or aspects of the same neurocognitive construct. CPT tasks are useful tools to assess both inhibitory control of pre-potent motor responses alongside sustained attention. Typically, the number of commission errors made (responding to a non-target) corresponds to inhibitory capacity and omission errors (not responding to targets) in inattention (Halperin et al., 1988; Moeller et al., 2005; Riccio et al., 2002).

In children and adolescents with TS, there is evidence of deficits during CPT performance with more errors made and longer RTs (Carter et al., 2000; Greimel et al., 2011; Huckeba et al., 2008; Lin et al., 2012; Oades, 2000; Rasmussen et al., 2009; Schuerholz, Baumgardner, Singer, Reiss, & Denckla, 1996; Sherman, Shepard, Joschko, & Freeman, 1998; Shin et al., 2001; Shucard, Benedict, Tekok-Kilic, & Lichter, 1997; Sukhodolsky et al., 2010). A proportion of these findings can be accounted for by comorbidity (Harris et al., 1995; Lucke et al., 2015; Sallee, Sethuraman, & Rock, 1994) and there remains evidence for intact CPT performance in those with and without comorbidity (Greimel et al., 2011; Lee, Chiu, Chiu, Chang, & Tang, 2009; Mahone et al., 2002; Milliery, Bouvard, Aupetit, & Cottraux, 2000; Rothenberger et al., 2000; Schultz et al., 1998). In adults with TS there is evidence for impairment (Schoenberg et al., 2015) and normal performance (Matsuda et al., 2012) on CPT tasks. Few CPT tasks have been used to examine attention and inhibition in adults with TS and further investigation is warranted.

There is evidence to suggest TS is associated with cognitive impairment, as a consequence of CSTC circuitry dysfunction (Eddy et al., 2009); whilst inhibitory and attentional deficits are observed, these are most apparent on particular tasks and conditions. Subsequently, deficits in attention and response inhibition remain inconclusive (Morand-Beaulieu, Leclerc, et al., 2017). Assessment of attention and inhibition in parallel warrants the opportunity to objectively measure both functions and dissociate their effects from each other. The importance of task choice and selection of appropriate parameters have been discussed previously in this chapter (Morand-Beaulieu, Leclerc, et al., 2017). In an attempt to address methodological pitfalls, variations of a CPT and RCF task were designed that were complex with minimal demands on working memory and able to assess attention and inhibition in

parallel. After controlling for the effects of antipsychotic medication, adult TS was not associated with increased rates of commission or omission errors on our CPT variant. Our results provide evidence to suggest that there are no deficits in sustained attention or inhibitory control during performance of a complex CPT variant with minimal working memory demands.

All participants displayed slowing in their HRTs proportional to increasing attentional loads and shorter ISI duration, corresponding with increased information processing demands. Furthermore, all participants displayed similar HRT reduction over time, in accordance with fatigue following sustained attention. Importantly, medication with antipsychotics could not account for the global HRT slowing of adults with TS. Our results therefore imply that adult TS is associated with typical reduction in information processing efficiency following an increased need for vigilance and maintenance of attention over time. Intriguingly, in comparison to HVs, adults with TS were significantly slower in responding, irrespective of attentional load or ISI duration. The global reduction in the adult TS HRT, were proportional to attentional demands (ISI duration, target set-size, experimental block) and did not affect accuracy. These results could indicate that in adult TS, information processing is slower to improve task accuracy. Interestingly, on incorrect trials, HVs and adults with TS displayed similar RTs; providing evidence that TS makes an individual no more impulsive in their responding.

Over the course of the CPT, participants displayed more errors, consistent with the effects of fatigue, relating to sustaining attention. In particular, commission errors were time-sensitive, decreasing significantly with experimental block. Such findings suggest that varying attentional load during sustained attention has an impact on inhibitory vigilance. There were no differences between HVs and adults with TS on the rate of commission errors made overtime; these results suggest typical rates of fatigue and a similar impact of attentional resource on inhibitory capacity overtime. Furthermore, there were significantly fewer commission errors during the first block, compared to the remainder of the experiment, reinforcing the finding that inhibitory control is sensitive to sustained attention over time. Such effects were observed to the same degree in both HVs and adults with TS. Conversely, omission error accuracy remained constant overtime, suggesting all participants facing variation to attentional load, were able to remain attentive throughout the experiment. These

results provide evidence that our CPT is able to vary attentional load without being overly demanding. Furthermore, the observation of intact vigilance allows us to be certain that alteration in inhibition would be distinct from mechanisms of attention, addressing issues of dissociation.

There were no significant differences in the ability to discriminate between targets and non-targets for HVs and adults with TS. These results suggest that participants were vigilant and attended equally to all stimuli to discriminate accurately, suggesting no attentional impairment. Intriguingly, for all participants, the highest detectability d scores occurred during target set-sizes of three. These results imply that working memory is not overly taxed during our CPT variant and there exists an optimum trade-off between task difficulty and attentional resource utilisation. This is in accordance of optimal cognitive processing when attentional capacity is utilised/ challenged; during tasks with lesser attentional demands, spare attentional capacity can be a hindrance and lead to distractibility (Bleckley, Durso, Crutchfield, Engle, & Khanna, 2003; Forster & Lavie, 2009; Forster, Robertson, Jennings, Asherson, & Lavie, 2014; Heitz & Engle, 2007; Sorqvist & Ronnberg, 2014).

All participants at lower levels of attentional demand were conservative in their responses, becoming more liberal with increasing attentional set-size. Despite similar discriminative ability, adults with TS were observed to have a significantly more conservative responding style, favouring accuracy over speed, compared to HVs who were liberal in their responding. Due to the absence of errors, these results could have been an objective example of compensating speed for accuracy to facilitate task performance in adult TS. Antipsychotic medication contributed significantly to this response style.

Considering this, the observation of reduced HRT compared to HVs, across all aspects of the task, suggests that adults with TS may be slower due to additional information processing demands occurring prior to responding. In TS, clinical features including tics, urges and comorbidities place demands on attention that HVs do not experience. Accordingly, slowing of HRTs could be to enhance motor output awareness and regulation to ensure effective tic control and task-specific motor performance (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). On a similar note, adults with TS made more perseverative and multiple responses than HVs, but this did not reach significance. Therefore, these

observations are another example of task hindrance due to tic-related phenomenon, such as tic evoked involuntary movement. Within TS research, it is difficult to distinguish between instances of cognitive dysfunction and the influence of motor dysfunction.

The effect of varying attentional load on the rate of errors revealed that omission and commission errors act differently. Low attentional demand was the most beneficial for inhibitory processing, with the fewest commission errors occurring. Following an increase from a target set-size of one to two, significantly more commission errors were made. Commission error rates were then consistent over the remaining increases to the highest target set-size. On the other hand, omission errors were at their highest at the lowest attentional demand. An increase in a target set-size of two significantly reduced the number of omission errors, an effect that also remained consistent up to the highest target set-size. Thus, our results found that with increasing attentional load, there is a decrease in inhibitory control corresponding to increased attentional vigilance. The observation that each construct, has opposing mechanistic actions that mirror each other in opposing directions across attentional loads, suggests that attention and inhibition are two separate, yet interlinked entities. Conversely, if they were the same construct they would be influenced similarly by changes in attentional load. The observation of a plateau reached in accuracy over higher attentional loads may be indicative of an optimum trade-off between each construct, mediating task accuracy/ demand across both domains. The results also provide evidence that in order to achieve enhanced inhibitory control in adult TS, this may come at the expense of worse attention.

Finally, the observation that increased attentional demand did not influence vigilance negatively, further supports that better attention may occur under conditions where attentional resources can be utilised; leaving fewer resources available to contribute to distractibility (Bleckley et al., 2003; Forster & Lavie, 2009; Forster et al., 2014; Heitz & Engle, 2007; Sorqvist & Ronnberg, 2014). In those with TS, tic severity is often reported to be worse during boredom (Bench & Lench, 2013; Caurin, Serrano, Fernandez-Alvarez, Campistol, & Perez-Duenas, 2014; Conelea & Woods, 2008; Hoekstra, Lundervold, Lie, Gillberg, & Plessen, 2013; Seib & Vodanovich, 1998) and better during engagement of attention in tasks (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015; Stern, 2018). The experience of tic related phenomenon and the need to

mediate this alongside typical cognitive functioning alludes to the existence of a sophisticated attentional system in those with TS. Our results therefore provide evidence to suggest that therapies based on attention distraction may be efficacious on adults with TS.

Our novel CPT variant designed to investigate inhibition and attention in parallel, despite being challenging with minimal working memory demands, did not find evidence of deficits in inhibition or attention in adults with TS. Adults with TS were significantly slower in their responding, with no impact on task accuracy. Exploration of signal detection parameters and antipsychotic medication revealed that slower responding is likely to represent enhanced motor output awareness and regulation to ensure effective tic control and task-specific motor performance (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). Slowing in HRT allows adults with TS to compensate for the additional information processing demand they experience, related to clinical features of TS, so they can achieve task goals. Such compensatory function does not achieve a gain of function over HVs. Our results are consistent with other observations of intact attention and inhibition in adult TS (Aukrust et al., 2003; Georgiou-Karistianis, 2006; Georgiou et al., 1998; Georgiou et al., 1996; Howells et al., 1998; Matsuda et al., 2012; Muller et al., 2003). Observations of inhibitory dysfunction in adult TS, observed on challenging, demanding tasks are therefore likely to be secondary to overly taxed attentional resources.

RCF tasks can be used to investigate action selection and conflict detection. Typically, where there is target-flanker congruency, facilitation of information processing occurs, as indicated by faster RTs and fewer errors on compatible trials. Conversely, target-flanker incongruency creates conflict, resulting in slower RTs with increased information processing required to resolve conflict. Additionally, more errors occur on incompatible trials, where flanker-generated response inhibition fails. On neutral trials, flankers are impartial and used as a point of reference for the effects of flanker compatibility.

In our sample, we observed compatibility effects in all participants, corresponding to task generated target-flanker conflict. Whilst adults with TS displayed normal compatibility effects, specifically on incompatible trials their RTs were significantly slower, an effect independent of medication with antipsychotics. Furthermore,

reduced RTs on incompatible trials did not occur alongside increased errors, which would have suggested inattention. Quick RTs and increased errors on incompatible trials would have indicated poor response inhibition, or impulsivity. In addition, reduced RTs did lead to enhanced accuracy, which would suggest employment of a compensatory speed for accuracy trade-off. Therefore, in accordance with our CPT findings, it is suggested that adults with TS reduce their motor output to accommodate both tic control and task-specific motor performance, especially under conditions of increased information processing demands (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). Despite this, there is no evidence to suggest adult TS is associated with gain or deficit in inhibitory control or attention.

As discussed previously, enhanced conflict detection occurs following successive processing of conflict (Beste et al., 2008; Botvinick et al., 1999; Eriksen & Eriksen, 1974; Mink, 1996). If conflict detection is intact, current trial performance is influenced by previous trial congruency, with quicker RTs following successive incompatible trials (Beste et al., 2008; Egner, 2008). Attentional deficits can influence conflict detection, as targets and flankers need to be salient to generate the initial conflict that enhances concurrent trial performance. Where single trial compatibility effects exist, indicating intact attention, but sequential trial conflict enhancement does not occur, could indicate alteration in ACC function (Beste et al., 2008; Botvinick et al., 1999; Eriksen & Eriksen, 1974; Gratton et al., 1992; Mink, 1996). Our results did not find evidence of a significant main effect between previous and current trial flanker types. Intact compatibility effects alongside the absence of sequential trial conflict error is consistent with alteration in ACC function; this pattern of results was observed however in both adults with TS and HVs. It is therefore concluded that the parameters of our RCF variant were optimal for producing this effect.

Task parameters such as flankers can create strong inhibitory interference, crucial to conflict detection examination (Stahl et al., 2014). In our RCF variant, we used compatible, incompatible and neutral flankers. As we were unable to generate conflict detection during our experiments, even following the removal of more than two consecutive trials (shown to influence the task/effect previously (Egner, 2008) it is likely that our inclusion of neutral flankers, may have affected performance. Neutral trials serve as a reference of flanker effects during evaluation of compatibility effects;

however, they appear to affect the generation of conflict detection. Failure to evoke conflict detection in our HVs rejects the idea that there is alteration in ACC function in our participants. In future experiments, conflict detection needs to be evaluated with appropriate task parameters.

Our RCF variant, designed to investigate action selection and conflict detection did not find evidence of deficits in inhibition or attention in adults with TS. Adults with TS displayed compatibility effects, identical to those seen in HVs. Furthermore, adults with TS were slower in responding specifically on incompatible trials, with no impact on task accuracy. Slower RTs on incompatible trials were independent of medication with antipsychotics and provided no benefit to task performance. We therefore reiterate that adults with TS likely reduce their motor output in order to mediate both tic control and task-specific motor performance (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). Interestingly, Chapter 9 will investigate the impact of tic management specifically on CPT task performance. Our results provide further support of intact attention and inhibition in adults with TS. However, further investigation is warranted, especially regarding conflict detection.

A recent study in children with TS (Brandt et al., 2019) requiring participants to lift their index or little finger in response to an auditory signal coinciding with compatible visual stimuli noted significantly slower RTs with high accuracy, demonstrating employment of a compensatory speed-accuracy trade off. Compensatory mechanisms have been observed to exist in children and adolescents with TS that enable typical or enhanced performance (Mueller et al., 2006; Plessen et al., 2009; Plessen et al., 2004; Roessner et al., 2008). Resources enabling compensation likely arise with plastic changes occurring with maturation (Jackson, Parkinson, Jung, et al., 2011).

Our results from variants of a CPT and RCF, have demonstrated that adults with TS display slower reaction times in order to regulate tic management alongside task performance (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). These observations do not necessarily reflect a speed for accuracy trade off, nor a gain in functioning. Rather, compromised speed appears to reflect increased information processing, occurring due to tic phenomenon, in order to achieve task demands.

The negative impact of tic and urges on cognition has previously been illustrated, whereby task performance is related to clinical severity (Channon et al., 2006; Eddy & Cavanna, 2017; Ozonoff et al., 1998). Subsequently, it is difficult to dissociate the effects of clinical severity from primary deficits existing in cognitive domains (Erenberg, 2005). Our results have identified alteration in performance across tasks that are attributable to increased information processing demands of the clinical features of TS and not mistakenly explained by deficits in executive functions. We provide evidence for intact attentional and inhibitory mechanisms and later, in Chapter 9, we explore in depth how tic management modulates CPT task performance.

By evaluating attention and inhibition in parallel, we have been able to dissociate task parameters relating to attentional capacity and those associated with inhibitory capacity. Furthermore, we revealed that action and inhibition are two separate but highly interlinked entities as increasing attentional load decreased response inhibition, corresponding to a gain of attentional vigilance. These observations reinforce impairment existing in either construct that can be compensated for, at the expense of the other. Also, it was observed that the opposing mechanistic actions of attention and inhibition mirrored each other, with increasing attentional demand. Intriguingly, with increasing attentional demand we found that the capacity to inhibit does not remain constant; rather, an optimum trade-off between attentional resources and inhibitory control occurs. Finally, the ability of adults with TS to mediate cognitive and motor demands related to tic phenomenon and task demands, without compromise of performance, alludes to the existence of a sophisticated symbiotic relationship between attentional and inhibitory mechanisms. Our results therefore provide evidence to suggest that therapies based on attention distraction may be efficacious for both inhibitory and attentional mechanisms in adults with TS.

Chapter 5. Interoceptive awareness

5.1. Introduction

The aim was to further characterise the relationship between interoceptive awareness and adult TS to be able to determine whether adult TS is associated with abnormal interoceptive awareness and examine how this can influence tic generation, clinical severity and tic management.

5.2. Results

Interoceptive awareness

There was no significant differences between HVs and adults with TS in resting heart rate, t (53) = -1.892, p = .064, d = -.531. Adults with TS were observed to have significantly reduced interoceptive awareness compared to HVs, U = 203, z = -2.750, p = .006, r = -.38.

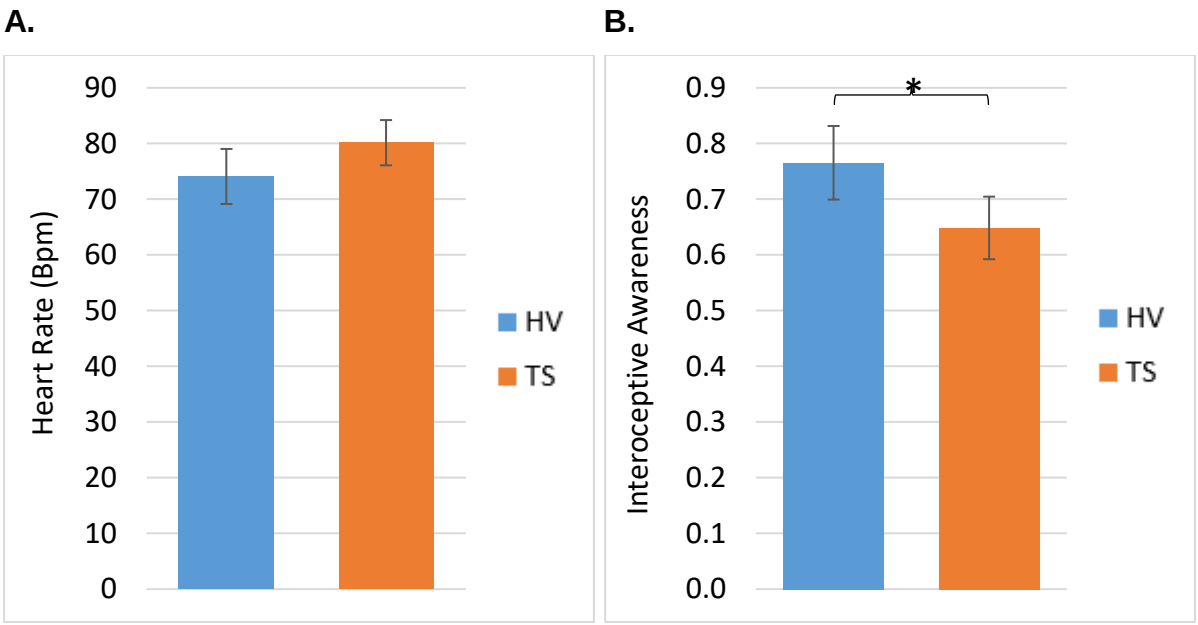


Figure 57. Mean A) resting heart rate (bpm); and B) interoceptive awareness scores for HVs and participants with TS. Errors bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Interoceptive awareness and attention

Interoceptive awareness significantly correlated with response style *c*' in those with TS, r_s = .370, p = .037, with better awareness associated with more conservative responding, prioritising accuracy over speed. In HVs, there was no significant relationship between these variables, r_s = .231, p = .314.

In Chapter 4, medication with antipsychotics was shown to account for the difference in response style *c* in adults with TS. Subsequently, a partial correlation was undertaken to determine the relationship between interoceptive awareness and response style *c*, whilst controlling for the effects of medication with antipsychotics. Following this, there remained a relationship with a medium effect size, but only trend level significance, r_p = .337, p = .064.

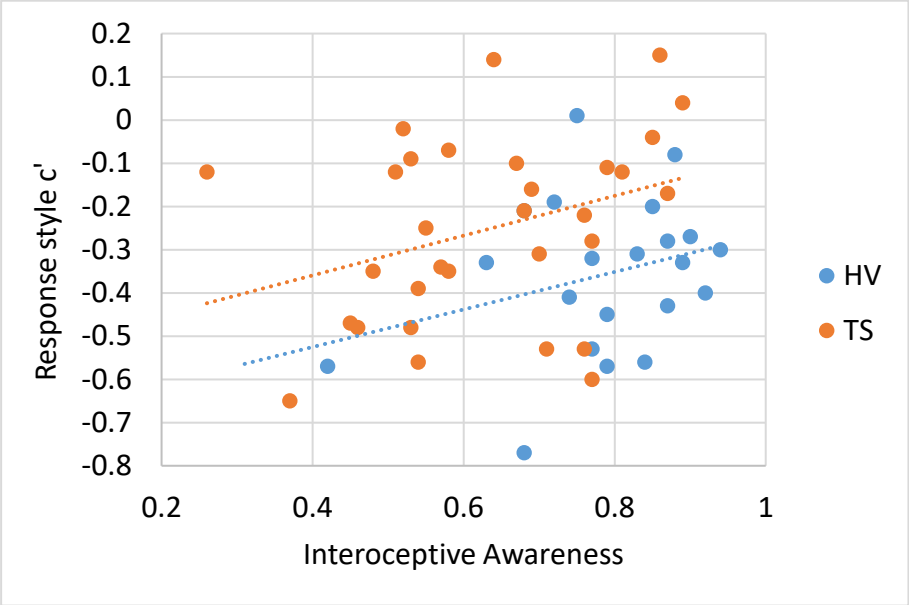
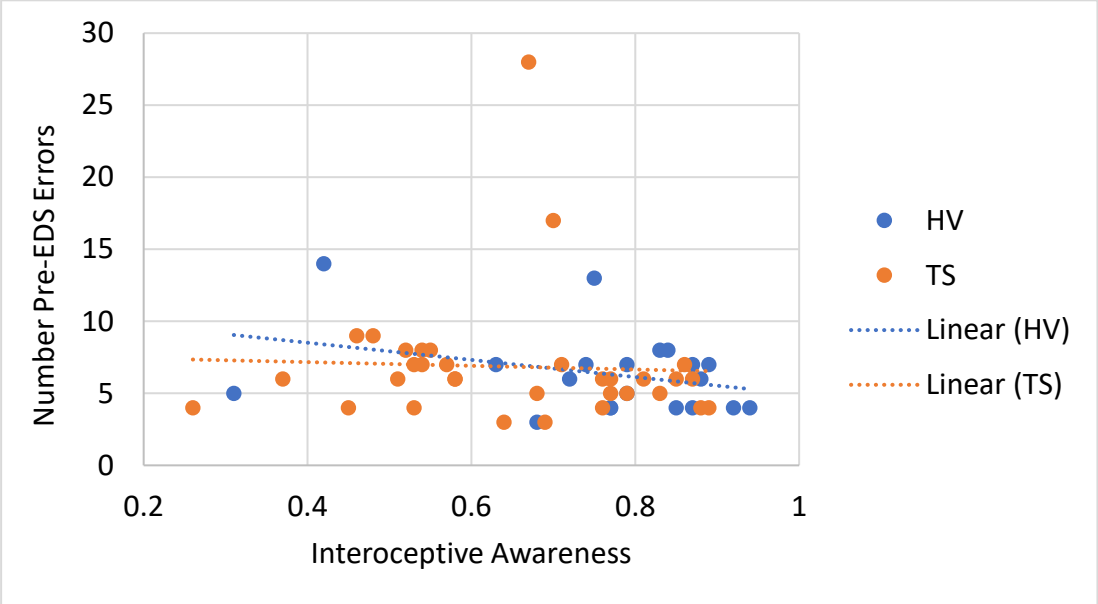


Figure 58. The relationship between interoceptive awareness and response style *c*' in HVs (blue) and those with TS (orange).

Interoceptive awareness and cognitive flexibility

Interoceptive awareness was not found to correlate with IED measures relating to cognitive flexibility (see Chapter 3) for HVs or adults with TS on the number of pre-EDS or EDS errors made on the IED task (all p > .05).

A.



B.

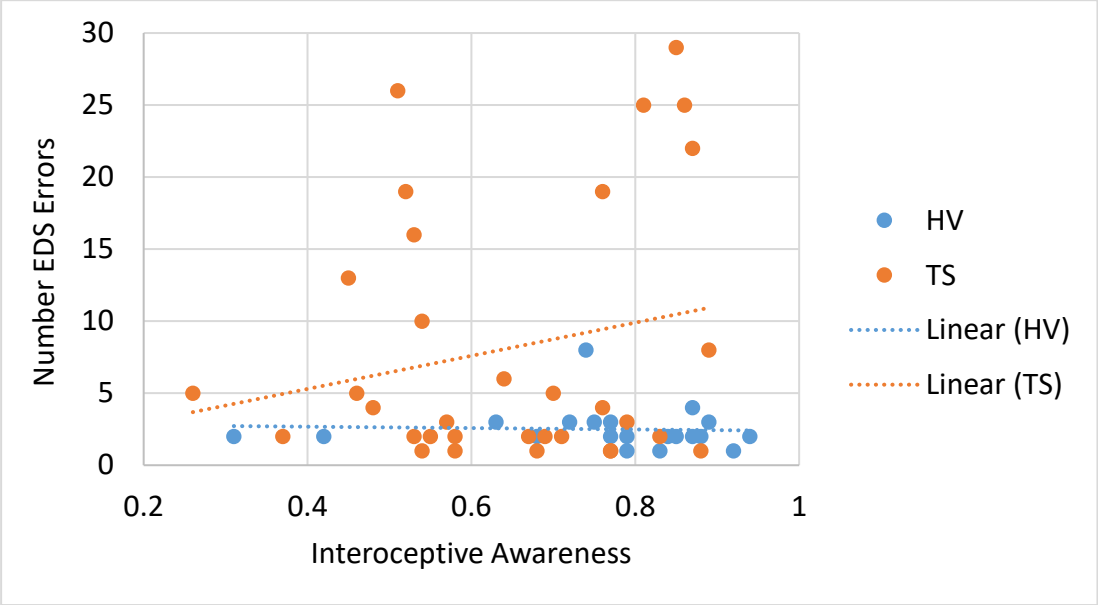


Figure 59. The relationship between interoceptive awareness and number of A) pre-EDS errors and B) EDS errors (both unadjusted) in HVs (blue) and those with TS (orange).

Interoceptive awareness and premonitory urges

There was no significant correlation between PUTS scores and interoceptive awareness for adults with TS, $r = .046$, $p = .798$.

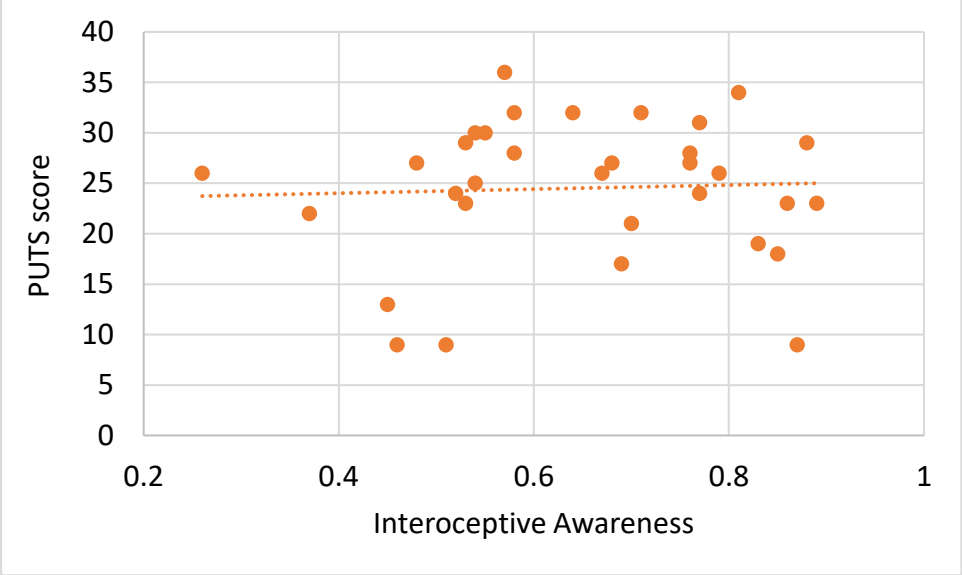


Figure 60. The relationship between interoceptive awareness and PUTS score for adults with TS (orange).

Medication

Medication with antipsychotics was not significantly related to interoceptive awareness, F (1, 52) = 3.506, p = .067, r = .25. There remained a significant effect of clinical status on interoceptive awareness after controlling for the effect of medication with antipsychotics, F (1, 52) = 10.427, p = .002, η^2 = .167. The effect of clinical status on interoceptive awareness after controlling for antipsychotic medication also reaches significance following Benjamini-Hochberg FDR correction procedure (see Chapter 2).

Summary

During the evaluation of interoceptive awareness, resting heart rate (bpm) measurements of those with TS and HVs did not significantly differ. From sensation alone, adults with TS were significantly less accurate at estimating how many times their heart beat, during set time intervals, compared to real-time heart rate monitor recordings. Alterations in interoceptive awareness in adult TS was independent from the effects of antipsychotics. Additionally, in adults with TS there was a significant relationship between interoceptive awareness and response style *c*, with more conservative responding associated with better awareness. Furthermore, following a

partial correlation, controlling for medication, the relationship between interoceptive awareness and response style *c* reduced to trend level significance. Interoceptive awareness was not found to correlate with the number of pre-EDS and EDS errors on the IED task of cognitive flexibility for HVs or adults with TS. Finally, in adults with TS, there was no correlation between interoceptive awareness and PUTS scores.

5.3. Discussion

Alongside premonitory urges, it has been observed that TS is associated with 'not just right' sensory experiences (Neal & Cavanna, 2013; Rajagopal & Cavanna, 2014; Rajagopal, Seri, & Cavanna, 2013; Sambrani, Jakubovski, & Muller-Vahl, 2016). Tics are often reported to be performed until the achievement of a 'just right' sensation (Leckman, Walker, Goodman, Pauls, & Cohen, 1994) and to be more akin to a mental, rather than physical sensation (Miguel et al., 2000; Neal & Cavanna, 2013; Worbe, Mallet, et al., 2010). Additionally, compulsions can have sensory features such as the desire to mirror others and the environment (echopraxia, echolalia) (Ganos, Ogrzal, Schnitzler, & Munchau, 2012) and are performed to relieve anxiety or an urge, with 'just right' goals driving these phenomena (Worbe, Mallet, et al., 2010). Due to the sensory aspects of TS, there is a growing appreciation for assessment of sensory phenomena to be included as a clinical evaluation standard (Cath et al., 2011). Furthermore, advancing our insight into these subjective experiences may provide insight into factors that exacerbate or improve tic severity. Such information is essential for advancement of tic management treatments and therapies (Cavanna et al., 2017).

Exteroception is the awareness of the body and perceptions relating to the external world. Such awareness includes multimodal sensation and both vestibular and proprioception (Valenzuela-Moguillansky, Reyes-Reyes, & Gaete, 2017). Interoception, on the other hand, relates to internal bodily sensations such as viscera and includes central nervous system regulation of homeostasis and encompasses self-awareness (Craig, 2003). Interestingly, the experience of premonitory urges, coinciding with sensory phenomenon, has been identified to be associated with interoceptive compared to exteroceptive awareness (Grados et al., 2018).

Individuals with TS often report abnormal perception, specifically hypersensitivity to external stimuli and bodily states (Eddy et al., 2014). Reports of 70-80% heightened sensitivity and aversion to visual, tactile, auditory and olfactory stimuli (Cavanna, 2014; Cavanna & Seri, 2015; Cohen & Leckman, 1992; Houghton et al., 2014) but not taste, have been documented (Belluscio, Jin, Watters, Lee, & Hallett, 2011; Taylor, Conelea, McKay, Crowe, & Abramowitz, 2014). Interestingly, variance in PUTS scores are independently accounted for by somatic and sensory features of panic, compared to cognitive features (Rozenman et al., 2015). In addition, PUTS scores correlate significantly with abnormal sensory features. The stronger the individual's abnormal experience of physical discomfort, energy build up and 'just right' experiences, the stronger the premonitory urges (Sutherland Owens, Miguel, & Swerdlow, 2011). Abnormal sensory experiences may trigger or exacerbate tics (Woods, Miltenberger, & Flach, 1996) and are proposed to be due to dysfunction of the insular cortex and sensorimotor areas (Cox et al., 2018).

Alterations of the primary somatosensory cortex has been observed in adults with severe tics (Ganos, Roessner, & Munchau, 2013; Hashemiyoon, Kuhn, & Visser-Vandewalle, 2017). Thus, tics could be a product of altered exteroception. In particular, individuals report sensitivity to faint compared to intense sensory input, however, sensory detection thresholds, of all modalities, are found to be intact/typical in children and adults with TS (Belluscio et al., 2011; Cox et al., 2018; Ganos, Garrido, Navalpotro-Gomez, et al., 2015; Schunke et al., 2016; Sutherland Owens et al., 2011; Weisman et al., 2018; Zebardast et al., 2013). Therefore, alteration likely lies with central sensorimotor gating processing and/or within the filter spectrum of interoceptive awareness.

Sensory gating is a mechanism that filters irrelevant stimuli in order to prevent sensory overload. In those with TS there are measures of elevated sensory gating scores, indicative of less efficient gating (Sutherland-Owens et al., 2011). Alongside perturbed central sensorimotor processing, alteration in interoception has been suggested to contribute to the perception of premonitory urges (Jackson, Parkinson, Kim, Schuermann, & Eickhoff, 2011a). The relationship between interoceptive awareness and premonitory urges was demonstrated in adults with TS whereby reduced awareness corresponded with PUTS scores (Ganos, Garrido, Navalpotro-Gomez, et al., 2015). Whilst awareness is significantly reduced in TS compared to

HVs, higher levels of awareness correlated with worse PUTS scores. The authors proposed that the perception of urges could be dependent on interoceptive awareness ability. Therefore, the better awareness of internal signals, the more aware individuals are of urges. Whilst sensory gating has not been directly related to tic and urge severity, there remains an unfortunate consequence of altered interoceptive awareness and sensory gating on tic severity (Cox et al., 2018; Sutherland-Owens et al., 2011; Swerdlow, 2013).

Neuroimaging techniques, including MRI, PET and MEG have identified limbic brain structures as neural correlates of the premonitory urge. Such structures are the insula, cingulate cortex and SMA (Bohlhalter et al., 2006; Debes, Preel, & Shov, 2017; Draganski et al., 2010; Draper, Jackson, Morgan, & Jackson, 2016; Hampson, Tokoglu, King, Constable, & Leckman, 2009; Lerner et al., 2007; Neuner, Werner, Arrubla, Stocker, et al., 2014; Sowell et al., 2008; Stern et al., 2000; Tinaz et al., 2014; Wang et al., 2011). The insula cortex, has been identified as important for the processing and integration of information relating to emotions and bodily sensations (Strigo & Craig, 2016) and has been observed to be overactive during the premonitory urge (Neuner, Werner, Arrubla, Stöcker, et al., 2014). Computational modelling has also identified the insula as a centre for interoception and limbic processing that assigns premonitory urges with negative reinforcement value that upon urge alleviation is used to calculate dopaminergic positive prediction error (Maia & Conceicao, 2018). Functioning as a hub during tic generation, the insula may mediate abnormal processing of the sensory and emotional experiences of urges (Conceicao et al., 2017). Thus, the insula could play a role in mediating the arousal of the autonomic nervous system in response to stress and anxiety, alongside modulating premonitory urge and tic severity (Hawksley et al., 2015; Nagai et al., 2014). Interestingly, following damage to the insula, those addicted to smoking report no longer having an urge to smoke (Naqvi, Rudrauf, Damasio, & Bechara, 2007).

Stress, both psychological and physical, can increase tic severity and frequency (Eapen, Fox-Hiley, Banerjee, & Robertson, 2004; O'Connor, Brisebois, Brault, Robillard, & Loiselle, 2003; Robertson, Banerjee, Eapen, & Fox-Hiley, 2002). Furthermore, experience of stressful life events often results in worse tic severity and earlier onset of tics (Bornstein, Stefl, & Hammond, 1990; Steinberg et al., 2013).

These effects can range from short-term influence on tic severity, due to prior week and daily life stressors (Findley et al., 2003; Hoekstra, Steenhuis, Kallenberg, & Minderaa, 2004) to cumulative long-lasting effects on tic severity (Lin, Wang, Wong, Wu, & Lin, 2007). It is possible that the waxing and waning nature of TS over time could coincide with fluctuating stress (Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Crncec, et al., 2017).

Opposing instances of stress can modulate tic severity and exacerbate tics. Exhaustion and overstimulation (such as multitasking, watching TV or playing video games) have been noted to increase tic severity as have situations that cause anxiety or boredom (Caurin et al., 2014; Conelea & Woods, 2008; Hoekstra, Lundervold, et al., 2013). Intriguingly, there are reports of increased negative self-awareness following low environmental stimulation or boredom (Bench & Lench, 2013; Seib & Vodanovich, 1998). Whilst instances of overstimulation are concordant with the proposed disinhibitory aetiology of TS, instances of reduced stimulation may lead to attention focusing inwards to urges and interoception, culminating in increased tic severity. Conversely, tic frequency reduces considerably with music or during physical exercise, instances where attention is engaged externally (Bodeck, Lappe, & Evers, 2015).

Misrepresentations of internal states, or a disconnect between bodily signals and the brain's interpretation and prediction of those signals, has been identified as a source of anxiety and depression (Paulus & Stein, 2010). Therefore, reduced interoceptive awareness is likely a source of anxiety and stress. On the other hand, heightened interoceptive awareness may result in stress due to the perception of stronger urges, despite corresponding to the same amount of tics experienced by those with lower awareness (Ganos, 2016). Unfortunately, stress can trigger tic behaviours and help consolidate their habitual maintenance as tic performance reduces urge discomfort due to its anxiolytic effects serving as a negative reinforcer (Godar & Bortolato, 2017).

Individuals with TS are susceptible and less tolerant to anxiety, frustration and boredom. At baseline, TS has been associated with a higher heart rate and blood pressure corresponding to a heightened emotional state (Hawksley et al., 2015). Furthermore, greater HPA axis activation occurs during stress responses and reduced evening cortisol levels are observed in those with TS, reflecting the complex

role of stress in driving and maintaining tics (Corbett, Mendoza, Baym, Bunge, & Levine, 2008). Importantly, these observations implicate a role of the autonomic nervous system in tic generation. This idea is reinforced by beneficial reduction in tic frequency following real-time modulation of physiology during relaxation biofeedback (Nagai et al., 2009) and the efficacy of relaxation based training for those whose tics are exacerbated easily by high arousal states (Buse et al., 2014).

How stress and anxiety can influence tic severity is unknown (Godar & Bortolato, 2017). However, there is a proposed interaction between neural and immune pathways in TS pathology (Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Crncec, et al., 2017). Therefore, triggering experiences, as discussed, may result in stress-mediated alteration in sensory gating and interoceptive awareness alongside autoimmune-mediated neuronal dysfunction (Bergink et al., 2014; Chao et al., 2014; Hoekstra, Dietrich, et al., 2013; Martino et al., 2015). Subsequent processing of altered sensation and interoception within perturbed CSTC circuitry, eventually culminates in both autonomic nervous system arousal and striatal stimulation, generating and reinforcing tic behaviours (Godar & Bortolato, 2017).

To increase our understanding of the role of interoceptive awareness in adults with TS we characterised interoceptive awareness using a heartbeat mental tracking method (Ganos, Garrido, Navalpotro-Gomez, et al., 2015). Our results found that interoceptive awareness is significantly reduced in adults with TS, compared to HVs, replicating previous findings (Ganos, Garrido, Navalpotro-Gomez, et al., 2015). Furthermore, this effect was found to be independent from the effects of antipsychotic medication.

Our results did not replicate previous findings of identifying a statistically significant relationship between interoceptive awareness and premonitory urge severity as indicated by PUTS score (Ganos, Garrido, Navalpotro-Gomez, et al., 2015). However, self-report measures of premonitory urges may not reflect/capture all aspects of sensory processing/gating identified to be abberant in those with TS (Cox et al., 2018; Sutherland-Owens et al., 2011; Swerdlow, 2013).

During the experiment, all participants were required to relax, and there was no evidence of differing resting heart rates between HVs and adults with TS. Reduced

interoceptive awareness in adult TS is therefore unlikely to be due to altered physiological arousal. Furthermore, the observation of similar resting heart rates between our adults with TS and HVs does not dispute that alteration in interoception is a source of stress and anxiety that can lead to worsened tic severity (Paulus & Stein, 2010). Rather, stress generated autonomic responses, that work to exacerbate tics, are likely to occur upstream of alteration in heart rates. Thus, our results remain consistent with literature.

Impaired attention is a possible explanation for reduced interoceptive awareness. In our adult TS sample, there is evidence for sophisticated attention and/or inhibition resource capacity, as evident by intact performance on a complex CPT variant, despite co-occurrence of tic and urge phenomenon that impacts information processing (see Chapter 4). During a simple mental heartbeat tracking task, those with a large capacity for attention may not be engaged fully in the task. Therefore, attentional resources that are spare may be available to distraction that reduces interoceptive accuracy (Forster & Lavie, 2009; Forster et al., 2014; Sorqvist & Ronnberg, 2014). Similarly, the heartbeat mental tracking method may be an example of low environmental stimulation (akin to boredom) results in increased negative self-awareness (Bench & Lench, 2013; Seib & Vodanovich, 1998). Such experience may reduce motivation to perform the task and/or reinforce obsessive-compulsive thoughts, anxiety and depression (Paulus & Stein, 2010) detracting from interoceptive focus.

Alternatively, impairments in specific forms of attention may explain reduced interoceptive awareness. However, we found little evidence to support the existence of attentional deficits in adult TS. Rather we observed typical accuracy on the CPT variant despite moderation of attention to both internal (clinical phenomenon) and external (task requirements) events. Whether attention arises from a limited resource or decoupling occurs to devote a finite resource for external and internal events is debatable (Chun, Golomb, & Turk-Browne, 2011; Kam & Handy, 2013; Kiyonaga & Egner, 2013). If the latter, reduced interoceptive awareness may arise due to internal events competing for attentional resources, resulting in the inability to utilise attention to internal events beyond those relating to clinical features of TS (e.g. premonitory urges). For example, we identified a specific deficit in cognitive flexibility for habitually learned behaviours and during the heartbeat mental tracking experiment, our adults

with TS may therefore have had difficulty shifting their attention away from and/or successfully inhibiting tic and urge behaviours to be able to focus effectively on interoceptive sensations. Despite this, significant correlations between interoceptive awareness and the number of pre-EDS or EDS errors made on the IED task, measuring cognitive flexibility, were not found.

Interestingly, exploration of the relationship between cognitive function and interoceptive awareness revealed a significant correlation with a signal detection measure, response style *c*. Furthermore, reduced awareness was associated with more liberal responding. During CPT task performance, liberal responding corresponded to quicker reaction times at the expense of accuracy. Thus, reduced interoceptive awareness was related to a CPT task parameter synonymous with inattention. Therefore, we may have identified a link between interoceptive inaccuracy and cognition related to inattention, but not cognitive inflexibility. Such a link implicates evidence that there may be a functional relationship between reduced interoceptive awareness and cognitive abilities. Further investigation is therefore warranted.

Thus far, we have replicated the observation of reduced interoceptive awareness in adults with TS compared to HVs. We propose that reduced interoception is most likely due to the inability of adults with TS to be flexible with cognition regarding habitually learned behaviours. Consequently, adults with TS are inaccurate as they are unable to shift attention to their heartrate and or/inhibit tics and urges to utilise their attention accurately. Currently, our results are in accordance with previous literature and extends our understanding as to why interoceptive awareness may be reduced. In subsequent chapters, how and whether reduced interoceptive awareness affects other clinical features and neurophysiological measures of attention/inhibition, is described. Finally, in Chapter 9, the role of interoceptive awareness in tic management is examined.

Chapter 6. Neurophysiology

6.1. Introduction

The aim was to explore the CSE of the motor system in adult TS using non-invasive TMS and the impact of active tic control on motor system neurophysiology. This allowed the determination of whether adult TS is associated with alteration of CSE and whether motor system neurophysiology reflects predicted excitatory and inhibitory imbalance, focusing on GABAergic and glutamatergic intra and inter-cortical mechanisms. Such information will advance our understanding of tic generation. Comparing motor system neurophysiology under active tic suppression and instruction to tic freely will advance our understanding of tic management and/or provide insight into how tic management may alter CSE.

6.2. Results

Motor thresholding

There was no significant difference amongst adults with TS and HVs in the stimulation intensity needed to reach RMT, t (53) = .968, p = .373, d = .271, AMT, t (53) = .986, p = .329, d = .276, or the intensity needed to elicit a 1mV peak-peak amplitude MEP, t (53) = .778, p = .440, d = .218.

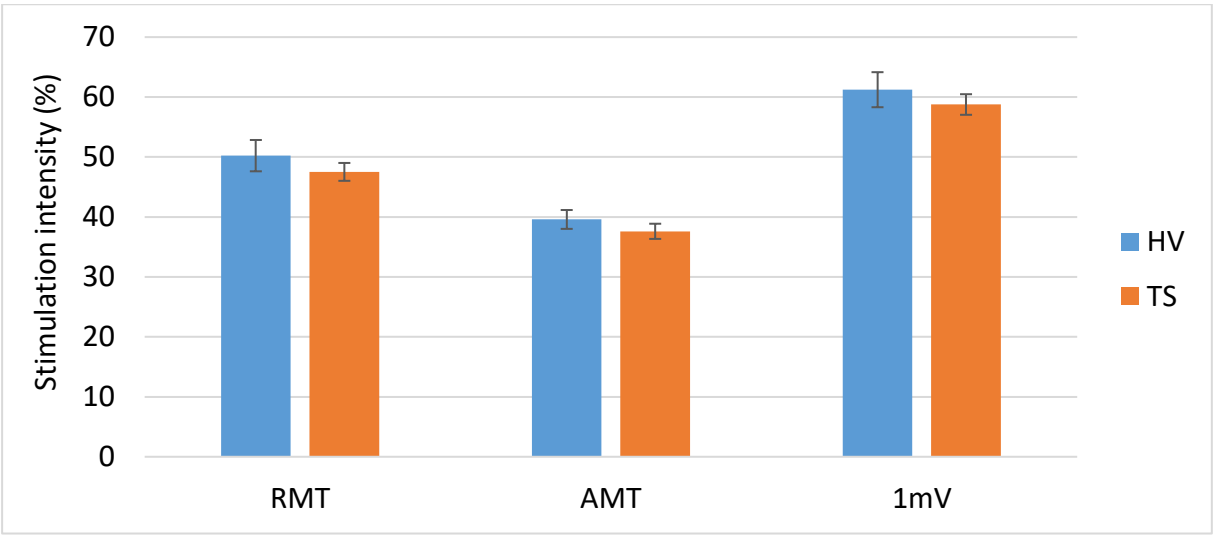


Figure 61. Mean percentage of maximum stimulation intensity needed to reach resting, active and 1mV thresholds for HVs and TS. Error bars represent SEM.

Summary

During motor thresholding, stimulation intensities needed to reach AMT were significantly lower than intensities needed to reach RMT. To reach 1mV threshold, stimulation was significantly higher than those needed to reach RMT and AMT. Whilst adults with TS required less stimulation to reach thresholds, this was not a significant finding.

Short Interval Intra-Cortical Inhibition (SICI) and Intra-Cortical Facilitation (ICF)

Results

There was a significant main effect of the SICI condition on the size of the normalised MEP, F (2, 104) = 97.867, p = .000, r = .70. Planned contrasts (repeated) revealed that normalised MEPs were significantly smaller at 3ms compared to 2ms, F (1, 52) = 8.469, p = .005, r = .37, and normalised MEPs at 12ms were significantly larger compared to 3ms, F (1, 52) = 15.806, p = .000, r = .86.

There was a significant interaction effect between the size of the MEPs elicited under different SICI conditions and clinical status of the participant, F (2, 104) = 8.911, p = .000, r = .28 and a significant main effect of clinical status, F (1, 52) = 11.742, p = .001, r = .43,

To break down the effects, independent t tests revealed that adults with TS had significantly smaller normalised MEPs compared to HVs at 2ms, t (52) = -2.104, p = .040, d = -.598, and 3ms, t (52) = -4.049, p = .001, d = -1.152 and similar normalised MEPs at 12ms, t (52) = -.707, p = .483, d = -.201. At 2 and 3ms, those with TS have significantly larger normalised MEPs indicative of reduced SICI compared to HVs and similar levels of ICF at 12ms.

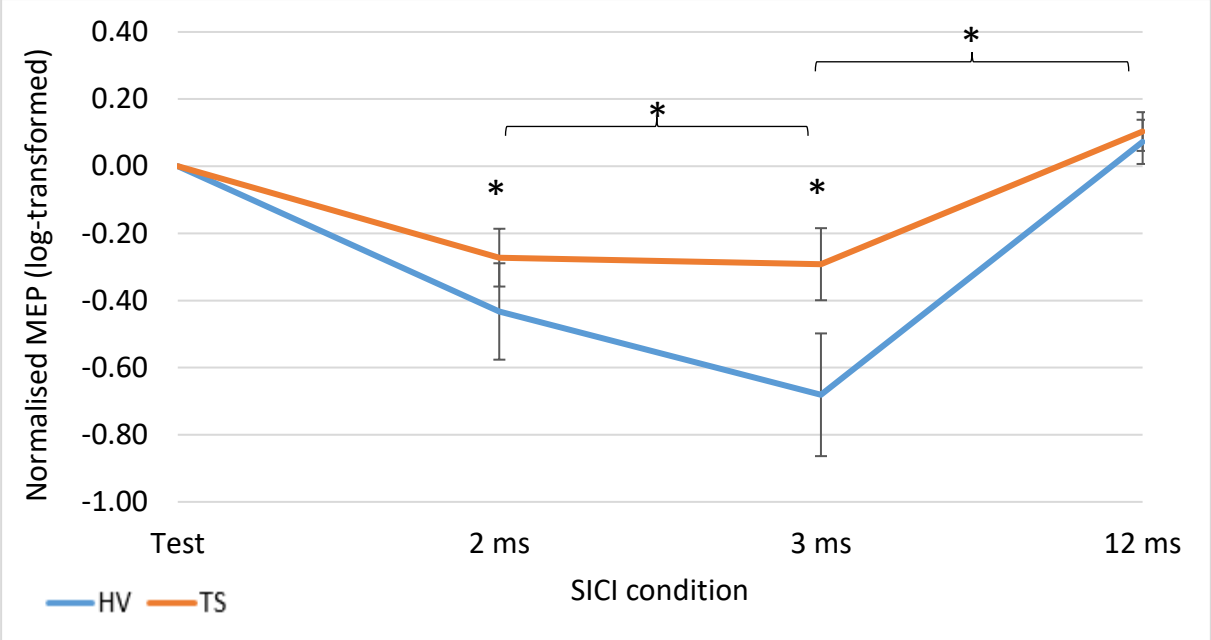


Figure 62. Mean normalised MEPs (log-transformed) elicited at test only and 2ms, 3ms or 12ms intervals, for HVs and TS. MEPs are normalised to test pulse condition, with negative values representing inhibition and positive facilitation. Error bars represent SEM. *Main effect of SICI condition and clinical status on normalised MEPs significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to normalised MEPs at 2ms (log-transformed), F (1, 51) = .364, p = .549, r = .29. There was a significant effect of group, clinical status, on normalised MEPs at 2ms after controlling for the effect of medication with antipsychotics, F (1, 51) = 4.705, p = .035, η^2 = .084; this remained significant following Benjamini-Hochberg FDR correction.

Medication with antipsychotics was not significantly related to normalised MEPs at 3ms (log-transformed), F (1, 51) = 2.411, p = .127, r = .21. There was a significant effect of group, clinical status, on normalised MEPs at 3ms after controlling for the effect of medication with antipsychotics, F (1, 51) = 19.246, p = .000, η^2 = .274; this remained significant following Benjamini-Hochberg FDR correction.

Medication with antipsychotics was not related to normalised MEPs at 12ms (log-transformed), F (1, 51) = 3.315, p = .075, r = .25.

Interoceptive awareness

There was no significant correlation between interoceptive awareness and 2ms SICI in HVs, r = -.139, p = .274, however, there was a trend level correlation for 2ms SICI for those with TS, r = -.238, p = .092 (one-tailed significance).

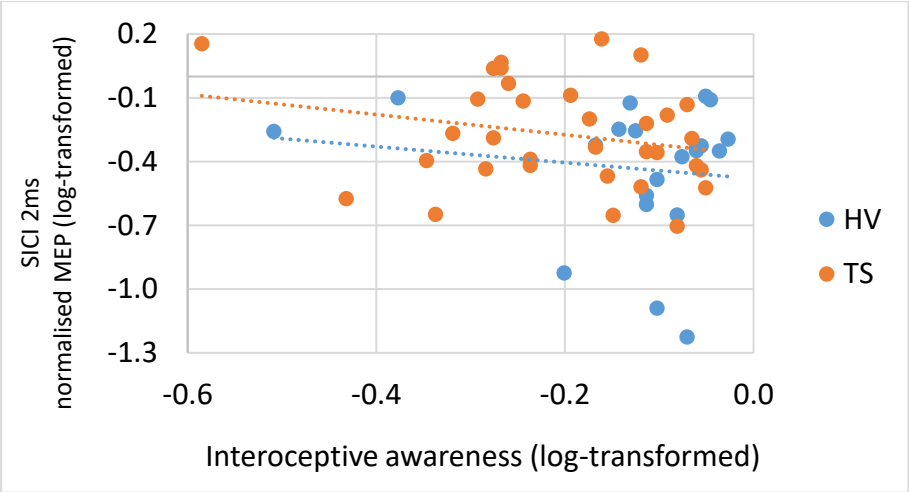


Figure 63. Relationship between interoceptive awareness and normalised MEPs (all log-transformed) at SICI 2ms for HVs and TS.

Interoceptive awareness (log-transformed) was found to correlate significantly with normalised MEPs evoked at 3ms SICI (log-transformed) in those with TS, r = -.341, p = .026; but not in HVs, r = .266, p = .122 (one-tailed significance); remaining significant following Benjamini-Hochberg FDR correction.

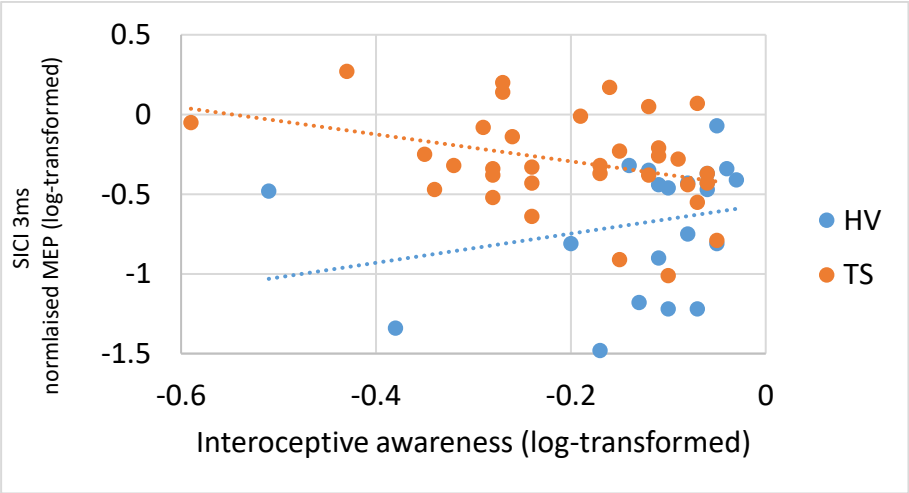


Figure 64. Relationship between interoceptive awareness and normalised MEPs (all log-transformed) at SICI 3ms for HVs and TS.

Summary

During the paired-pulse SICI and ICF paradigm, it was found that in comparison to test pulse only, MEPs elicited at 2ms and 3ms intervals were significantly reduced, indicative of successfully inducing short interval intra-cortical inhibition. Conversely, at 12ms intervals, MEPs were significantly larger than those elicited at test pulse only, indicative of excitation in accordance with successfully inducing intra-cortical facilitation.

There was a significant interaction between SICI/ICF condition and clinical status, whereby those with TS had significantly reduced SICI at 2ms and 3ms compared to HVs. However, there was no difference between TS and HVs for ICF. Antipsychotic medication was not significantly related to SICI induced at 2 or 3ms, with reduced SICI in adults with TS remaining significant after controlling for antipsychotics.

Interoceptive awareness was found to correlate significantly with normalised MEPs evoked at 3ms, and at trend level at 2ms, SICI in adults with TS but not in HVs. Reduced awareness was associated with less inhibition at 2ms and 3ms SICI, identifying a link between altered interoceptive awareness and a deficit in inhibitory mechanisms in adults with TS.

Short-latency Afferent Inhibition (SAI)

Results

There was a significant main effect of SAI condition on the size of the normalised MEP, F (3, 147) = 3.074, p = .030, r = .14. Planned contrasts (Helmert) revealed that normalised MEPs evoked from N20 were significantly larger than the mean effect of all subsequent SAI conditions, F (1, 49) =7.562, p = .008, r = .37; indicative of inhibition at all subsequent time points. There was no significant interaction effect between the size of the MEPs elicited under different SAI conditions and clinical status of the participant, F (3, 147) = 1.416, p = .240, r = .10.

There was however a significant main effect of clinical status, F (1, 49) = 10.388, p = .002, r = .42, whereby the clinical status of the participants influences the size of the MEPs. To break down the effect, independent t tests revealed that adults with TS had smaller normalised MEPs compared to HVs at $N20^{+4ms}$, t (49) = -3.195, p = .002,

d = -.904, and N20^{+6ms}, *t* (49) = -3.330, *p* = .002, *d* = -0.974. There was a trend for a difference in the size of normalised MEPs recorded at N20, *t* (49) = -1.936, *p* = .059, *d* = -.648, and N20^{+2ms}, *t* (49) = -1.712, *p* = .093, *d* = -.502, between TS and HVs.

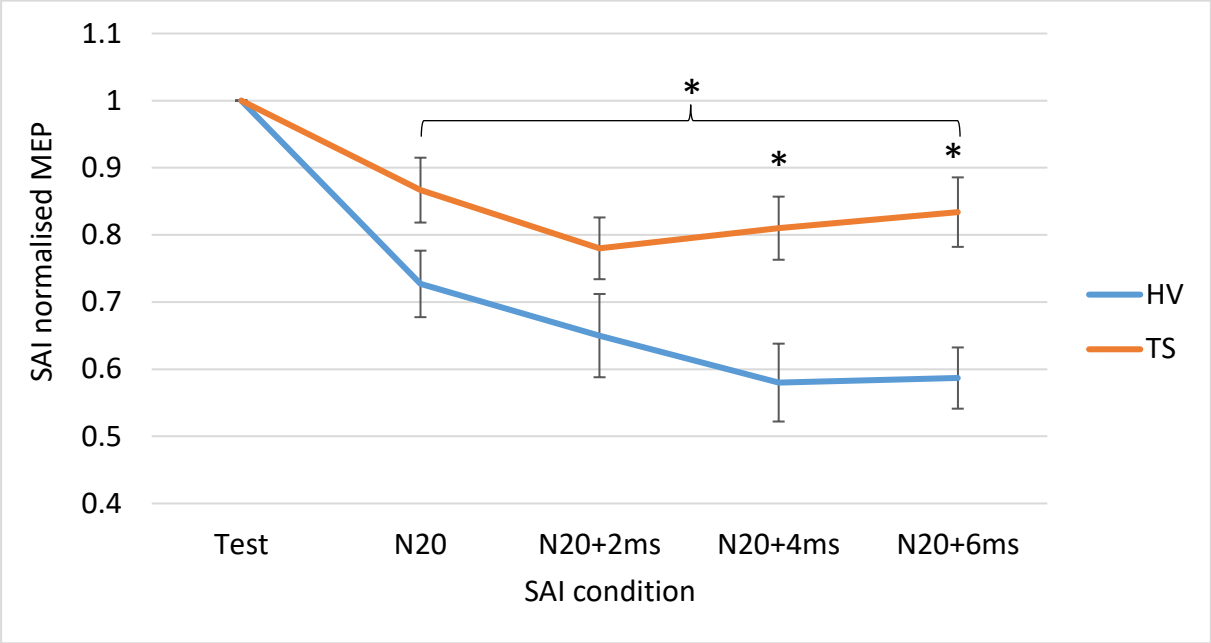


Figure 65. Mean normalised MEPs elicited at test only and N20, N20^{+2ms}, N20^{+4ms} and N20^{+6ms} intervals, for HVs and TS. MEPs are normalised to test pulse condition, with negative values representing inhibition and positive facilitation. Error bars represent SEM. *Main effect of SAI condition and clinical status on normalised MEPs significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to normalised MEPs at N20^{+4ms}, *F* (1, 48) = .539, *p* = .466, *r* = .11. There was a significant effect of group, clinical status, on normalised MEPs N20^{+4ms} after controlling for the effect of medication with antipsychotics, *F* (1, 48) = 10.400, *p* = .002, η^2 = .178; this remained significant following Benjamini-Hochberg FDR correction.

Medication with antipsychotics was not significantly related to normalised MEPs at N20^{+6ms}, *F* (1, 48) = 3.109, *p* = .084, *r* = .25. There was a significant effect of group, clinical status, on normalised MEPs N20^{+6ms} after controlling for the effect of

medication with antipsychotics, F (1, 48) = 14.536, p = .000, η^2 = .232; this remained significant following Benjamini-Hochberg FDR correction.

Interoceptive awareness

Interoceptive awareness (log-transformed) was found to correlate significantly with normalised MEPs evoked at SAI N20^{+6ms} in those with TS, r = -.456, p = .010; but not in HVs, r = -.290, p = .244 (two-tailed significance); this remained significant following Benjamini-Hochberg FDR correction. No other significant correlations existed between interoceptive awareness and normalised MEPs evoked at other SAI intervals (all > p =.05).

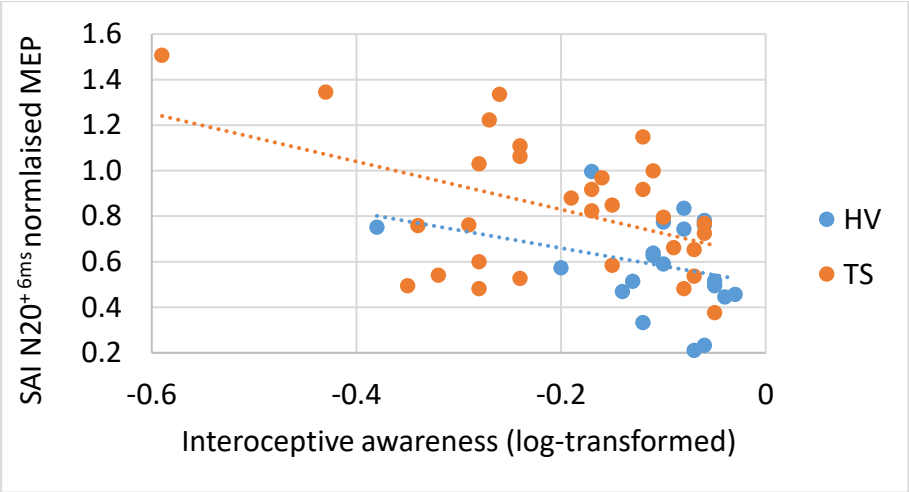


Figure 66. Relationship between SAI N20$^{+ 6ms}$ normalised MEPs and interoceptive awareness (log-transformed) for HVs (blue) and TS (orange).

Summary

During the paired-pulse SAI paradigm, it was found that, in comparison to test pulse only, MEPs elicited at all time-points relative to the N20 SEP component (between conditioning and test pulses) were significantly reduced, indicative of successfully inducing short-latency afferent inhibition in all participants.

There was a significant interaction between SAI condition and participant clinical status, whereby adults with TS had significantly reduced inhibition at N20$^{+ 4ms}$ and

$N20^{+\ 6ms}$ compared to HVs. Furthermore, these abnormalities in SAI in adult TS were not attributable to antipsychotics, remaining significant after controlling for medication. In addition, interoceptive awareness was significantly related to SAI at $N20^{+\ 6ms}$ in adults with TS but not HVs, whereby worse interoceptive awareness related with reduced inhibition. Our results have identified a further link between abnormal interoceptive awareness and a deficit in inhibitory mechanisms in adults with TS.

Tic control

Results

There was a significant main effect of the tic control condition on the size of the recorded normalised MEPs, F (2, 64) = 12.501, p = .000, r = .40. Planned contrasts (simple) making comparisons to MEPs recorded at baseline (no tic-related instructions) revealed that MEPs were significantly smaller when participants were asked to inhibit their tics, F (1, 32) = 11.491, p = .002, r = .51, and larger when participants were asked to allow their tics to happen, F (1, 32) = 3.963, p = .055, r = .33; reaching significance following Benjamini-Hochberg FDR correction.

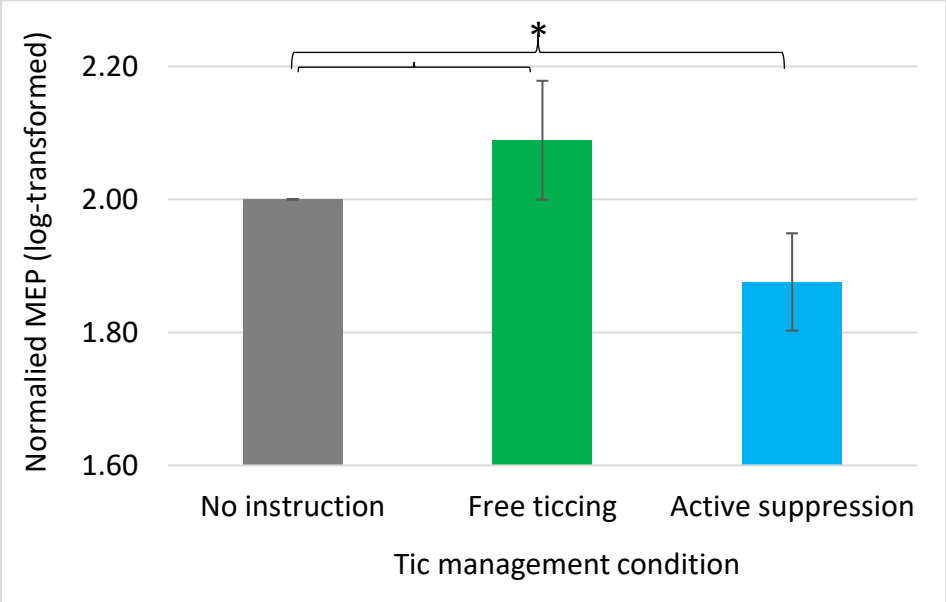


Figure 67. Mean normalised MEPs (log-transformed) recorded under no tic-related instructions, when free to tic and during active tic suppression tics. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to normalised MEPs (log-transformed) recorded under instruction to allow tics, F (1, 31) = .063, p = .803, r = .05 or normalised MEPs (log-transformed) recorded under instruction to inhibit tics, F (1, 31) = .601, p = .444, r = .14.

Summary

Following the establishment of stimulation thresholds to evoke a 1mV peak-peak amplitude MEP, instruction to allow tics resulted in a significant increase in MEP size compared to the active tic suppression condition. Similarly, when instructed to inhibit tics there was a reduction in MEP size, compared to no tic-related instruction, which was of trend level significance. There was no effect of antipsychotic medication on the neurophysiological effects of tic management.

6.3. Discussion

During motor thresholding, as expected, the stimulation intensities needed to reach RMT were higher than AMT, consistent with the observations that intensities needed to generate MEPs are significantly lower during voluntary action compared to rest. Such observations are due to spinal motor neurons being active and randomly firing during voluntary action and, lower levels of excitatory input can both synchronise and summate spinal motor neuron firing (Day et al., 1989; Rossini et al., 2015).

The stimulation intensities needed to reach AMT did not differ between adults with TS and HVs. Our results are therefore consistent with previous findings of normal AMT in adult TS (Orth et al., 2005; Orth, Münchau, et al., 2008; Ziemann et al., 1997). Furthermore, our results support the proposal that voluntary action regulates motor system CSE (Orth, 2009; Orth, Münchau, et al., 2008), whereby less stimulation intensity is required to both summate pre-threshold and recruit additional neurons. In our sample, whilst our adults with TS required less stimulation, the stimulation intensities needed to reach RMT did not differ between adults with TS and HVs, consistent with previous findings (Orth, Münchau, et al., 2008). Previously, alongside typical motor thresholds, adult TS has been associated with reduced CSE at rest (Orth, Münchau, et al., 2008). There have however, been observations that

compared to adults, children with TS have increased RMT (Pepes, Draper, Jackson, & Jackson, 2016). Typical RMT in adulthood could therefore represent maturation of CSTC circuity, corresponding to both stabilisation of neurophysiological imbalance and acquisition of compensatory control mechanisms (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Mueller et al., 2006; Thomalla et al., 2014). We also observed similar stimulation intensities required to evoke MEPs of 1mV peak-peak amplitude in our HVs and adults with TS. These results also suppose that in our adults with TS, CSE remains consistent during thresholding; supporting the proposal that maturation coincides with regulation of CSE.

TMS has illustrated that the distribution of CSE appears to be altered in TS during rest (Orth, Münchau, et al., 2008). For example, when TMS is administered above established thresholds, the subsequent generated motor activity is smaller in TS than HVs (Orth, Münchau, et al., 2008). Such observations suggest that fewer additional neuronal connections are being recruited, indicating uneven distribution of CSE (Orth, 2009). As these alterations are not evident during tonic activity (Orth et al., 2005; Orth, Münchau, et al., 2008; Ziemann et al., 1997) and are more extensive with increasing tic severity (Orth, Münchau, et al., 2008) it suggests that voluntary action may serve to regulate corticospinal excitability in TS (Orth, 2009; Orth, Münchau, et al., 2008) with benefits to tic control.

In our sample of adults with TS, we found significantly reduced SICI compared to HVs, an effect independent from antipsychotic medication. These results are consistent with previous findings that in TS there is reduced SICI (Orth, 2009; Orth et al., 2005; Orth & Rothwell, 2009). SICI was found to be significantly related to interoceptive awareness in adults with TS but not HVs at 3ms and at the level of a trend at 2ms. This relationship implicates that disruption to GABAergic inhibitory mechanisms within the motor cortex has an impact on the ability to perceive interoceptive events accurately. Intriguingly, there is an overlap between the stimulation intensities and paired-pulse ISIs for eliciting SICI and short-interval intracortical facilitation (SICF) (Rossini et al., 2015). Therefore, the significant relationship observed at 3ms, compared to a trend at 2ms, may reflect an association between interoceptive awareness and the glutamatergic mechanisms of SICF (Rossini et al., 2015). In this instance, reduced interoceptive awareness in adult TS may be due to background motor system noise, likely arising due to facilitatory

mechanisms. Furthermore, SICF could account for the apparent reduction in SICI at 3ms in adult TS. Despite this, since a relationship at trend level was observed between interoceptive awareness and SICI at 2ms in adult TS, alongside the observation that optimal inhibition was elicited in HVs and TS at 3ms SICI, it is likely that our results represent GABAergic inhibitory mechanisms. Our results have therefore identified a potential neurophysiological correlate of perturbed sensory attention and a role of the motor cortex in interoceptive awareness.

Whilst MEPs evoked at 12ms were enhanced in adults with TS, there was no significant differences in the levels of ICF compared to HVs. Dopamine modulation with antipsychotics may have reduced the levels of ICF in our TS group as alteration to the excitability of glutamatergic pyramidal neurons can be influenced both directly and indirectly via mesocortical dopaminergic input from the ventral tegmental area (Cheon et al., 2004). Previously, where ICF was enhanced in adult TS, participants were non-medicated. In our sample, medication with antipsychotics was related to ICF at the level of a trend and controlling for antipsychotics made the difference in MEP size for adults with TS and HVs (enhanced ICF in TS) more significant. Thus, medication confounds are likely responsible for the discrepancy within the literature and our results.

During the SAI paradigm, we successfully induced SAI in all participants. Adults with TS had reduced SAI on all conditions relative to the N20 SEP component compared to HVs and significantly so at $N20^{+4ms}$ and $N20^{+6ms}$. Reduced SAI in adult TS was an effect independent from medication with antipsychotics. Our results are therefore consistent with observations of reduced SAI in adult TS (Orth, 2009; Orth et al., 2005; Orth & Rothwell, 2009). Intriguingly, SAI at $N20^{+6ms}$, where optimal inhibition was elicited in all participants, was found to be significantly related to interoceptive awareness in TS adults but not HVs. Specifically, reduced interoceptive awareness correlated with reduced SAI. This relationship implies that disruption of the cholinergic and $GABA_A$ergic inhibitory mechanisms of the sensorimotor cortex has an impact on the ability to perceive interoceptive events accurately (Tokimura et al., 2000). Our results have identified another neurophysiological correlate of perturbed sensory attention and a role of the sensorimotor cortex in interoceptive awareness.

The relationship between interoceptive awareness and SAI was found to be specific for late (N20+6ms) SAI compared to early SAI. Recently, it has been found that there

is a time-specific influence of cerebellar activity, as assessed by cerebellar-brain inhibition (CBI), on sensory processing (Spampinato, 2019). Specifically, CBI reduced late SAI but not early SAI; these results suggests that the observed relationship between reduced interoceptive awareness and reduced late SAI ($N20^{+6ms}$) in our study, could be due to alteration of sensory gating and processing to the motor cortex (M1) related to the cerebellar-thalamic-tract (Spampinato, 2019).

In our sample of adults with TS, when instructed to inhibit tics, the amplitude of generated MEPs significantly reduced in size compared to MEPs when there were no tic-related instructions. Furthermore, instruction to allow tics to occur, resulted in larger MEPs that reached trend level significance. Our results occurred independent of the effects of antipsychotic medication. As mentioned, above threshold stimulation (120% RMT in this instance) and reduced MEP amplitude are indicative of fewer additional neurones being recruited and uneven distribution of CSE (Orth, 2009). Conversely, larger MEP amplitudes indicate that all components of the corticospinal system are equally excitable. Our results therefore suggest that active tic control involves cognitive control mechanisms that exert an inhibitory effect on the motor system by altering the distribution of CSE. Attempts at removing this cognitive control, by allowing tics to occur, appears to regulate the distribution of CSE. Previously, reduced CSE in adult TS has been suggested as reflecting compensatory adaptions to reduce involuntary movement (Orth, Munchau, et al., 2008). More recently, during a go/no-go paradigm, delivery of a single TMS test pulse preceding finger movement resulted in those with TS having significantly reduced MEP amplitude (Draper et al., 2015), corresponding to altered distribution of CSE. The authors propose that TS is associated with alteration in the modulation of CSE prior to tics. These results further suggest that modulation of CSE, by altering the distribution of CSE, may be a putative tic control mechanism.

We have found in our adults with TS evidence for typical excitability of corticospinal neurons during the establishment of AMT, RMT and 1mV thresholds. When recording MEPs during rest, with above threshold intensities, we found that adult TS is associated with alteration in the distribution of CSE. Furthermore, in adults with TS, we found impairment in inhibitory intra-cortical mechanisms of the motor cortex and inter-cortical inhibition of the motor cortex by the sensorimotor cortex. Furthermore, such impairments have been identified as neurophysiological correlates

of perturbed sensory attention and identify a role of the motor and sensorimotor cortex in interoceptive awareness. Finally, we have established that active tic control is associated with alterations in the distribution of CSE that has an inhibitory effect on motor system excitability.

TS is a neurodevelopmental disorder associated with abnormalities of a number of transmitter systems including glutamate, GABA, dopamine, serotonin and histamine (Grados et al., 2018; Paschou, Fernandez, Sharp, Heiman, & Hoekstra, 2013; Yael, Vinner, & Bar-Gad, 2015). Widespread alteration in these transmitter systems across CSTC pathways makes TS pathophysiology complex and difficult to elucidate (Yael et al., 2015). Deficits in dopamine transmission are considered central to TS pathology (Albin & Mink, 2006; McNaught & Mink, 2011; Mink, 2001a, 2001b, 2006; Yael et al., 2015) with disruption in dopaminergic signalling resulting in hyperinnervation of the striatum (Fraint & Pal, 2015; Graybiel, 2008; McNaught & Mink, 2011; Novotny et al., 2018). TS is considered a basal ganglia disorder of inhibition (Mink, 2001b). Typically, the globus pallidus interna and the substantia nigra pars reticular form an output pathway of the basal ganglia and work via tonic inhibition to inhibit unwanted movements. Prolonged over-activation of striatal neurons, due to disrupted neurodevelopment, can lead to inhibition of these nuclei, resulting in disinhibition of thalamo-cortical targets, critical to tic generation (Mink, 2001b). Alongside its role in the generation of tics, alteration in dopamine results in the complex maintenance of tic behaviours due to activity-dependent reinforcement learning and enhanced habit formation (Albin & Mink, 2006; Delorme et al., 2016; Kim et al., 2018; Leckman, 2002). Furthermore, computational modelling proposes a parsimonious dopaminergic hyperinnervation account, whereby overabundance of dopaminergic terminals can explain the original generation and the learned maintenance of tics occurring via increased phasic and tonic dopaminergic transmission within the basal ganglia (Conceicao et al., 2017; Maia & Conceicao, 2017, 2018).

Alongside dopamine, excessive glutamate (NMDA receptor) is recognised widely in the aetiology of TS (Ernst et al., 1999; Serra-Mestres et al., 2004) with a role of cortical and amygdala glutamatergic output circuits within CSTC loops recognised in the generation of tics and compulsive behaviours (Milad & Rauch, 2012; Nordstrom, Bittner, McGrath, Parks, & Burton, 2015; Singer, Morris, & Grados, 2010).

Furthermore, disruption of GABAergic inhibition is increasingly recognised in TS pathology (Kataoka et al., 2010; Leckman et al., 2010). Interestingly, during early fetal development GABA is the primary excitatory transmitter (Johnson et al., 2003). With typical neurodevelopment, GABA switches from excitatory to inhibitory within neurocircuitry. When this switch fails to develop, conditions such as dystonia and epilepsy can occur (Furukawa et al., 2017; Rakhade & Jensen, 2009; Selten, van Bokhoven, & Nadif Kasri, 2018; Tomiyasu et al., 2017). Delayed or perturbed maturation of basal ganglia interneurons in TS likely contributes to CSTC disinhibition and the subsequent generation of involuntary tics (Church, Fair, et al., 2009).

Tic and premonitory urge generation is primarily associated with enhanced activation within the SMA, somatosensory and motor cortices. However, over-activation has also been observed within pre-frontal and frontal cortices, in the parietal operculum, inferior parietal and superior temporal gyrus and the cerebellum (Biswal et al., 1998; Bohlhalter et al., 2006; Eidelberg et al., 1997; Hampson et al., 2009; Stern et al., 2000). Furthermore, urge and tic behaviours have been observed to correspond with hyperactivity within limbic and paralimbic structures such as the insula, amygdala and ACC and in subcortical regions including the claustrum, putamen, globus pallidus, caudate nucleus and thalamus (Biermann-Ruben et al., 2012; Bohlhalter et al., 2006; Jackson, Parkinson, Kim, et al., 2011b; Kalanithi et al., 2005; Kataoka et al., 2010; Lennington et al., 2016; Lerner et al., 2012; Neuner, Werner, Arrubla, Stocker, et al., 2014; Puts et al., 2015; Tinaz et al., 2014; Vaccarino, 2013; Wang et al., 2011; Worbe, Marrakchi-Kacem, et al., 2015; Ziemann et al., 1997).

Widespread over activity is proposed to occur due to the lack of inhibitory neuronal function secondary to abnormal neurodevelopment affecting the distribution and function of cortical and striatal GABAergic and cholinergic interneurons throughout CSTC circuitry (Grados et al., 2018; Kalanithi et al., 2005; Kataoka et al., 2010; Lerner et al., 2012; Puts et al., 2015; Tinaz et al., 2014; Vaccarino, 2013; Ziemann et al., 1997). Furthermore, hypoactivity of executive control circuits, including the PFC, whereby cognitive control is altered, also contributes to the generation and management of tics, urges and compulsions (Burguiere, Monteiro, Feng, & Graybiel, 2013; Jung et al., 2013; Kalanithi et al., 2005; Kataoka et al., 2010; McNaught &

Mink, 2011; Singer et al., 2010; Swerdlow & Sutherland, 2005; Worbe, Marrakchi-Kacem, et al., 2015; Xu et al., 2015).

Motor system noise, resulting in the generation of involuntary movement, arises due to loss of inhibitory control mechanisms within sensorimotor and motor systems (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Plessen et al., 2009). Interestingly, alteration in the limbic input of the SMA corresponds with changes within local SMA network GABAergic activity. These results demonstrate how abnormalities of GABAergic sensorimotor processing may influence tic generation (Tinaz et al., 2014). Furthermore, structural MRI and spectroscopy analysis revealed that in children and adolescents with TS, there was reduction in *in vivo* GABA within the sensorimotor cortex, indicative of dysfunction of inhibition of both motor and somatosensory cortices in TS (Puts et al., 2015). Compensatory tic control mechanisms may therefore involve local inhibition in over-excitatory primary and supplementary motor regions via tonic inhibition of GABA (Jackson et al., 2015).

When TMS is applied to the SMA, sensory and motor events occur that are similar to tics (Finis et al., 2013), consistent with the proposal that over activity in the SMA contributes to the generation of tics and urges. Interestingly, application of repetitive TMS to the motor cortex reduces sensory cortex excitability (Enomoto et al., 2001; Seyal, Shatzel, & Richardson, 2005). These results demonstrate that inter-cortical communication between the sensory and motor cortices occurs. Furthermore, use of MEG during a self-paced movement task, illustrated that movement-generated field amplitudes were negatively correlated with tic frequency and severity (Biermann-Ruben et al., 2012). The authors noted that these results highlight how changes in sensory feedback loops can influence the motor system during voluntary movement. These results implicate the role of the sensory system in mediating local inhibition of the motor cortex in moderating tic behaviours (Biermann-Ruben et al., 2012; Jackson et al., 2015). Therefore, following movement, the motor cortex may exert inhibition to reduce the excitability of the sensory cortex that typically serves as a signal for movement (Biermann-Ruben et al., 2012). Accordingly, where over-activation in the sensory cortex contributes to the premonitory urge, inhibition of cortical excitability likely contributes to the temporary alleviation of urges (Enomoto et al., 2001; Seyal et al., 2005). Premonitory urge and tic control is likely to be achieved by recruitment of

compensatory mechanisms that regulate neurophysiological imbalance to reduce motor and sensory system noise.

Adaptive changes over the course of TS, in response to over-activity within CSTC circuits, usually occurs via structural (changes to white matter micro-structure) and functional abnormalities in both pre-frontal and fronto-parietal networks (Jackson, Parkinson, Jung, et al., 2011; Thomalla et al., 2014). With these changes, inhibitory control is better achieved over unwanted tic behaviours, with more optimal control associated with enhanced frontal activity (Johannes, Wieringa, Mantey, et al., 2001; Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007; Morand-Beaulieu et al., 2015; Serrien et al., 2005; Thibault et al., 2009). Better inhibitory control in TS has been proposed to be due to increased tonic GABAergic inhibition within regions relating to motor planning as well as mechanisms to distribute local cortex excitability (Jackson et al., 2015; Jung et al., 2013). Such compensation may result in better regulation of motor region hyper-excitability.

Our results provide evidence of neurophysiological imbalance in the corticospinal motor system in adults with TS. We observed typical CSE during motor thresholding as well as evidence of altered intercortical and intracortical inhibition of motor and sensory cortices. Furthermore, we found that, at rest, TS is associated with alteration in the distribution of CSE and that modulation of this is a tic control mechanism. Our results provide evidence of maturation of CSTC circuitry overtime, alongside the acquisition of compensatory changes, likely to local tonic GABAergic inhibition of sensory and motor areas, that corresponds to stabilisation of neurophysiological imbalance and enhanced cognitive control (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Mueller et al., 2006; Thomalla et al., 2014).

Chapter 7. Clinical profile

7.1. Introduction

Clinical features associated with adult TS may underlie an individual's ability to engage in successful tic inhibition or benefit from attention distraction. The aim was to characterise the clinical profile of adult TS to advance our understanding of which factors influence tic severity and treatment response.

7.2. Results

Urge and tic severity

Results

Premonitory urge

PUTS

In our sample of TS participants, the mean total PUTS score was 24.52 with a standard deviation of 7.1.

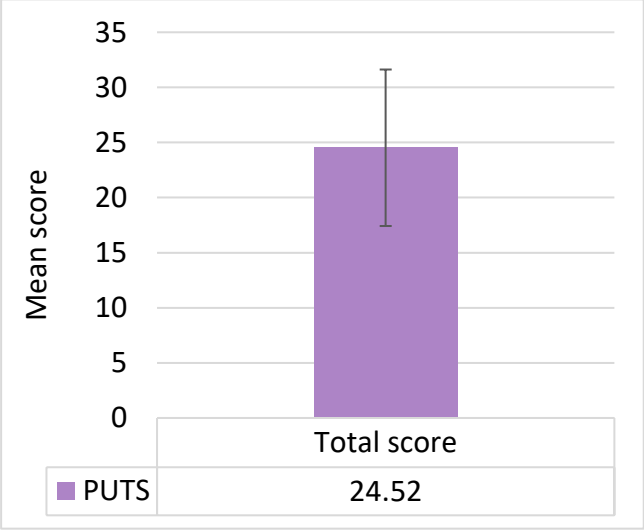


Figure 68. Mean PUTS total score for participants with TS. Error bars represent standard deviation.

Tic severity

YGTSS

In our sample of TS participants, the mean scores from the YGTSS assessment were 55.27 ± 18.1 (*M, SD)* for total score, 30.91 ± 9.48 for impairment, 15.36 ± 6.78 for motor tic score, 9 ± 6.22 for phonic tic score and 24.36 ± 11.72 for combined score.

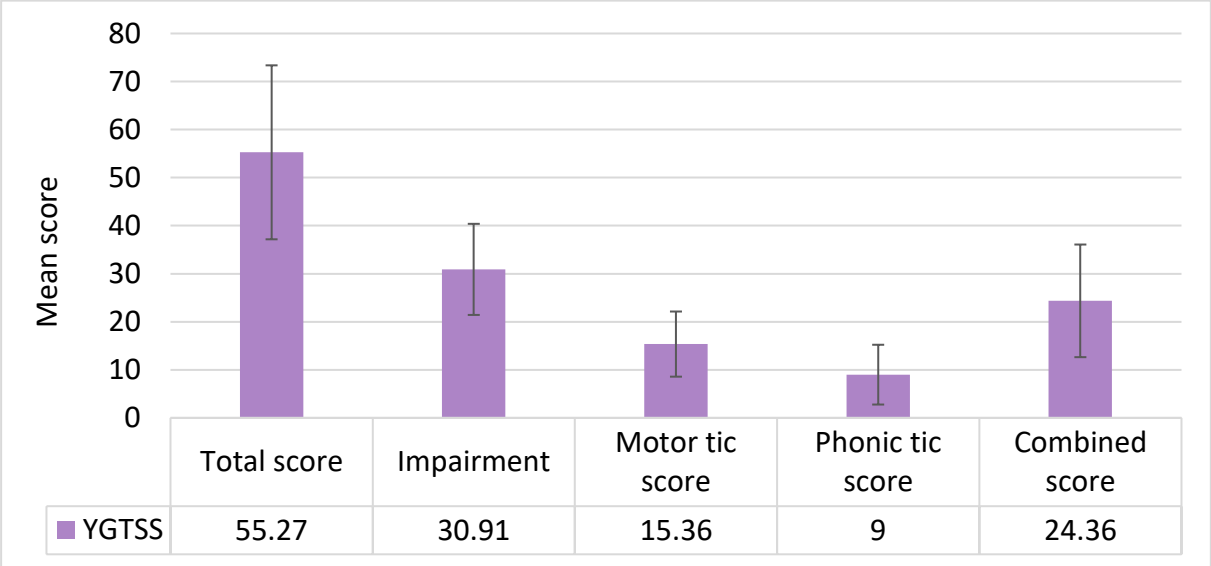


Figure 69. Mean YGTSS assessment scores for participants with TS. Error bars represent standard deviation.

Age onset

In our total sample of thirty-three adults with TS, the mean reported age of onset for motor tics was 9.28 years (± 1.49) and the mean reported age for the worst motor tic severity was 22.29 (± 2.19). Additionally, the mean reported age of onset for vocal tics was 13.55 years (± 2.14) and the mean age for the worst vocal tic severity was 19.76 (± 2.24).

Thirty adults within our sample had onset of tics in their childhood, with the earliest reported onset at 1 year and latest at 15 years age. Three adults within our sample reported onset of tics in adulthood, with the earliest reported onset at 21 years and the latest at 46 years age.

Those with childhood onset reported the mean age of motor tic onset as 7.17 years (± 3.92) and age for the worst motor tic severity was 21.24 (± 11.67). Additionally, those with childhood onset reported mean age of vocal tic onset as 11.82 years (± 10.53) and mean age for the worst vocal tic severity 11.82 years (± 11.13).

Those with adult onset reported the mean age of motor tic onset as 29.67 years (± 14.15) and age for the worst motor tic severity was 37.50 (± 12.02). Additionally, those with adult onset reported mean age of vocal tic onset as 29.67 years (± 14.15) and mean age for the worst vocal tic severity 38 years (± 11.31).

MRVS

In our sample of TS participants, the mean scores from the MRVS assessment were 9.21 (± 3.95) for total score, 2.73 (± 1.01) for number of body areas, 1.18 (± 0.47) for motor tic frequency, 1.12 (± 1.17) for phonic tic frequency, 2.88 (± 1.17) for motor tic severity and 1.3 (± 1.26) for phonic tic severity.

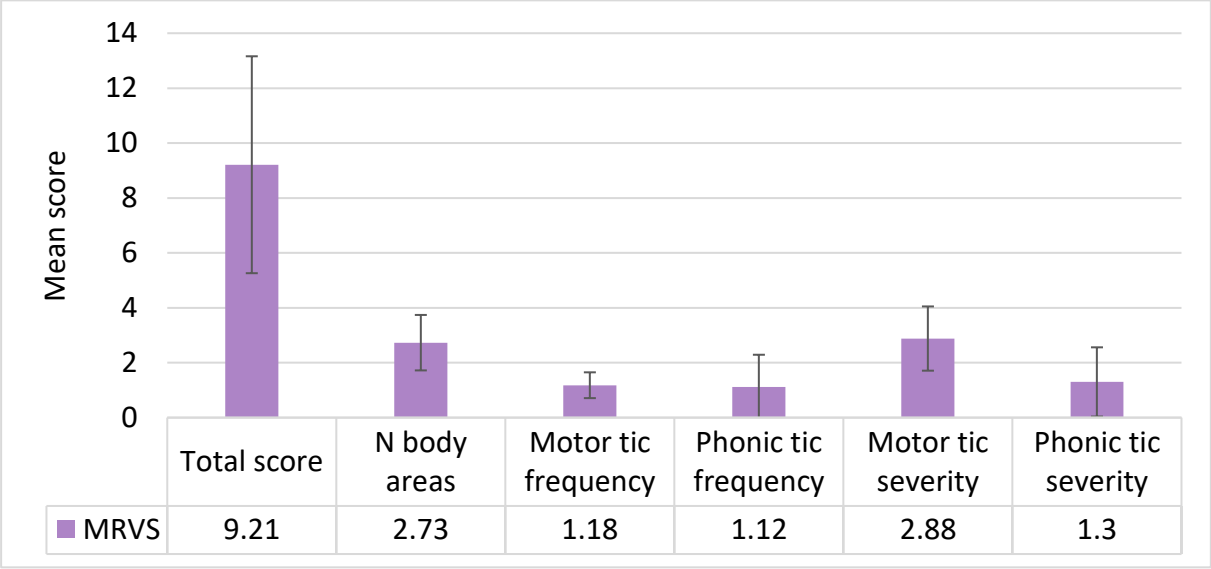


Figure 70. Mean MRVS assessment scores for participants with TS. Error bars represent standard deviation.

Relationship between premonitory urges and tic severity

PUTS score was found to correlate significantly with total YGTSS score, r_s = .579, *p* = .000, and MRVS total score, r_s = .392, *p* = .024. Worse tic severity ratings were associated with worse premonitory urge experiences.

A. **B.**

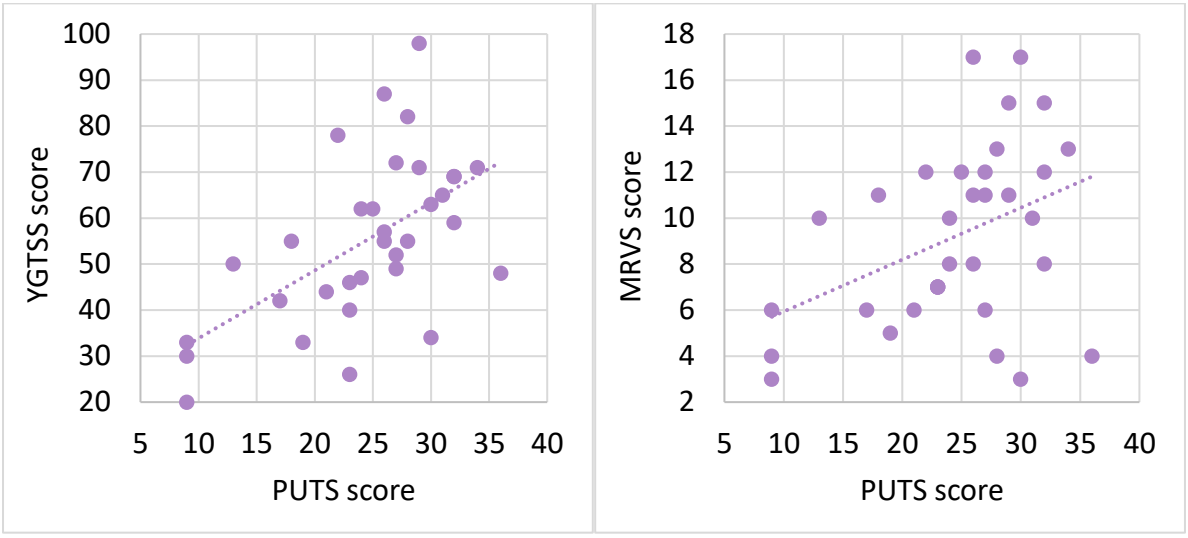


Figure 71. Relationship between total PUTS score and A) YGTSS total score and B) MRVS scores for adults with TS.

YGTSS scores correlated significantly with MRVS total score, r_s = .840, *p* = .000, in accordance with both being measures of tic severity.

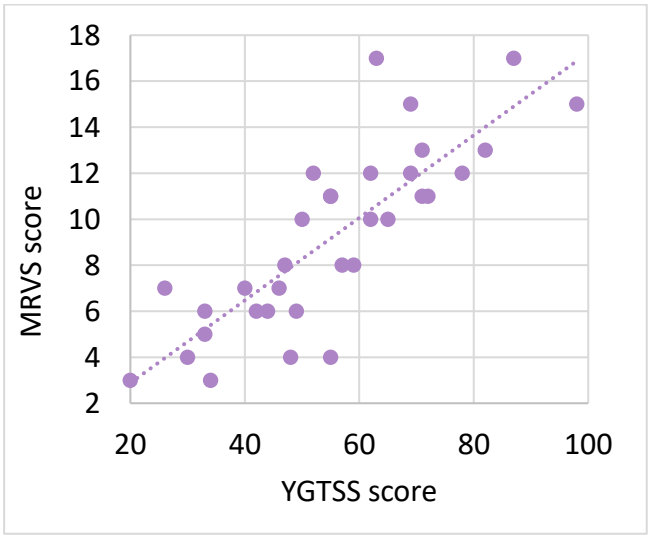


Figure 72. Relationship between total YGTSS and total MRVS scores for TS.

General cognition and urge and tic severity

General cognition

IED

EDS errors

PUTS score correlated significantly with the number of EDS errors, r = -.371, p = .033, but not with the number of pre-EDS errors, r = -.008, p = .964 (log-transformed variables). Lower PUTS scores were associated with making more EDS errors.

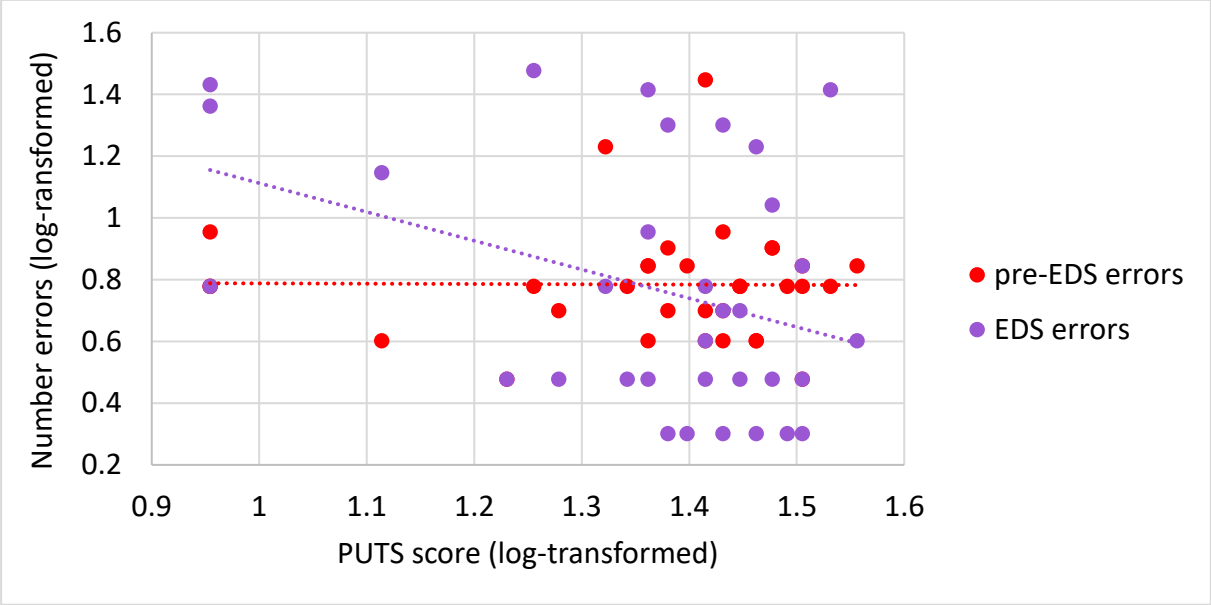


Figure 73. Relationship between PUTS score, pre-EDS errors and EDS errors (log-transformed variables).

Comorbid OCD was found to be associated with higher PUTS scores and fewer EDS errors. Consequently, a partial correlation was undertaken to determine the relationship between PUTS score and EDS errors, whilst controlling for OCD composite score (all log-transformed). Following this, there no longer remained a significant relationship between PUTS scores and EDS errors, r_p = -.190, p = .299.

RVP

Mean Latency

PUTS correlated significantly with RVP mean latency (log-transformed variables), r = -.381, p = .029. A higher PUTS score was associated with faster latency.

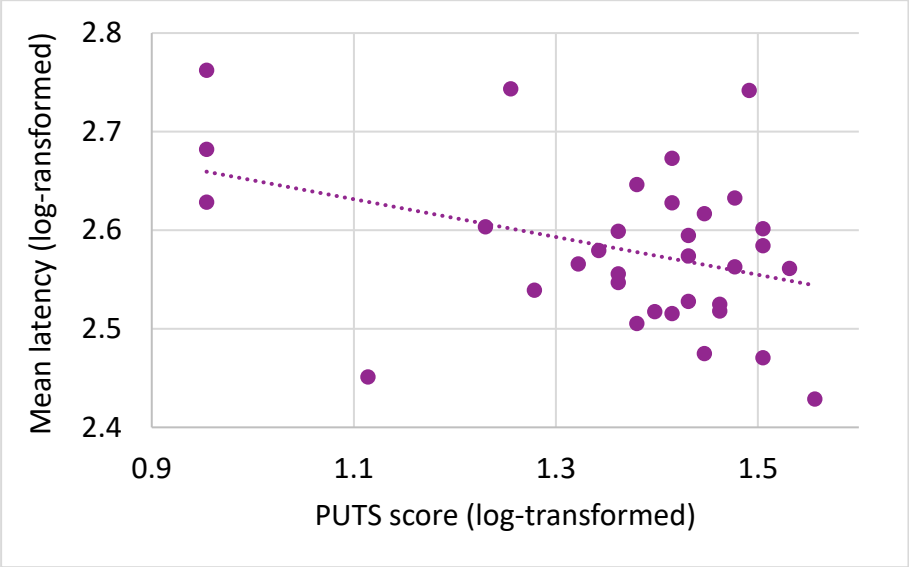


Figure 74. Relationship between PUTS score and RVP mean latency (log-transformed variables).

B'

YGTSS and MRVS total scores correlated significantly with RVP *B'* (log-transformed variables), r = -.416, p = .016 and r = -.377, p = .031, respectively. Lower tic rating severity was associated with better target sensitivity (fewer false alarms).

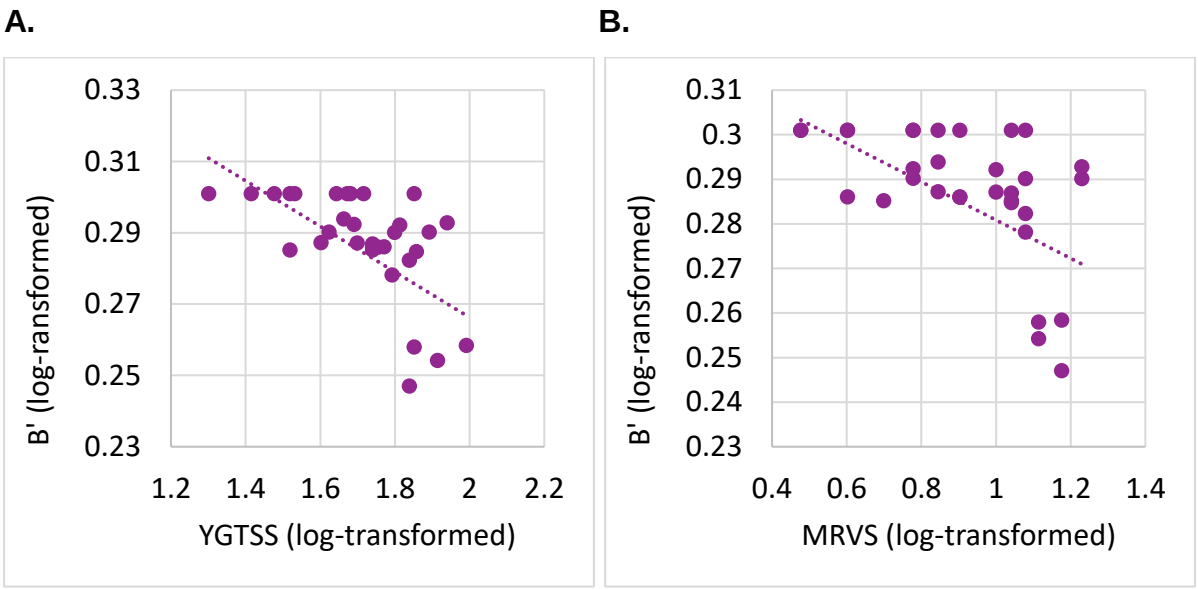


Figure 75. Relationship between RVP *B*' and A) YGTSS score and B) MRVS score (log-transformed variables).

Total false alarms

YGTSS and MRVS total scores correlated significantly with RVP total false alarms (log-transformed variables), $r = .508$, $p = .003$ and $r = .482$, $p = .005$, respectively. Better tic severity was associated with fewer false alarms.

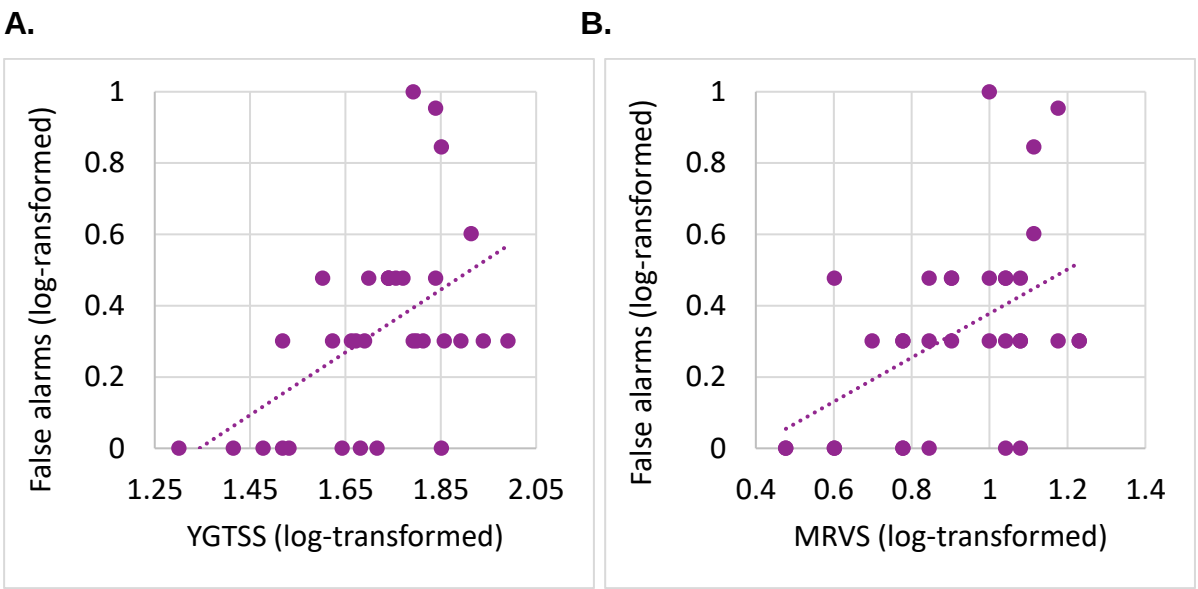


Figure 76. Relationship between RVP total false alarms and A) YGTSS score and B) MRVS score (log-transformed variables).

Neurophysiology and urge and tic severity

Tic control

YGTSS and MRVS total scores correlated significantly with the size of normalised MEPs recorded under instruction to tic freely (log-transformed variables), $r = .433$, $p = .012$ and $r = .363$, $p = .038$, respectively. Worse tic severity was associated with larger normalised MEPs during instruction to tic freely.

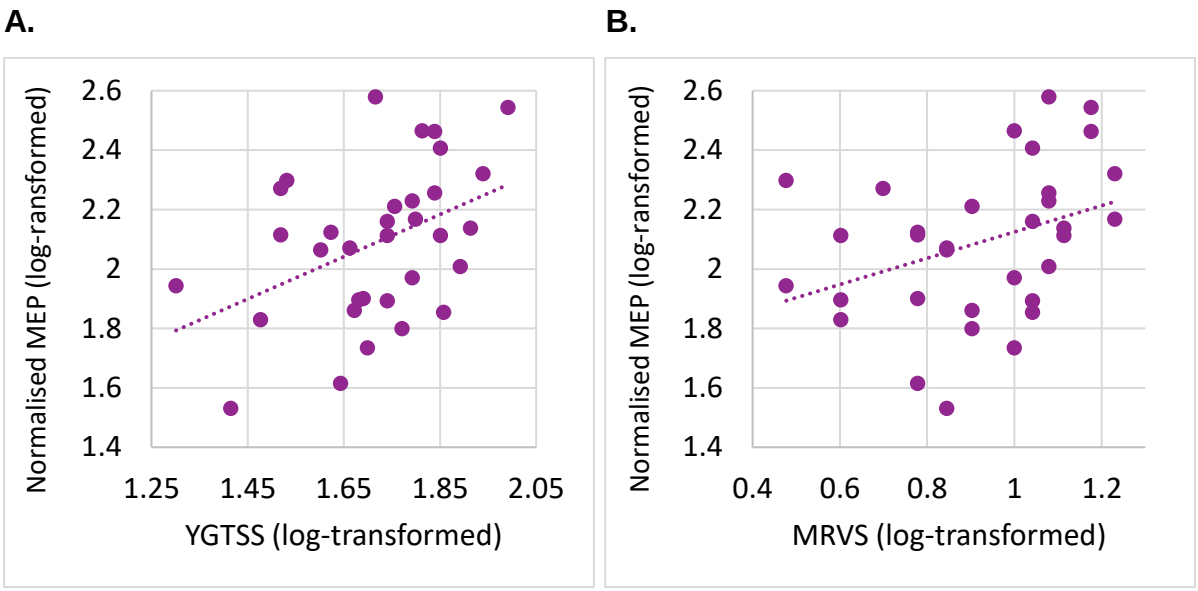


Figure 77. Relationship between normalised MEPs recorded under instruction to tic freely and A) YGTSS score and B) MRVS score (log-transformed variables).

Summary

In our sample of adults with TS the mean PUTS was 24.52 ± 7.1 out of a maximum score of 36, corresponding to marked impairment (≥25 PUTS) (Bloch et al., 2006; Byler et al., 2015; Lewin et al., 2012; Tinaz et al., 2014).

The mean total YGTSS was 55.27 ± 18.1 out of a maximum score of 100; comprised of a combined severity score 24.36 ± 11.72 and an impairment score of 30.91 ± 9.48, each with maximum scores of 50. YGTSS total tic severity and ratings of impairment corresponded to severe impairment (>30 YGTSS) (Bloch et al., 2006; Byler et al., 2015; Lewin et al., 2012; Tinaz et al., 2014).

The mean MRVS score for our sample was 9.21 ± 3.95 out of a maximum score of 25. Motor tics were observed to be more frequent and more severe than vocal tics, as indicated on the YGTSS and the MRVS.

As part of the YGTSS, participants were asked to report age of tic onset and worse tic severity. In our total sample, mean age onset for motor tics was 9.28 years with worst severity at 22.29 years. The mean age onset for vocal tics was 13.55 years with the worst vocal tic severity at 19.76 years.

Thirty participants reported childhood onset ranging from 1-15 years with mean age of onset of motor and vocal tics 7.17 and 11.82 years. Conversely, three participants reported onset in adulthood ranging from 21-46 years with mean age of motor and vocal tics 37.50 and 29.67 years.

We found that worse experiences of premonitory urges, measured by PUTS, was significantly related to worse tic severity. Higher PUTS scores were associated with better cognitive flexibility for habitually learned behaviours, as evident by fewer EDS errors on the CANTAB IED task. Higher PUTS scores were also associated with faster reaction times on the CANTAB RVP task. Worse tic severity was associated with worse sensitivity to targets and consequently, more false alarms.

Finally, worse tic severity scores were associated with significantly larger normalised MEPs recorded during instruction to allow tics to occur.

Table 14. Summary of Chapter 7 Section Urge and tic severity

Chapter Section	Results Summary					Main Finding(s)
	Cognition	**Interoceptive Awareness**	**Clinical Symptoms**	**Neurophysiology**	**Tic control**	
Urge and tic severity	PUTS correlated significantly with RVP mean latency $p = .029$. YGTSS and MRVS total scores correlated significantly with RVP *B'* $p = .016$ and $p = .031$, respectively. YGTSS and MRVS total scores correlated significantly with RVP total false alarms $p = .003$ and $p = .005$, respectively. No other findings between urge or tic severity for any other cognitive measure (all $p > .05$)	No relationship identified between premonitory urges and interoceptive awareness (all $p > .05$) No relationship identified between tic severity and interoceptive awareness (all $p > .05$)	Adults with TS had mean total PUTS score of 24.52 ± 7.1 Adults with TS had mean YGTSS scores of: 55.27 ± 18.1 for total 30.91 ± 9.48 for Impairment 15.36 ± 6.78 for motor 9 ± 6.22 for phonic 24.36 ± 11.72 for Combined Adults with TS had mean MRVS scores of: 9.21 (± 3.95) for total 2.73 ± 1.01) for number of body areas, 1.18 ± 0.47 for motor tic frequency 1.12 ± 1.17 for phonic tic frequency 2.88 ± 1.17 for motor tic severity 1.3 ± 1.26 for phonic tic severity. PUTS score correlated significantly with total YGTSS score, $p = .000$, and MRVS total score, $p = .024$. YGTSS scores correlated significantly with MRVS total score $p = .000$	No relationship identified between premonitory urges or tic severity and motor thresholds, SICI/ICF or SAI (all $p > .05$)	YGTSS and MRVS total scores correlated significantly with the size of normalised MEPs recorded under instruction to tic freely $p = .012$ and $p = .038$, respectively. No other findings between urge or tic severity and tic control measures (all $p > .05$)	In adults with TS there is marked premonitory urge impairment (≥ 24 PUTS) and severe tic severity impairment (>30 YGTSS). We found that worse experiences of premonitory urges was significantly related to worse tic severity. Higher PUTS scores were associated with better cognitive flexibility for habitually learned behaviours, as evident by fewer EDS errors on the CANTAB IED task Higher PUTS scores were also associated with faster reaction times on the CANTAB RVP task. Worse tic severity was associated with worse sensitivity to targets and consequently, more false alarms on the CANTAB RVP task Worse tic severity was associated with significantly larger normalised MEPs recorded during instruction to tic freely.

Psychopathology

Results

Mini Psychiatric Interview (MINI)

Major depressive episode

The prevalence rate of major depressive disorder within the last 2 weeks was 13.33% (current) and 6.66% for recurrent episodes.

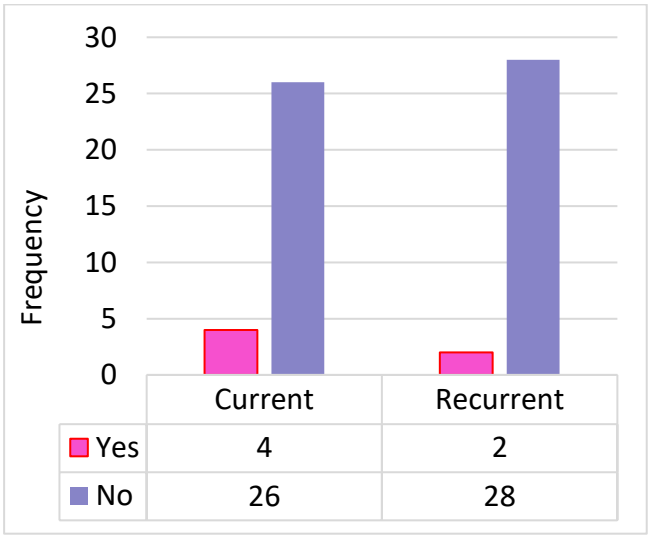


Figure 78. Number of adults with TS that met diagnostic criteria in accordance with the MINI for major depressive episode current and recurrent.

Dysthymia

The prevalence of current dysthymia, over the past 2 years, was 6.66%.

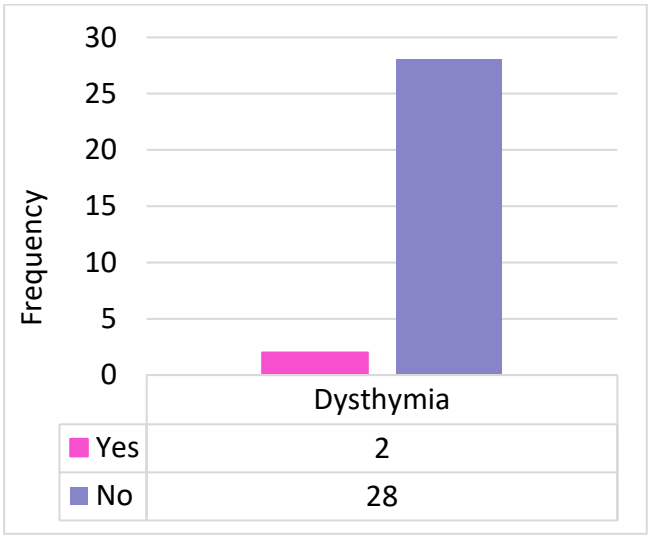


Figure 79. Number of adults with TS that met diagnostic criteria in accordance with the MINI for dysthymia.

Manic episode

There were no current manic episodes reported. The prevalence of past manic episodes was 23.33% and past hypomanic episodes was 13.33%.

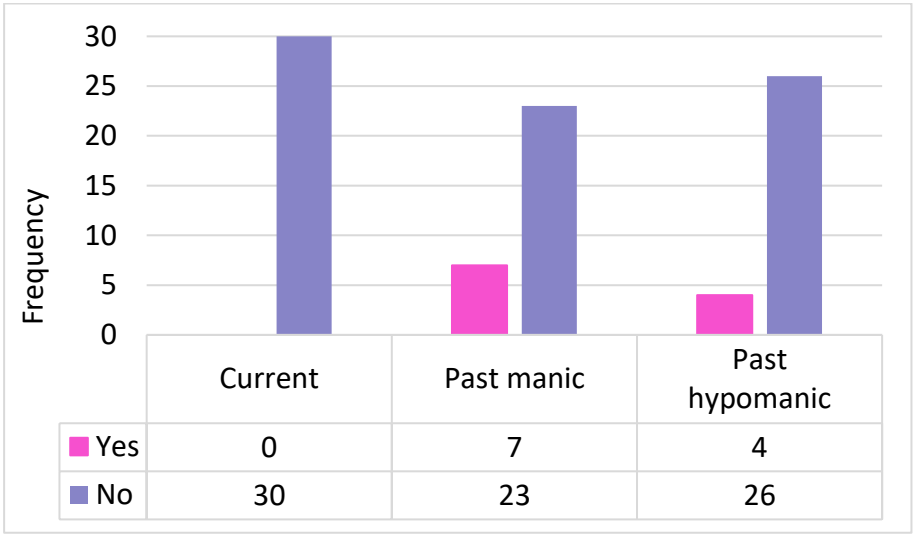


Figure 80. Number of adults with TS that met MINI diagnostic criteria for manic episode current, manic episode past and past hypomanic episode.

Panic disorder

The prevalence of current (last month) panic disorder was 13.33% and lifetime prevalence of 16.66%.

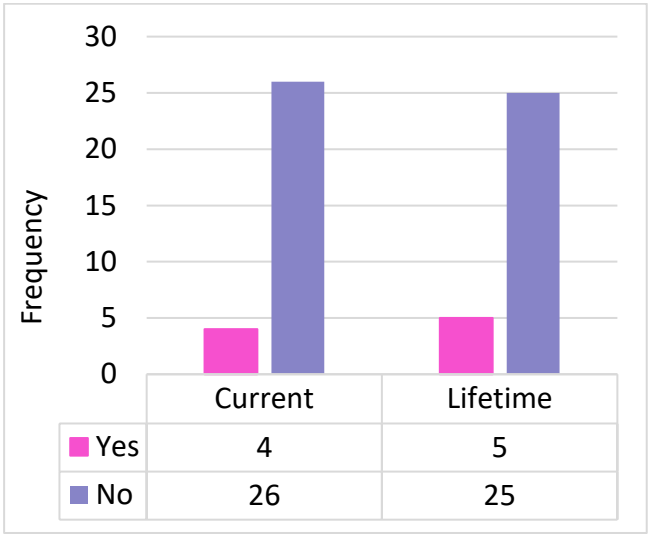


Figure 81. Number of adults with TS that met diagnostic criteria in accordance with the MINI for panic disorder current and lifetime.

Agoraphobia

The prevalence of current agoraphobia was 30%.

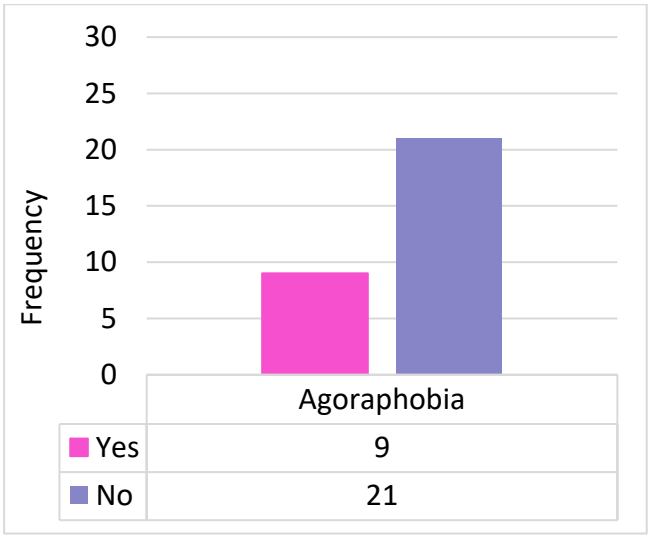


Figure 82. Number of adults with TS that met diagnostic criteria in accordance with the MINI for current agoraphobia.

Obsessive-Compulsive Disorder and Behaviours

The prevalence of current (past month) OCD was 46.66%. Furthermore, the prevalence of current obsessive-compulsive behaviours was 63.33% for obsessions and 70% for compulsions.

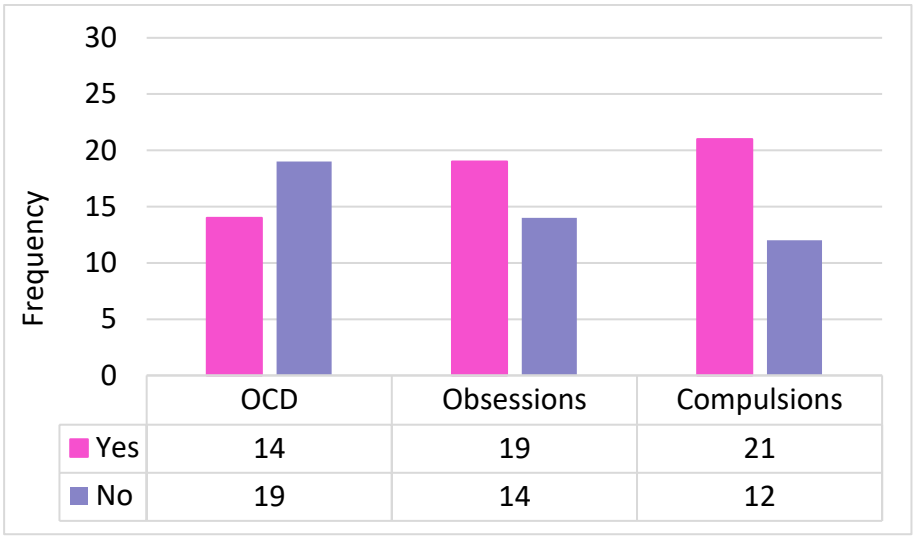


Figure 83. Number of adults with TS that met diagnostic criteria in accordance with the MINI for OCD, obsessions and compulsions.

Social anxiety disorder

The prevalence of current (past month) social anxiety disorder was 10%. Those reaching diagnostic criteria were identified as having non-generalised social anxiety.

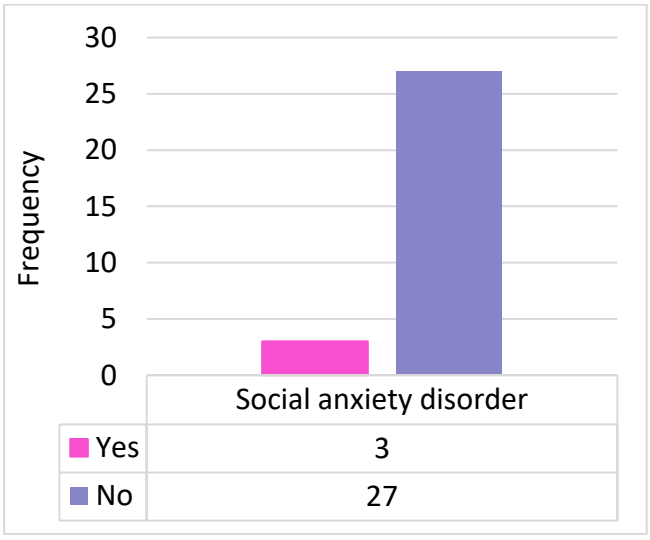


Figure 84. Number of adults with TS that met diagnostic criteria in accordance with the MINI for social anxiety disorder (non-generalised).

Alcohol misuse

The prevalence of current (past 12 months) alcohol dependence was 13.33% and current alcohol abuse was 10%.

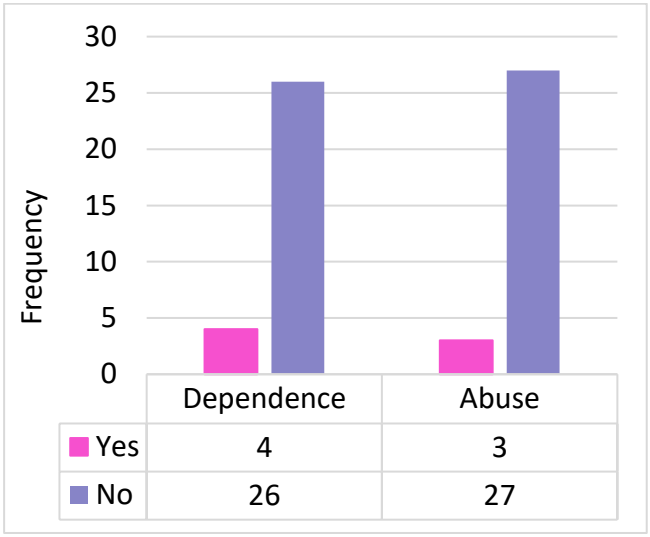


Figure 85. Number of adults with TS that met diagnostic criteria in accordance with the MINI for alcohol misuse with dependence and abuse over the last 12 months.

Psychoactive substances

The prevalence of current (past 12 months) psychoactive substance dependence was 3.33% and current psychoactive substance abuse was 6.66%.

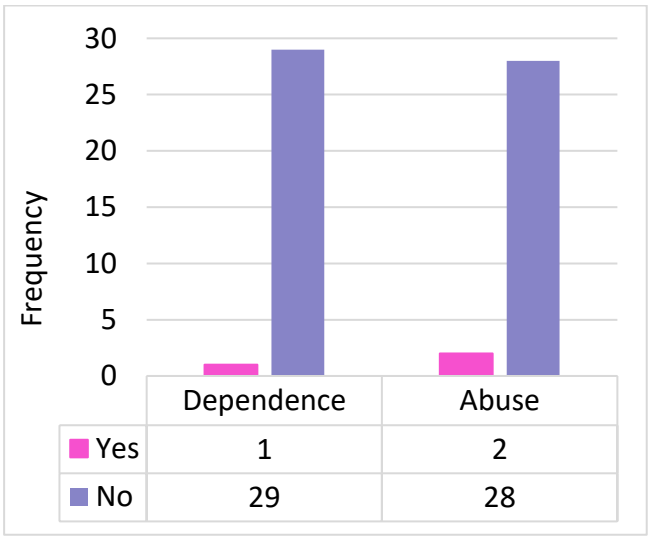


Figure 86. Number of adults with TS that met MINI diagnostic criteria for psychoactive substance dependence and abuse over the last 12 months.

Psychotic disorders

There was no occurrence of current psychotic disorders. The prevalence of psychotic disorders within the lifetime was 10%; upon investigation these were revealed to involve mood disorders with psychotic features.

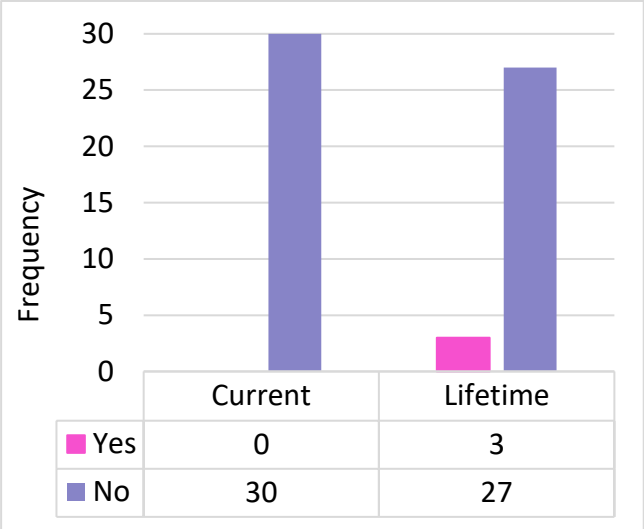


Figure 87. Number of adults with TS that met diagnostic criteria in accordance with the MINI for psychotic disorders current and lifetime.

Generalised anxiety disorder

The prevalence of current (past 6 months) generalised anxiety disorder was 36.66%.

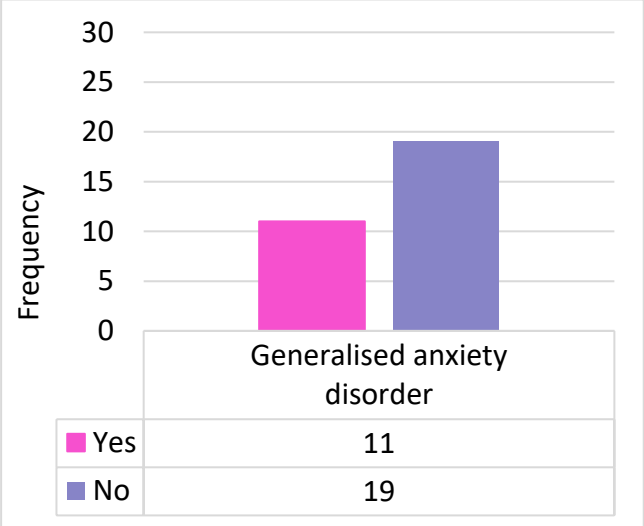


Figure 88. Number of adults with TS that met diagnostic criteria in accordance with the MINI for current generalised anxiety disorder.

Summary

The MINI identified current major depressive disorder in 13.33% and dysthymia 6.66%. There was no current mania but 23.33% reported a previous manic episode and 13.33% a previous hypomanic episode. The prevalence of anxiety disorders was: 36.66% for current generalised anxiety disorder; 13.33% for current and 16.66% for lifetime panic disorder; 30% for current agoraphobia; and 10% for current social anxiety disorder. None of our participants presented with current psychotic disorder whilst 10% reported a previous mood disorder with psychotic features. OCD was present in 46.66% of our sample and currently 63.33% experience obsessions and 70% compulsions that do not reach criteria for diagnosis with OCD. Current alcohol dependence existed in 13.33% and current alcohol abuse in 10%. Prevalence rates of psychoactive substance use was lower, with 3.33% reporting dependence and 6.66% abuse.

Table 15. Summary of Chapter 7 section Psychopathology

Results Summary					**Main Finding**
Mood Disorders	**Anxiety Disorders**	**Psychotic Disorders**	**Comorbidities**	**Substance Misuse**	
13.33% of our sample of adult TS met criteria for current major depressive disorder and 6.66% for dysthymia. There was no current mania but 23.33% reported a previous manic episode and 13.33% a previous hypomanic episode.	The prevalence of anxiety disorders was: 36.66% for current generalised anxiety disorder; 13.33% for current and 16.66% for lifetime panic disorder; 30% for current agoraphobia; and 10% for current social anxiety disorder.	None of our participants presented with current psychotic disorder whilst 10% reported a previous mood disorder with psychotic features.	OCD was present in 46.66% of our sample and currently 63.33% experience obsessions and 70% experience compulsions but do not reach criteria for diagnosis with OCD.	Current alcohol dependence existed in 13.33% and current alcohol abuse in 10%. Prevalence rates of psychoactive substance use was lower, with 3.33% reporting dependence and 6.66% abuse.	Our sample of adults with TS have prevalent psychopathologies and are representative of cases recruited from both clinical and community.

Comorbidities

Attention Deficit Hyperactivity Disorder (ADHD)

Results

ASRS

In our sample of adults TS, the ASRS was used to screen for the presence of likely comorbid ADHD and evaluate ADHD severity. Based on the classification of the ASRS, 20 participants were identified as having ADHD, with all having more severe ADHD symptoms.

A. **B.**

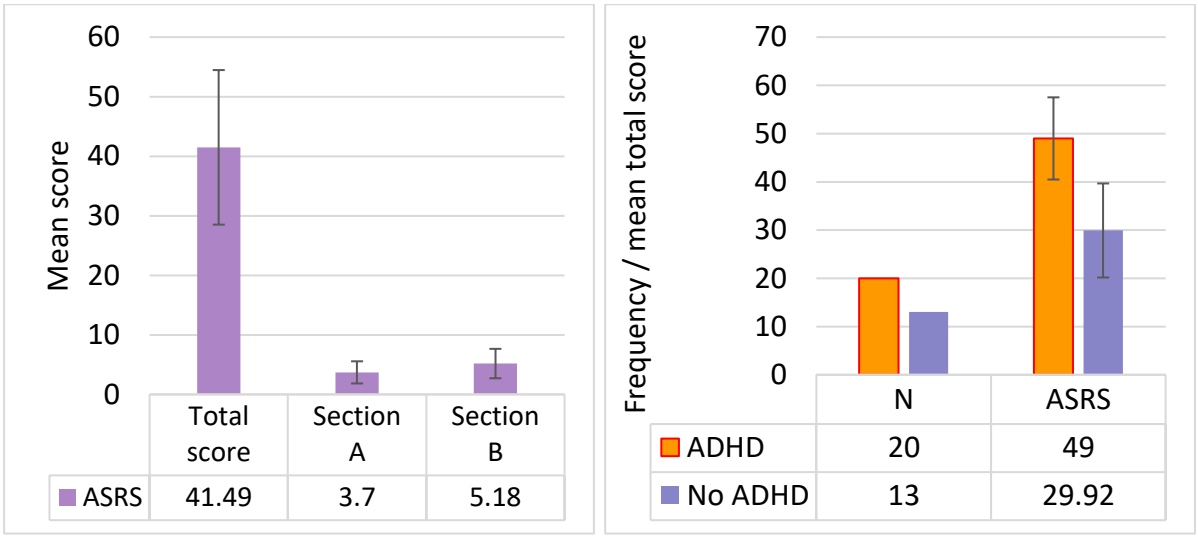


Figure 87. A) Mean ASRS total, section A and section B scores and B) number of adults with TS identified using the ASRS as likely to have ADHD or not, and their respective mean total ASRS scores. Error bars represent standard deviation.

BAARS-IV

In our sample of adult TS, the BAARS-IV was used to explore current ADHD symptoms and domains of impairment including inattention, hyperactivity, impulsivity and sluggish cognitive tempo. The BAARS-IV is tailored to age norms and therefore mean percentile, not raw scores are derived. Our sample of participants had similar levels of impairment across all domains (see below).

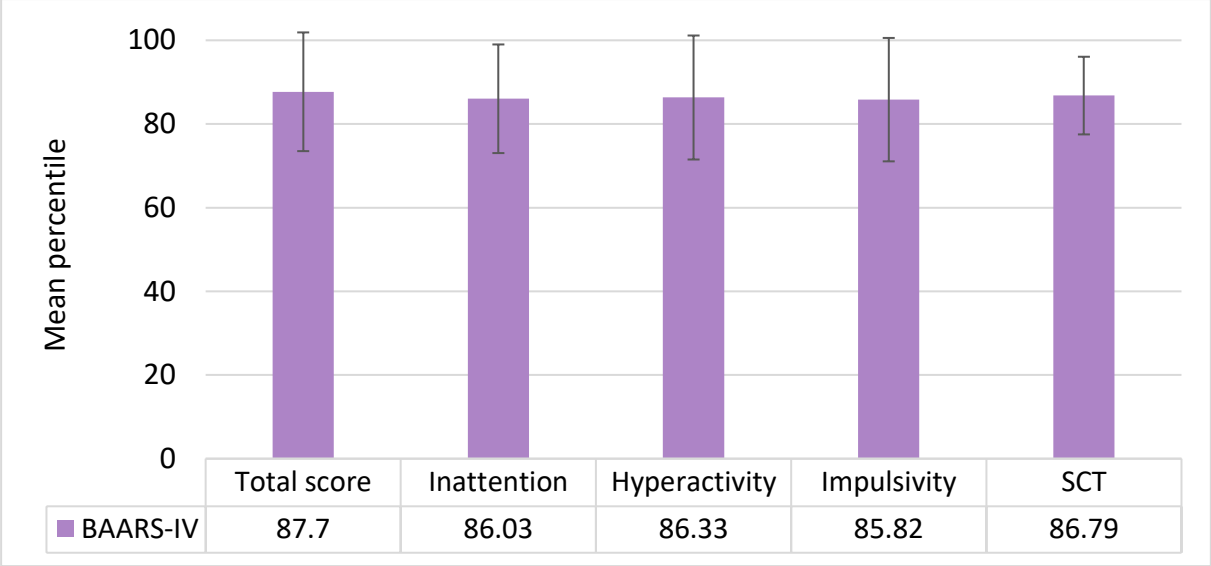


Figure 90. Mean percentile score of the total BAARS-IV assessment and impairment domains of attention, hyperactivity, impulsivity and sluggish cognitive tempo. Error bars represent standard deviation.

Based on the classification of the BAARS-IV, 19 participants were identified as likely to have ADHD.

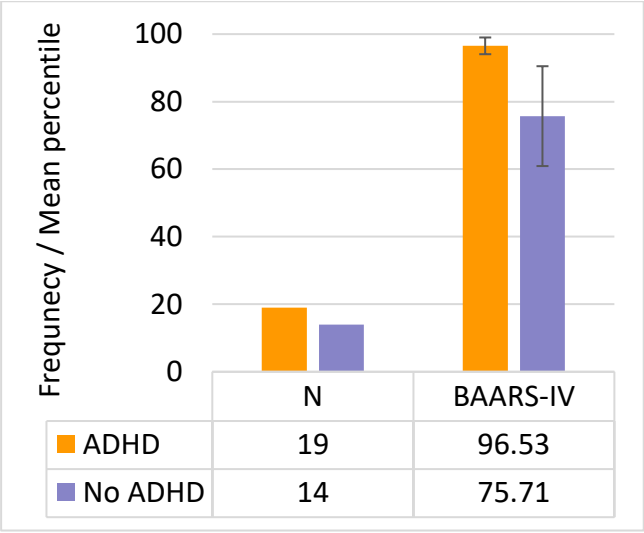
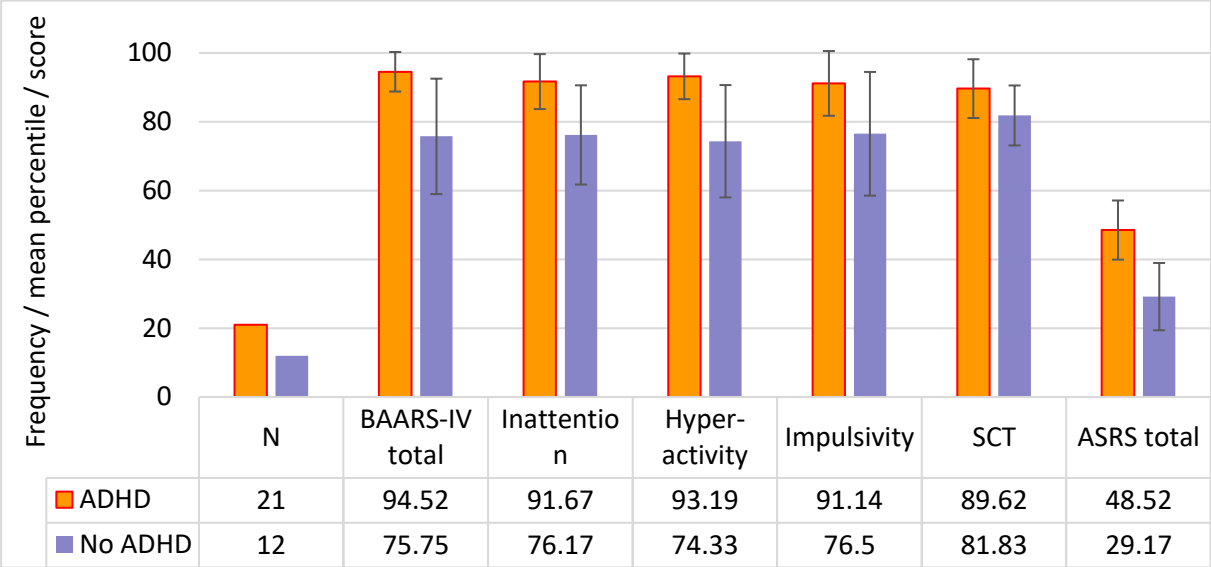


Figure 91. Adults with TS that were identified using the BAARS-IV as likely to have ADHD or not and their respective mean total BAARS-IV percentile scores. Error bars represent standard deviation.

Comorbid ADHD

Classification

Classification of comorbid ADHD was made using both the ASRS and BAARS-IV. Where scales differed (N= 5), classifications were made on an individual basis, including evaluation of attention shown during research sessions. Of the 33 adults with TS, 21 were classified as having comorbid ADHD.



	N	BAARS-IV total	Inattention	Hyper-activity	Impulsivity	SCT	ASRS total
ADHD	21	94.52	91.67	93.19	91.14	89.62	48.52
No ADHD	12	75.75	76.17	74.33	76.5	81.83	29.17

Figure 92. Adults with TS classified with comorbid ADHD and their respective mean scores on ADHD measures. Error bars represent standard deviation.

ADHD composite

In order to encompass all ADHD symptom dimensions for correlational analyses, an ADHD composite measure was created from the sum of each participants' ASRS total score and the BAARS-IV total percentile scores.

Premonitory urges and ADHD

There was no significant difference in PUTS scores in those with and without comorbid ADHD, $U = 98$, $z = -1.05$, $p = .294$, $r = -.18$. Total PUTS score correlated significantly with the ADHD composite measure, $r_s = .390$, $p = .025$, where more severe ADHD symptoms was associated with stronger experience of premonitory urges; remaining significant following Benjamini-Hochberg FDR correction.

A. **B.**

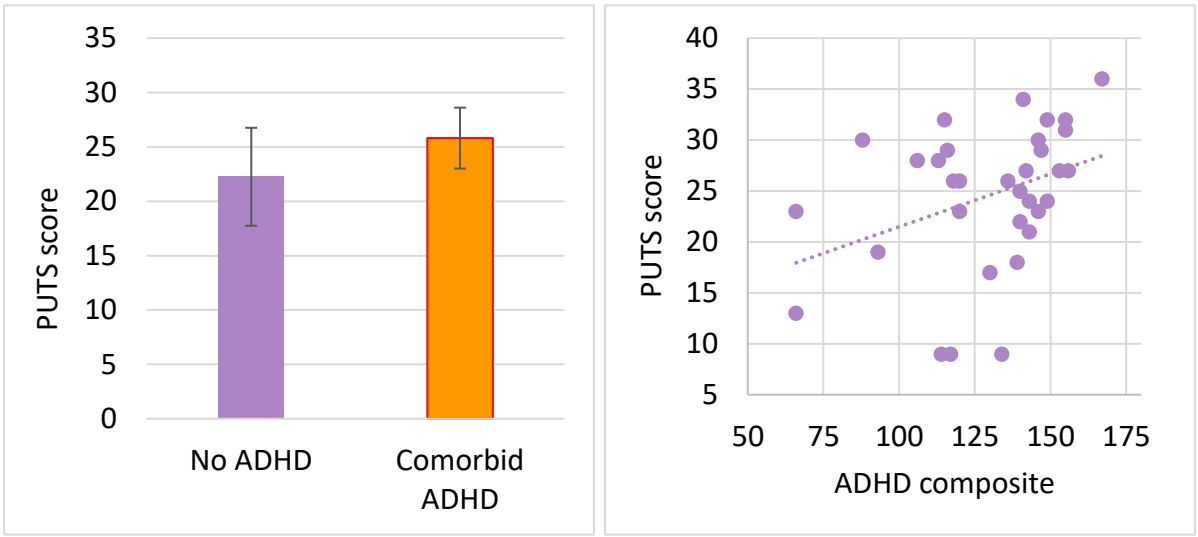


Figure 93. A) Mean PUTS score for adult TS with and without comorbid ADHD and B) relationship between PUTS score and ADHD composite scores. Error bars SEM.

Tic severity and ADHD

There was no significant difference in those with or without comorbid ADHD on the YGTSS total scores, $U = 92$, $z = -1.273$, $p = .203$, $r = -.22$. Additionally, the composite ADHD measure was not significantly correlated with YGTSS total, $r_s = .296$, $p = .094$.

A. **B.**

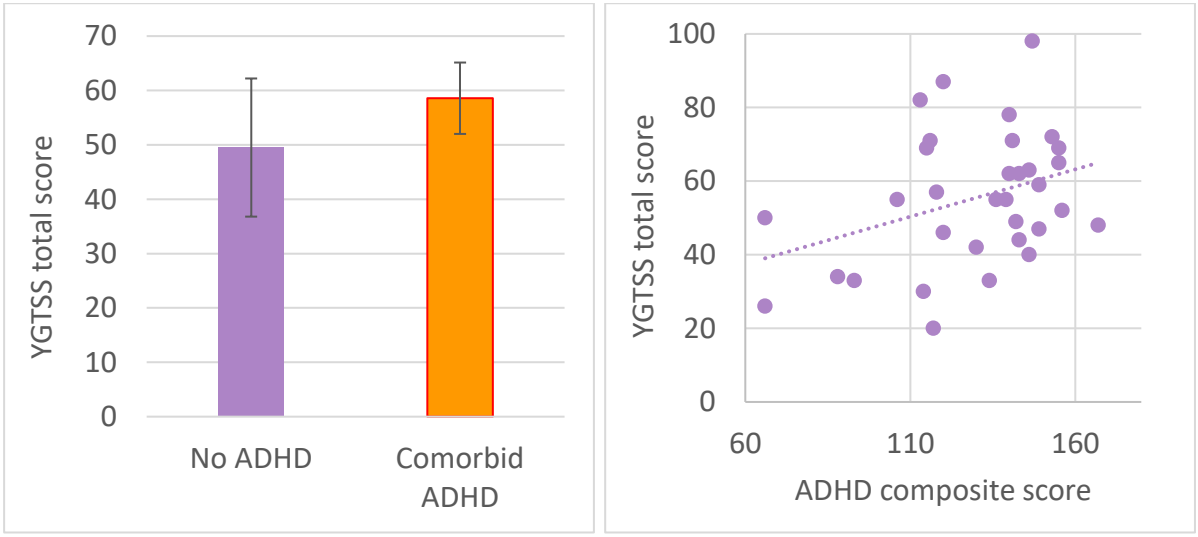


Figure 94. A) Mean YGTSS score for adult TS with and without comorbid ADHD and B) relationship between YGTSS and ADHD composite scores. Error bars SEM.

There was no significant difference in those with or without comorbid ADHD on the tic severity measure of MRVS total score, U = 75, z = -1.917, p = .058, r = -.21. Additionally, the composite ADHD measure was not significantly correlated with MRVS total score, r_s = .300, p = .090.

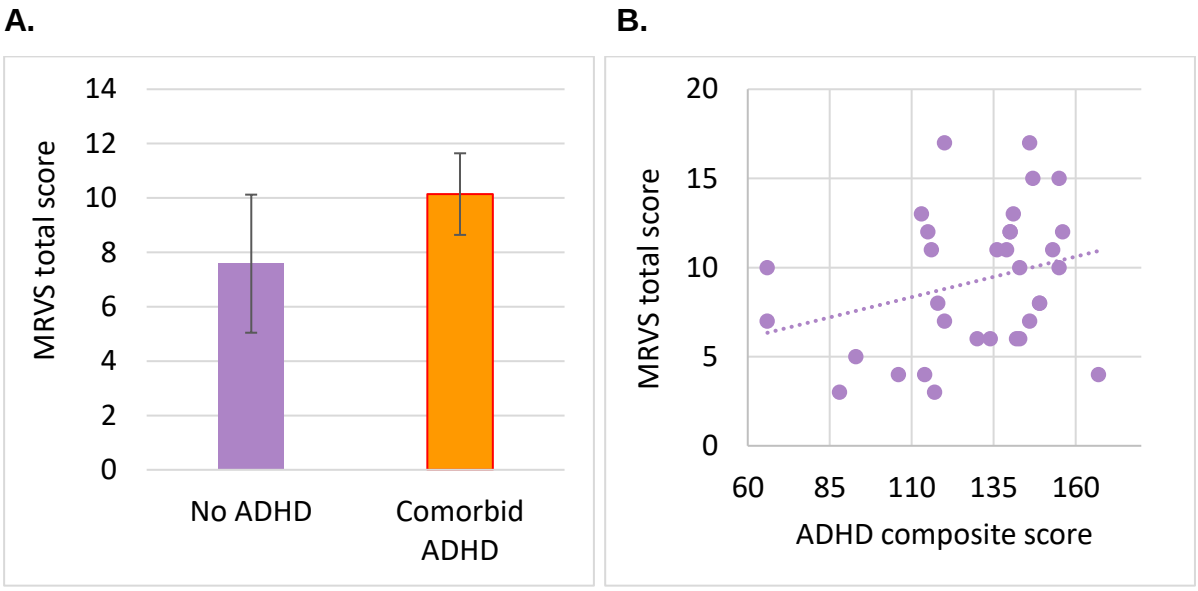


Figure 95. A) Mean MRVS score for adult TS with and without comorbid ADHD and B) the relationship between MRVS and ADHD composite scores. Error bars SEM.

Interoceptive awareness and ADHD

There was no significant difference in interoceptive awareness, t (31) = -.402, p = .690, d = -.150, or resting heart rate, t (31) = -1.278, p = .211, d = -.478, amongst those with and without comorbid ADHD.

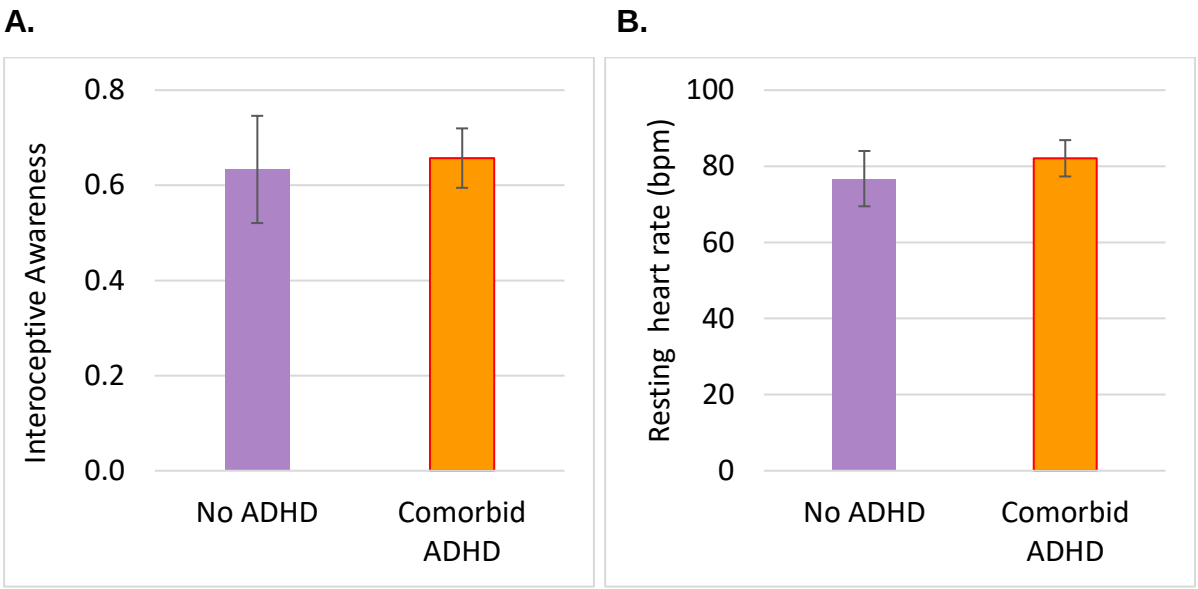


Figure 96. Mean A) interoceptive awareness and B) resting heart rate (bpm) in adult TS with and without comorbid ADHD. Error bars represent SEM.

There was no significant correlation between the ADHD composite score and interoceptive awareness, r_s = .035, p = .845.

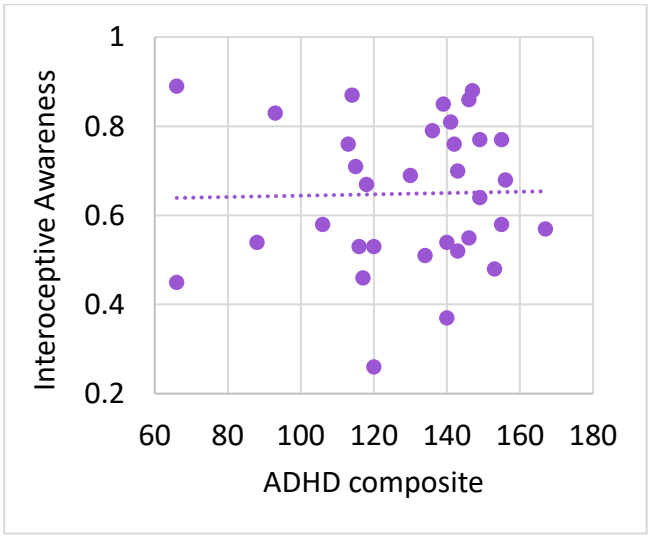


Figure 97. Relationship between interoceptive awareness and the ADHD composite score.

Motor thresholds and ADHD

There were no differences in adult TS with and without comorbid ADHD in the percentage stimulation output needed to reach RMT, U = 116, z = -.376, p = .707, r =

-.07; AMT, *U* = 120.5, *z* = -.206, *p* = .837, *r* = -.04; or 1mV threshold, *U* = 125, *z* = -.038, *p* = .970, *r* = -.01.

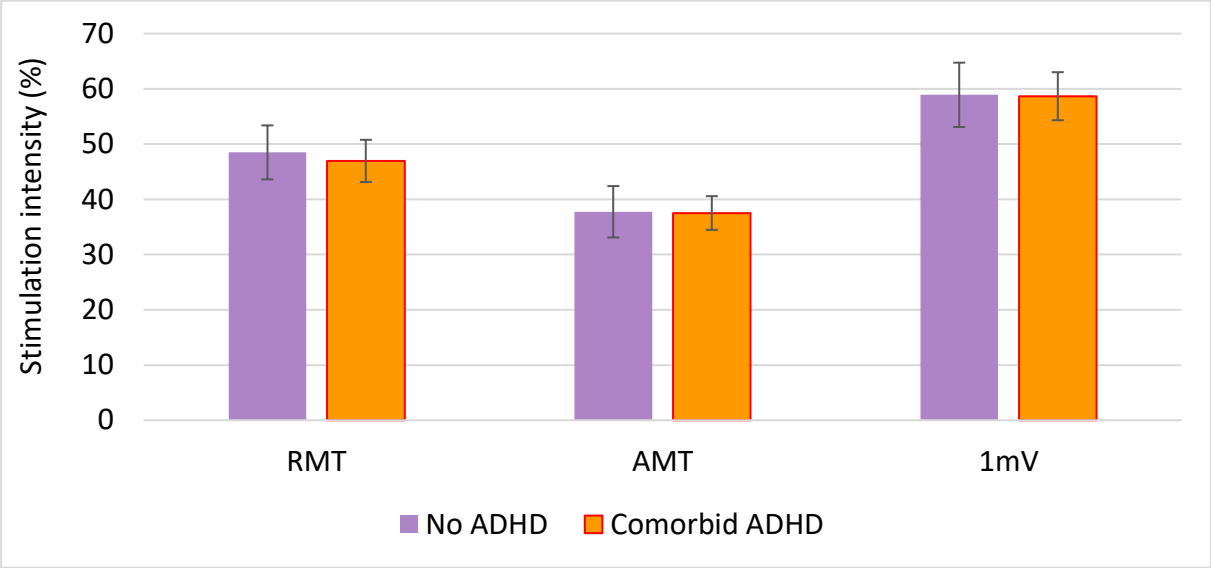


Figure 96. Mean percentage of maximum stimulation intensity needed to reach resting, active and 1mV thresholds for adult TS with and without comorbid ADHD. Error bars represent SEM.

SICI and ADHD

There was a significant main effect of SICI condition on the size of the normalised MEP, *F* (2, 62) = 38.772, *p* = .000, *r* = .62. Planned contrast (repeated) revealed that there was no differences in the size of MEPs at 2 and 3ms *F* (1, 31) = .169, *p* = .684, *r* = .07, and a significant increase in the size of MEPs at 12ms compared to 3ms, *F* (1, 31) = 51.216, *p* = .000, *r* = .79.

There was no significant interaction effect between SICI condition and ADHD comorbidity, *F* (2, 62) = .248, *p* = .781, *r* = .06, and no significant effect of ADHD comorbidity on the size of the normalised MEPs, *F* (1, 31) = .484, *p* = .492, *r* = .12. Those with ADHD appear to have marginally less inhibition and more excitation but this was not significant. All significant results remained following Benjamini-Hochberg FDR correction.

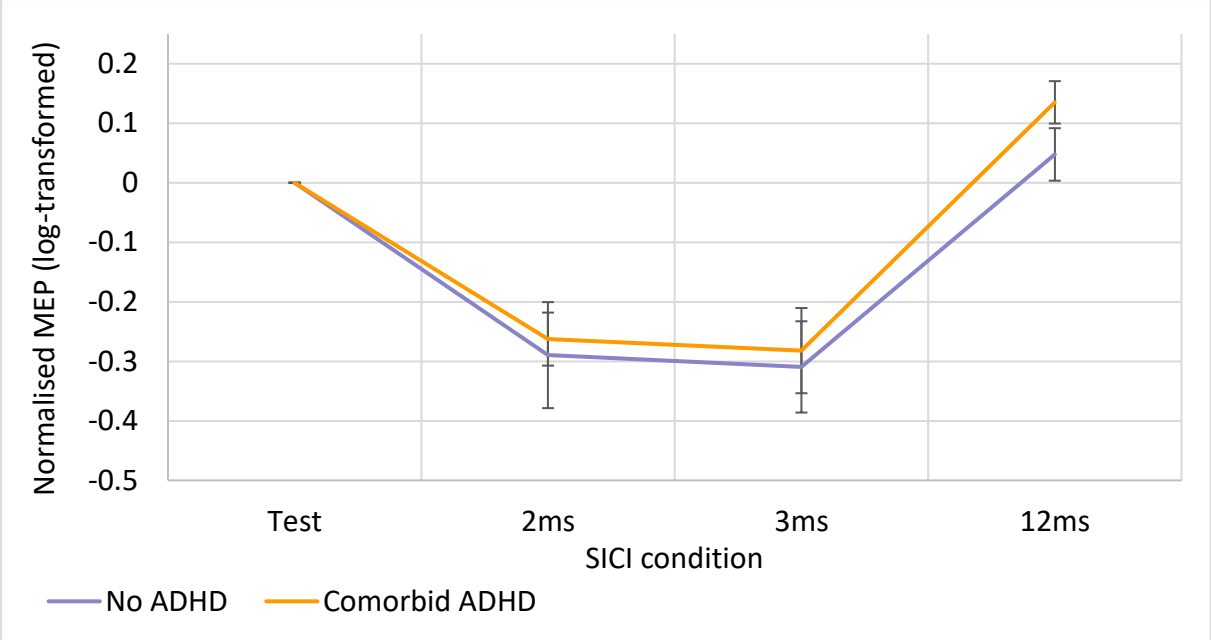


Figure 99. Mean normalised MEPs (log-transformed) elicited at different SICI conditions for adult TS with and without comorbid ADHD. MEPs are normalised to test pulse condition, with negative values representing inhibition and positive facilitation. Error bars represent SEM.

The ADHD composite measure was not significantly correlated with SICI (all $p > .05$) but there was a significant correlation with ICF, $r_s = .423$, $p = .014$, whereby worse ADHD symptoms were associated with enhanced ICF; remaining significant following Benjamini-Hochberg FDR correction.

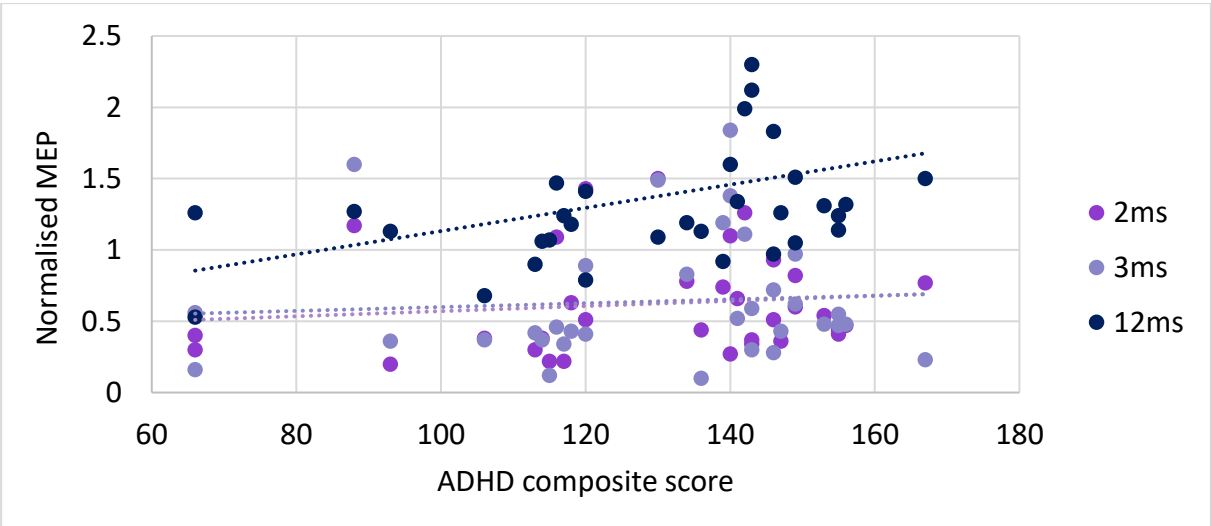


Figure 100. Relationship between size of normalised MEPs elicited during SICI (2 and 3ms) or ICF (12ms) and ADHD composite score.

SAI and ADHD

There was a no significant main effect of SAI condition on the size of the normalised MEP, F (2.469, 71.611) = 1.086, p = .360, r = .07. There was no significant interaction effect between SAI condition and ADHD comorbidity, F (2.469, 71.611) = .588, p = .593, r = .09, and no significant effect of ADHD comorbidity on the size of the normalised MEPs, F (1, 29) = .008, p = .928, r = .02.

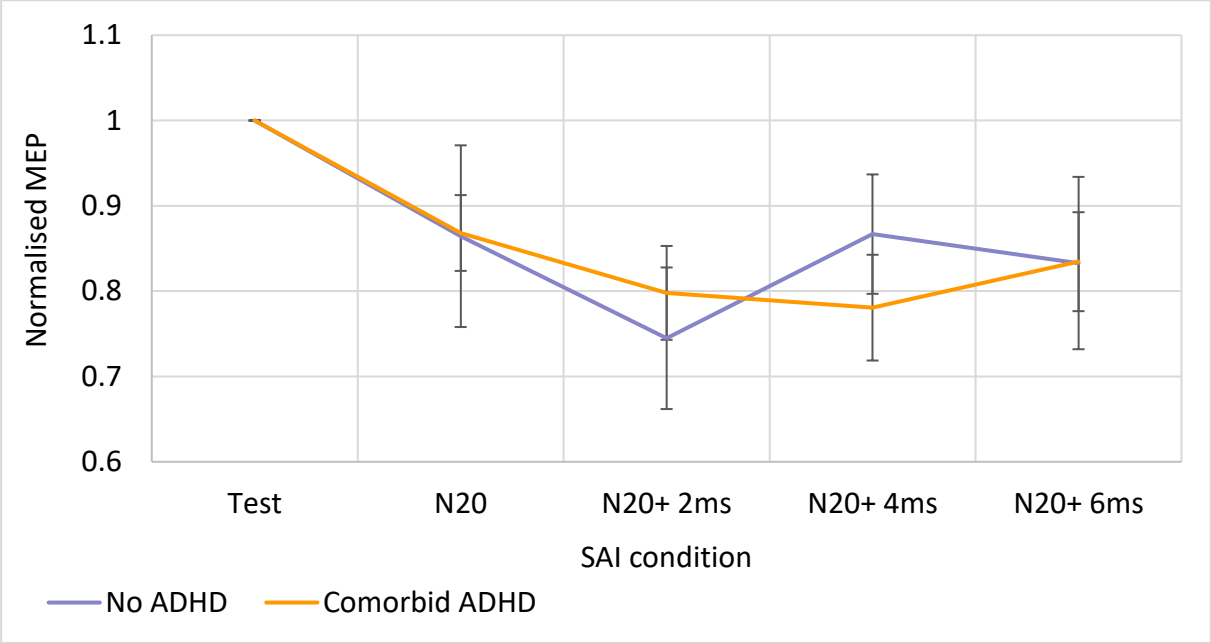


Figure 101. Mean normalised MEPs elicited at test only and N20, N20^{+2ms}, N20^{+4ms} and N20^{+6ms} intervals, for adult TS with and without comorbid ADHD. MEPs are normalised to test pulse condition, with negative values representing inhibition and positive facilitation. Error bars represent SEM.

There were no significant correlations between ADHD composite score and SAI (all p > .05).

ADHD and relationship to cognition

ADHD composite score was significantly related to number of CPT task perseverative errors, r = -.373 p = .035; remaining significant following Benjamini-Hochberg FDR correction. Higher scores on the ADHD composite score was associated with fewer perseverative errors.

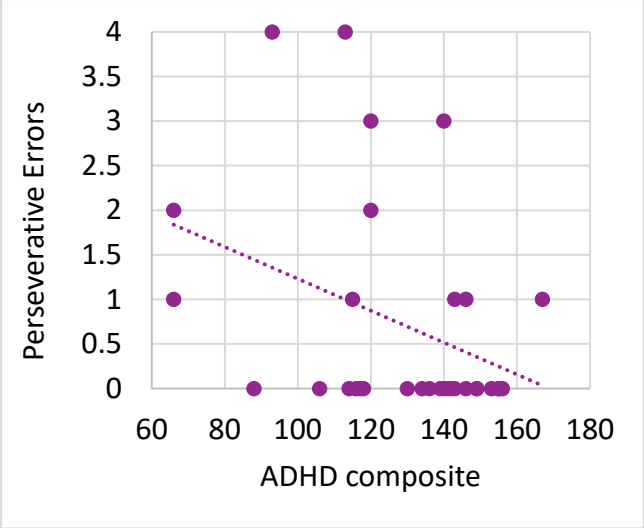


Figure 102. Relationship between the mean perseverative errors on the CPT task and mean ADHD composite score.

Summary

Assessment with the BAARS-IV and ASRS were undertaken and twenty-one participants, 64% of our sample, were identified as likely having comorbid ADHD. Scores were similar across the BAARS-IV subscales. Furthermore, ADHD composite scores were found to be significantly associated with PUTS score, whereby the more severe the ADHD symptoms, the stronger the experience of urges. There were no differences amongst those with and without likely comorbid ADHD on PUTS scores and there was no relationship between ADHD and tic severity.

Individuals with likely comorbid ADHD appeared to have less SICI and more ICF, however, this was not significant. Additionally, more severe ADHD symptoms were related significantly to enhanced ICF whilst SAI levels in TS were unaffected by comorbid ADHD.

Comorbid ADHD was not related to interoceptive awareness. Worse ADHD symptoms were associated with significantly fewer perseverative errors on the CPT task. However there were no differences in the number of perseverative errors made by those with and without comorbid ADHD.

Table 16. Summary of Chapter 7 section Comorbities ADHD

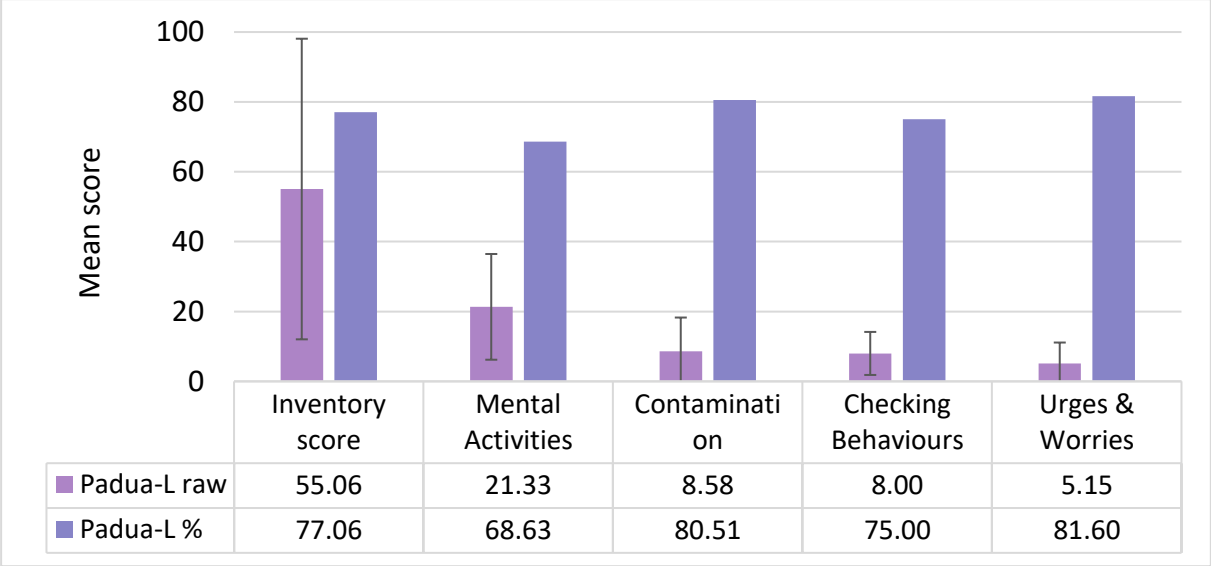
Chapter Section	Results Summary					Main Finding(s)
	Cognition	**Interoceptive Awareness**	**Clinical Symptoms**	**Neurophysiology**	**Tic control**	
Comorbidities - ADHD	ADHD composite score was significantly related to number of CPT task perseverative errors, *p* = .035; but no difference in the number of perseverative errors made for those with and without likely comorbid ADHD.	There was no significant difference in interoceptive awareness *p* = .690 or resting heart rate, *p* = .211, amongst those with and without comorbid ADHD. There was no significant correlation between the ADHD composite score and interoceptive awareness, *p* = .845.	Assessment with the BAARS-IV and ASRS were undertaken and twenty-one participants, 64% of our sample, were identified as likely to have comorbid ADHD. Mean scores were similar across the BAARS-IV subscales. There was no significant difference in PUTS scores in those with and without comorbid ADHD, *p* = .294. Total PUTS score correlated significantly with the ADHD composite measure, *p* = .025. There was no significant difference in those with or without comorbid ADHD on the YGTSS total scores *p* = .203 and no relationship between ADHD composite measure and YGTSS total score, *p* = .094. There was no significant difference in those with or without comorbid ADHD on MRVS total score *p* = .058 and no relationship between composite ADHD score and MRVS total score, *p* = .090.	There were no differences in adult TS with and without comorbid ADHD in the percentage stimulation output needed to reach RMT *p* = .707, AMT *p* = .837 or 1mV threshold *p* = .970. There was no significant interaction effect between SICI condition and ADHD comorbidity, *p* = .781 and no effect of ADHD comorbidity on the size of normalised MEPs *p* = .492. ADHD composite was not related to SICI (all *p* > .05) but there was a significant correlation with ICF, *p* = .014 There was no relationship between SAI condition and ADHD comorbidity, *p* = .593 and no significant effect of ADHD comorbidity on the size of the normalised MEP *p* = .928 There were no significant correlations between ADHD composite scores and SAI (all *p* > .05). .	No relationship identified between ADHD (comorbidity or composite score) and mechanisms of tic control (all *p* > .05)	64% of our sample, were identified as likely to have comorbid ADHD. The more severe the ADHD symptoms, the stronger the experience of urges. There were no differences amongst those with and without likely comorbid ADHD on PUTS scores and there was no relationship between ADHD symptoms and tic severity. There were no differences amongst those with likely comorbid ADHD and SICI. More severe ADHD symptoms were related significantly to enhanced ICF. SAI levels in TS were unaffected by comorbid ADHD. Comorbid ADHD was not related to interoceptive awareness. Whilst worse ADHD symptoms were associated with significantly fewer perseverative errors on the CPT task, comorbid ADHD did not affect the number of perseverative errors made.

Obsessive Compulsive Disorder (OCD)

Results

Padua-L inventory

The Padua-L inventory was used to assess comorbidity presence and symptom severity of core obsessive-compulsive features such as impaired control over mental activities, contamination, checking behaviours and urges and worries. Scores were highest for contamination and urges and worries core obsessive-compulsive features; raw scores were normalised to reflect discrepancies in the subscale item weightings, (important for examining % of total possible score).



	Inventory score	Mental Activities	Contamination	Checking Behaviours	Urges & Worries
Padua-L raw	55.06	21.33	8.58	8.00	5.15
Padua-L %	77.06	68.63	80.51	75.00	81.60

Figure 103. Mean scores for the total Padua-L inventory score and each of the subscales, presented as a raw score and as a percentage of the total possible score. Error bars represent standard deviation.

A total disturbance raw score of 60 or more on the Padua-L inventory is indicative of symptom severity consistent with likely OCD. Based on the classification of the Padua-L inventory, 11 participants were identified as likely to have comorbid OCD.

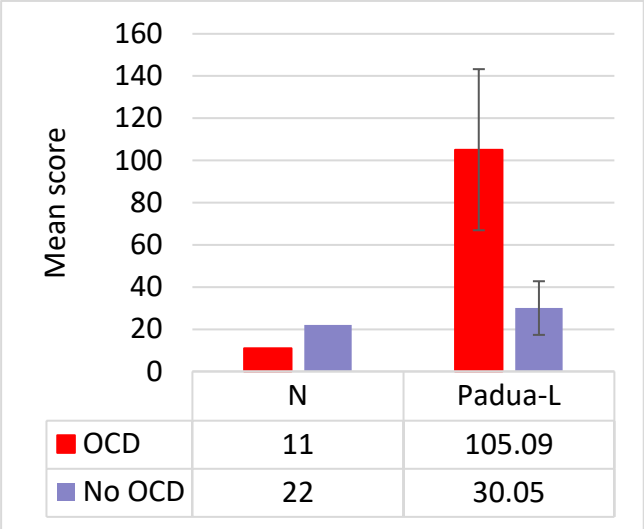
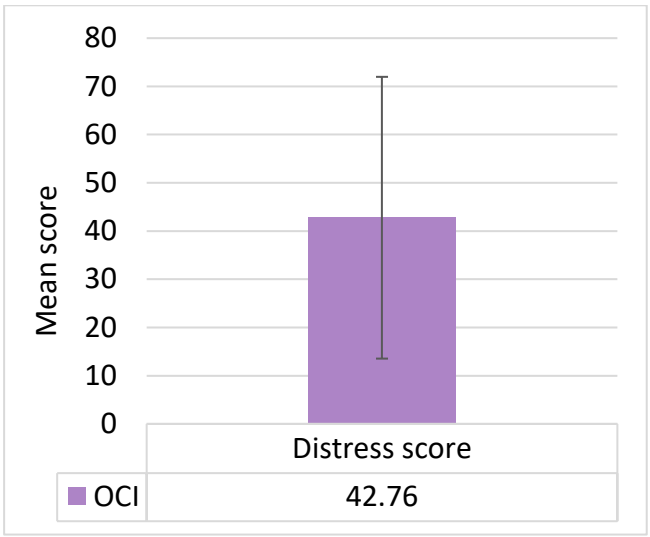


Figure 104. Number of adults with TS that were identified using the Padua-L as likely to have comorbid OCD or not, with their respective mean total Padua-L disturbance scores. Error bars represent standard deviation.

Obsessive-compulsive inventory

In our sample of adult TS, the OCI was used to calculate an overall mean distress score and composite subscale scores to assess the severity of obsessive-compulsive symptoms in relation to washing, checking, doubting, ordering, obsessing, hoarding and mental neutralising. The highest subscale scores were related to doubting, ordering and obsessions.

A.



B.

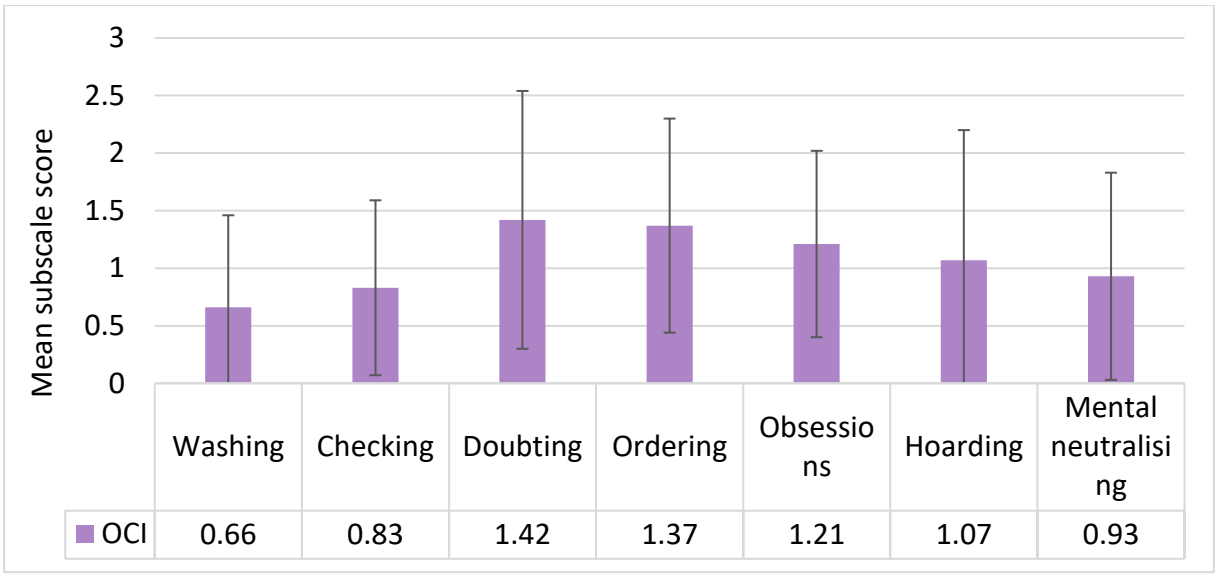


Figure 105. Mean A) total distress score and B) subscale scores derived from the OCI. Error bars represent standard deviation.

A total distress score of 42 or more or a mean score of 2.5 or more in any subscale is indicative of OCD. Based on the classification of the OCI, 12 participants were identified as likely to have OCD.

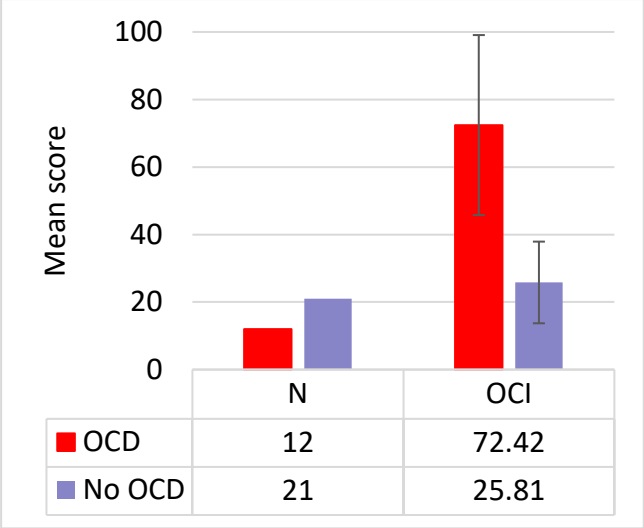


Figure 106. Number of adults with TS that were identified using the OCI as likely to have OCD or not and their respective mean total OCI distress scores. Error bars represent standard deviation.

Yale Brown Obsessive Compulsive Scale

The Y-BOCS was used to measure OCD symptom severity, calculating a score for the severity of obsessions and compulsions. A total Y-BOCS score is calculated by adding these scores.

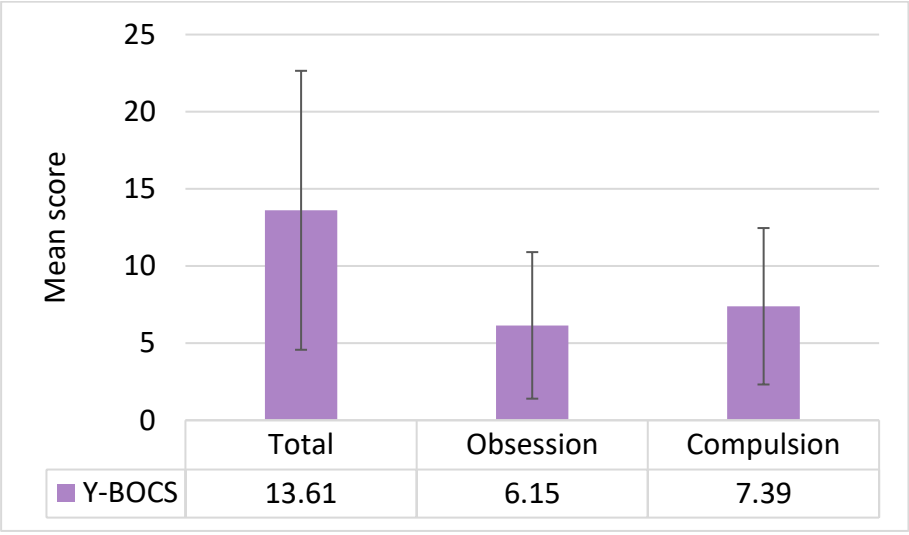
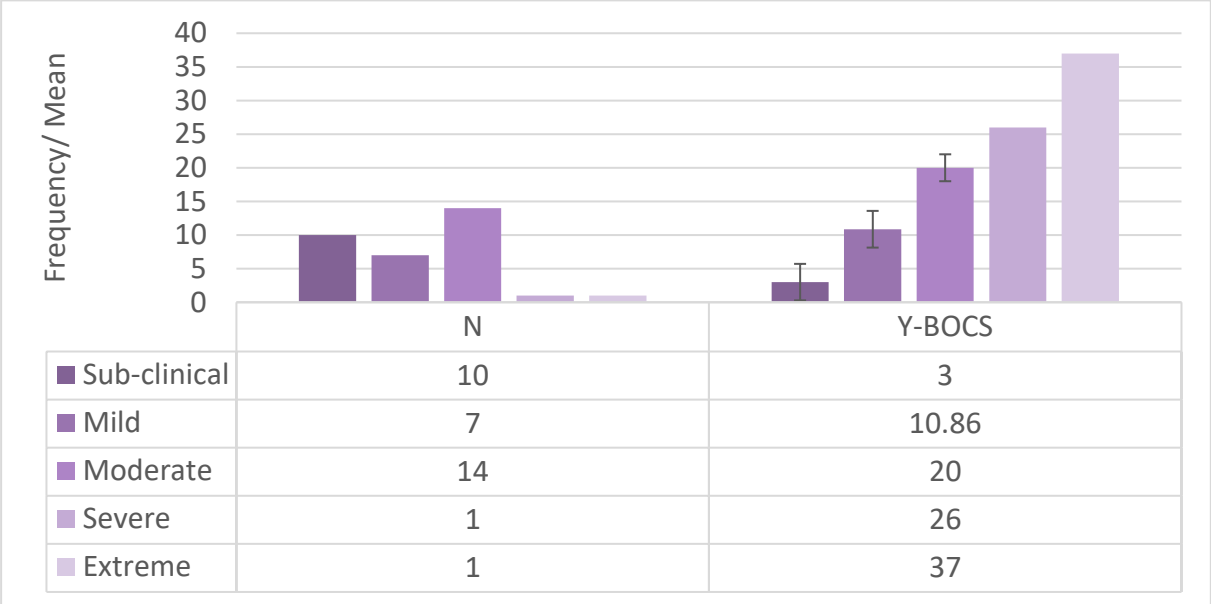


Figure 107. Mean Y-BOCS total, obsession and compulsion scores. Error bars represent standard deviation.

Scores on the Y-BOCS between 0–7 are considered nonclinical, 8-15 mild, 16-23 moderate, 24–31 severe and 32–40 are considered extreme. Based on the classification of the Y-BOCS, 23 participants were identified as having OCD symptoms within the clinical range, consistent with likely OCD, and 10 with sub-clinical OCD symptoms.



	N	Y-BOCS
Sub-clinical	10	3
Mild	7	10.86
Moderate	14	20
Severe	1	26
Extreme	1	37

Figure 108. Mean number of adults TS with different OCD symptom severity classifications and their respective mean total Y-BOCS scores. Error bars represent standard deviation.

Comorbid OCD

Classification

Classification of comorbid OCD was made using all OCD symtom severity assessments. Where likely OCD was evident in every scale, participants were deemed to have comorbid OCD. Where scales differed, classifications were made on an individual basis with weighting given to the number of scales indicating likely OCD and how near the cut-off criteria participants were. Of the 33 adults with TS, 21 were classified as having comorbid OCD.

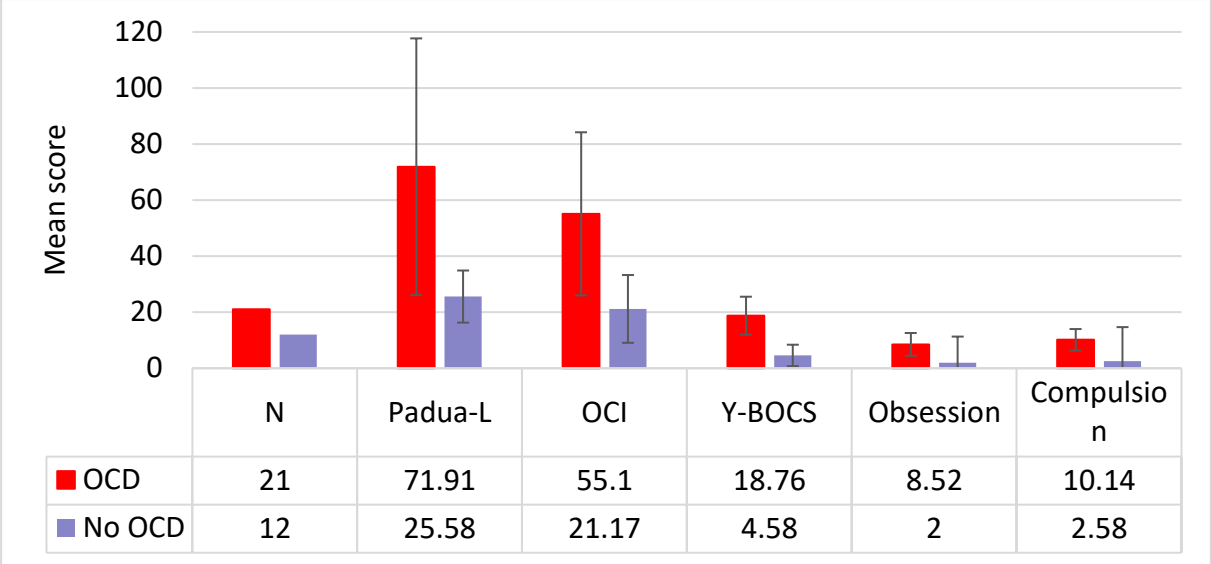


Figure 109. Number of adult TS with and without comorbid OCD and their respective mean total Padua-L, OCI and Y-BOCS scores alongside Y-BOCS obsession and compulsion scores. Error bars represent standard deviation.

OCD composite

In order to encompass all OCD symptom dimensions for correlational analyses, an OCD composite measure was created from the sum of each participants' Padua-L inventory score, OCI distress score and total Y-BOCS score.

Clinical symptoms

Premonitory urges

TS participants with likely comorbid OCD had significantly higher PUTS scores, U = 60.50, z = -2.456, p = .013, r = -.43, than those without comorbid OCD. PUTS scores correlated significantly with the OCD composite measures, r_s = .529, p = .002, whereby stronger experiences of premonitory urges was associated with more severe OCD symptoms. Results remained significant following Benjamini-Hochberg FDR correction.

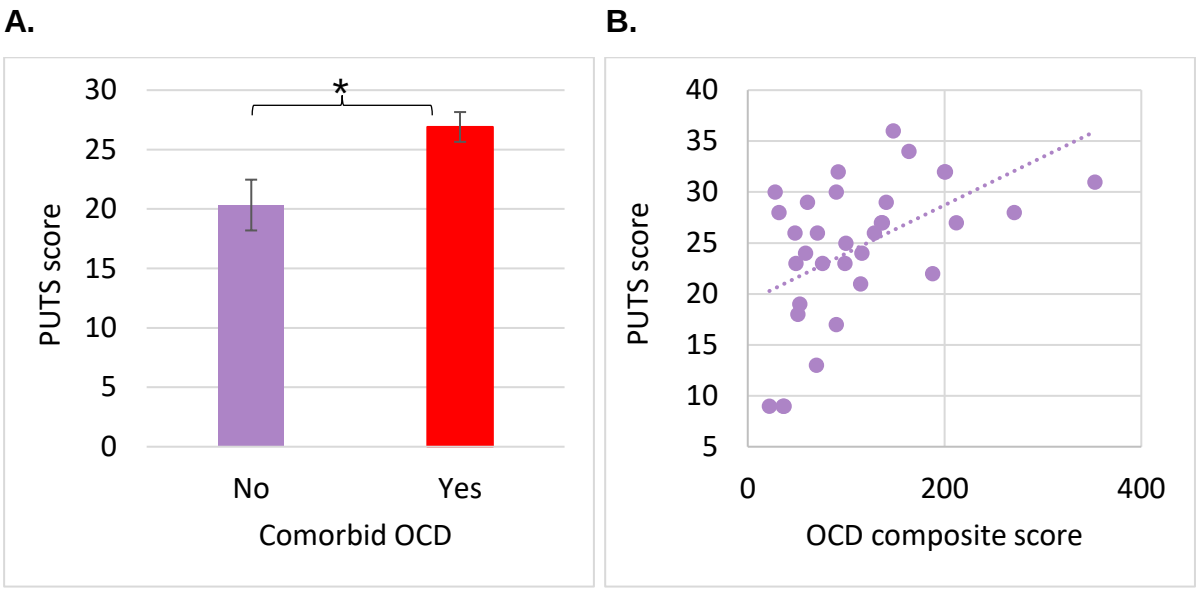


Figure 110. A) Mean PUTS score for adult TS with and without comorbid OCD and B) relationship between PUTS score and OCD composite score. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Tic severity

TS participants with likely comorbid OCD were found to have significantly higher YGTSS total scores, U = 47.5, z = -2.940, p = .002, r = -.51, and MRVS total scores, U = 58.5, z = -2.537, p = .010, r = -.44, than those without comorbid OCD. Furthermore, YGTSS total score significantly correlated with the OCD composite, r_s = .600, p = .000, as did the MRVS total score, r_s = .548, p = .001. More severe tic severity was associated with more severe OCD symptoms. Results remained significant following Benjamini-Hochberg FDR correction.

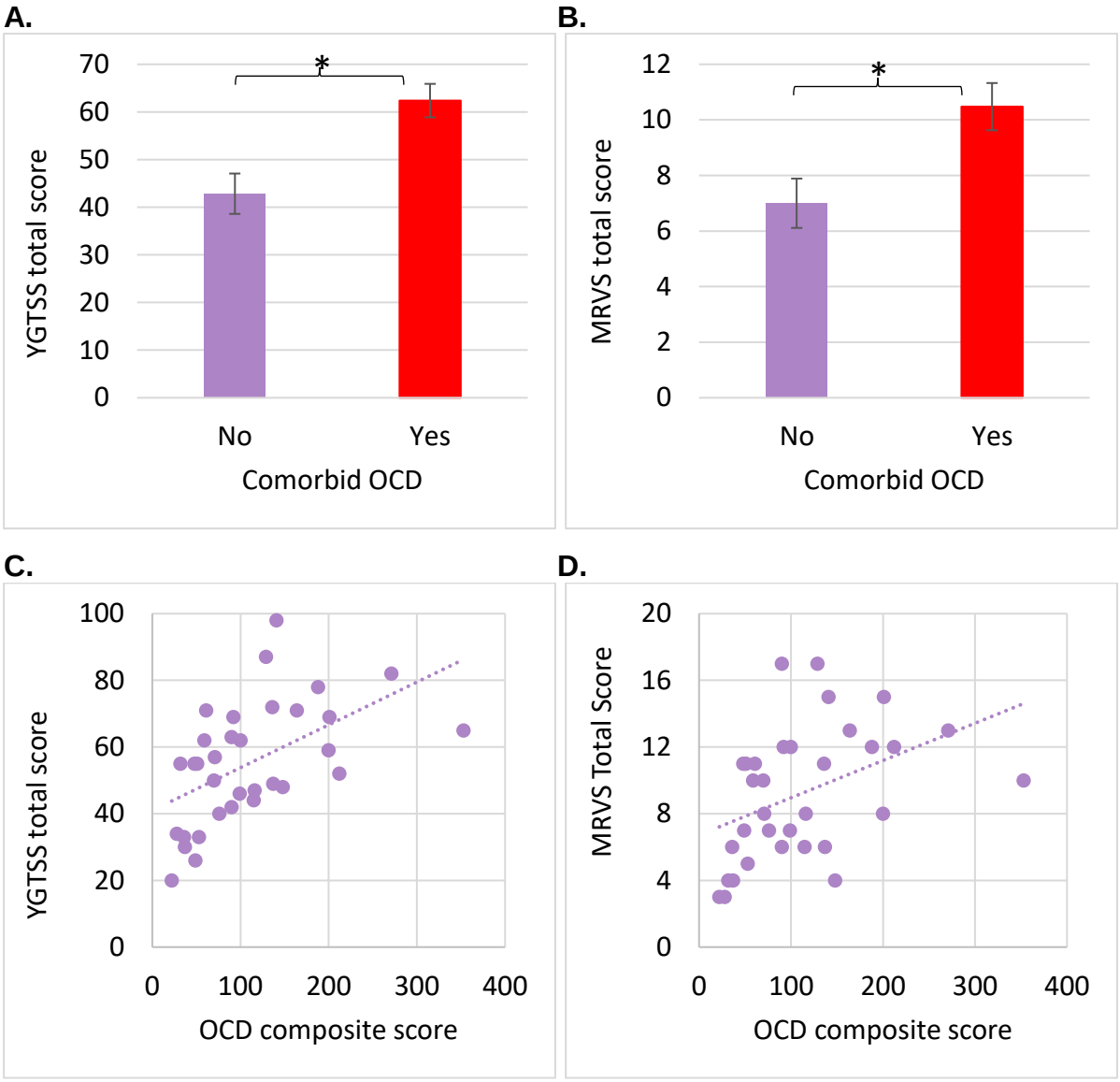


Figure 111. Mean scores for adult TS with and without comorbid OCD for A) YGTSS and B) MRVS and the relationship between OCD composite scores and C) YGTSS score and D) MRVS scores. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

General cognition

IED

Those with comorbid OCD made significantly fewer EDS errors on the IED task compared to those without comorbid OCD, t (31) = 2.193, p = .036, r = .39.

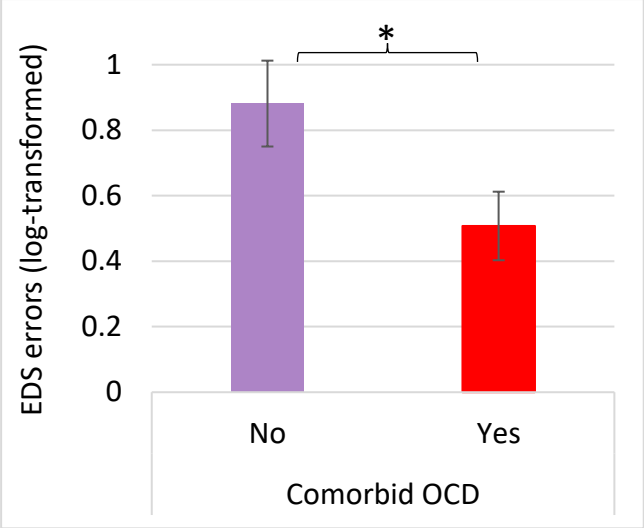


Figure 112. Mean EDS errors (log-transformed) made on the IED subtask by adult TS with and without comorbid OCD. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Furthermore, on the IED subtest, OCD composite score was found to be significantly correlated with the number of EDS errors, r = -.413, p = .017, but not pre-EDS errors, r = -.147, p = .413. Higher OCD composite scores, indicative of worse OCD symptoms was significantly related to fewer EDS errors made on the IED task. Results remained significant following Benjamini-Hochberg FDR correction.

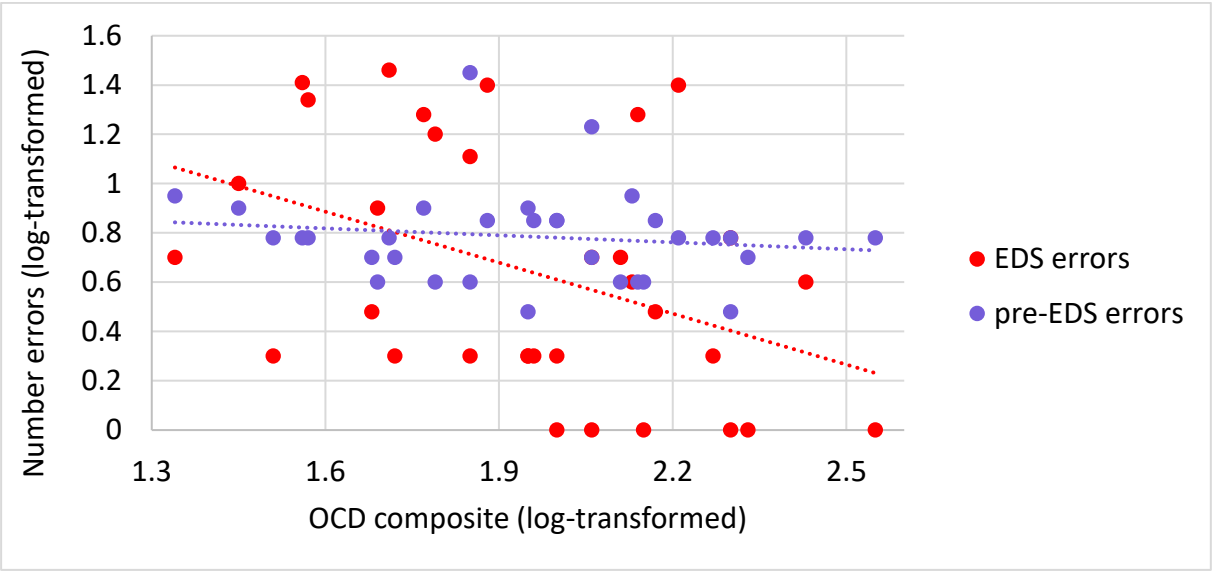


Figure 113. Relationship between the number of pre-EDS and EDS errors made on the IED subtest and OCD composite score (all log-transformed).

Investigation into the specific OCD symptoms that were related to the number of EDS errors made on the IED task revealed significant relationships with mental activities, r_s = -.410, p = .018, and urges and worries, r_s = -.676, p = .000, Padua-L subscores; remaining significant following Benjamini-Hochberg FDR correction.

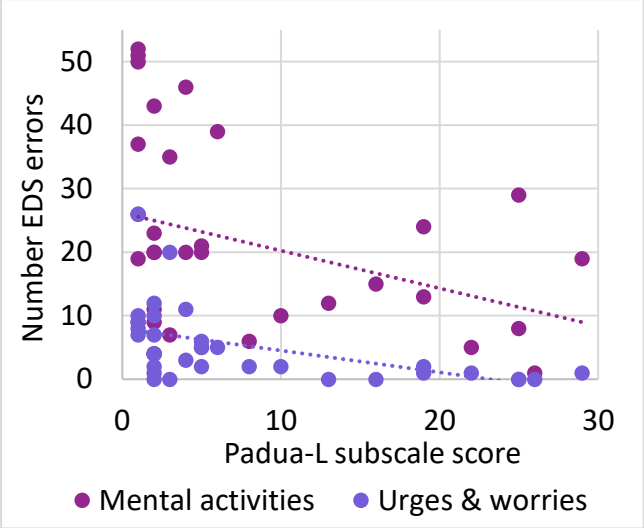


Figure 114. Relationship between the number of EDS errors made on the IED task and Padua-L subscores.

Similarly, the number of EDS errors made on the IED subtest was significantly related to the OCI doubting, r_s = -.387, p = .029, and hoarding subscores, r_s = -.417, p = .017; remaining significant following Benjamini-Hochberg FDR correction.

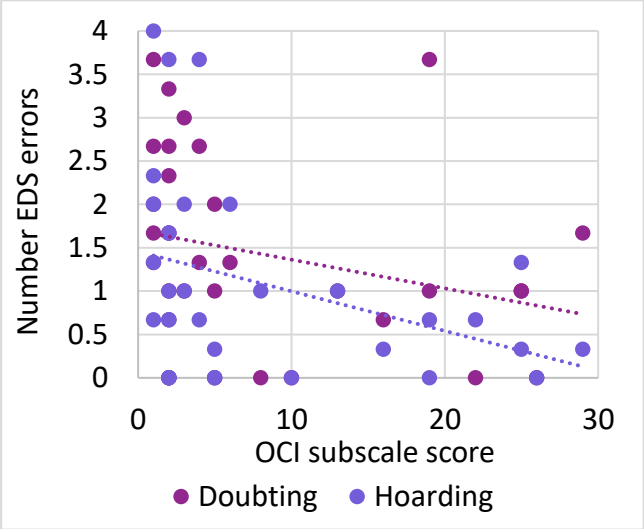


Figure 115. Relationship between EDS errors made on the IED subtest and OCI subscores.

Finally, the number of EDS errors was also significant related to total, r_s = -.441, p = .010, obsession, r_s = -.408, p = .018 and compulsion Y-BOCS scores, r_s = -.358, p = .041; remaining significant following Benjamini-Hochberg FDR correction.

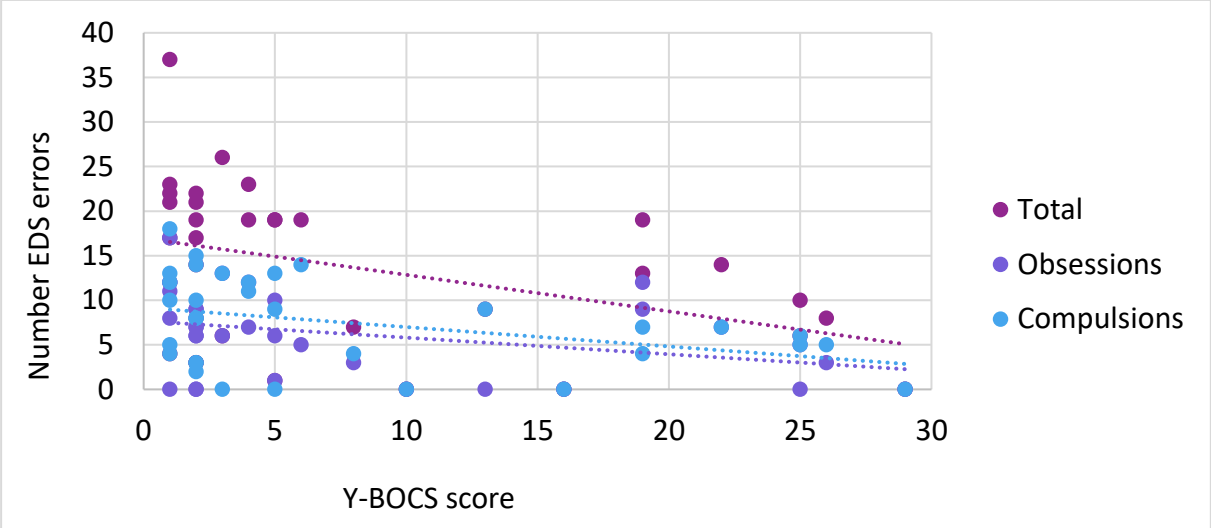


Figure 116. Relationship between IED task EDS errors and Y-BOCS subscores.

SWM

OCD composite score was found to be significantly correlated with SWM strategy score, r_s = -.493, p = .004. Higher OCD composite scores, indicative of worse symptoms was related to a lower strategy score, indicative of better strategy utilisation. Significance remained following Benjamini-Hochberg FDR correction.

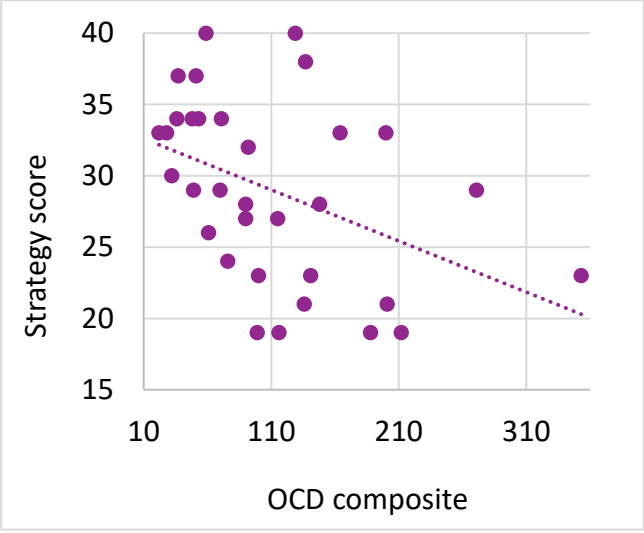


Figure 117. Relationship between SWM strategy score and OCD composite scores.

Investigation into the specific OCD symptoms that are related to the SWM strategy score revealed significant relationships with the mental activities, r_s = -.483, p = .004, contamination, r_s = -.387, p = .026, and urges and worries, r_s = -.527, p = .000, subscales of the Padua-L inventory. Results remained significant following Benjamini-Hochberg FDR correction.

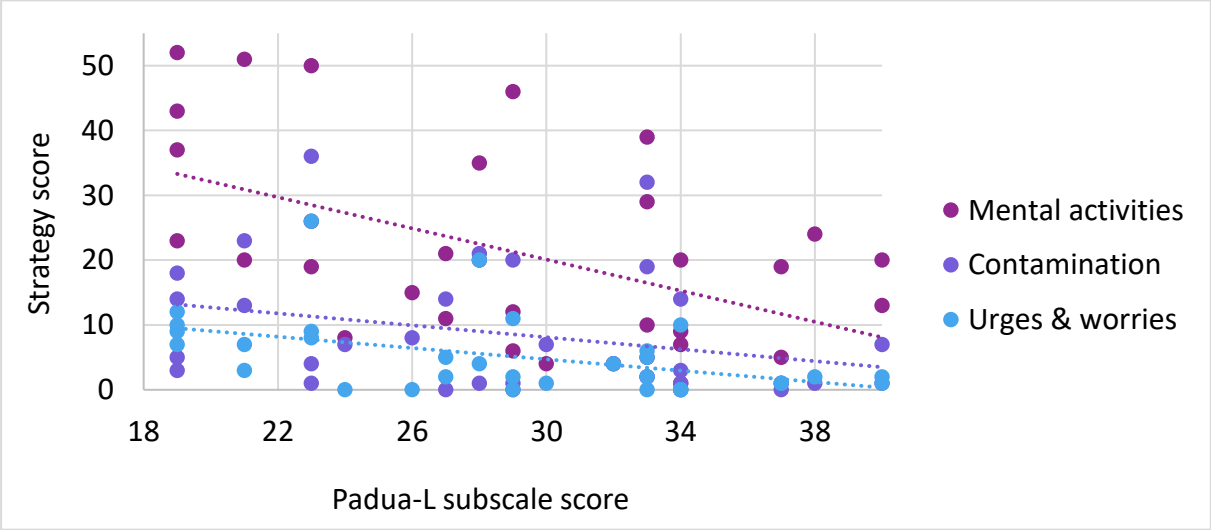


Figure 118. Relationship between SWM strategy and Padua-L subscale scores.

Similarly, strategy score from the SWM task was significantly related to the OCI doubting, r_s = -.412, p = .019 and OCI hoarding subscales, r_s = -.573, p = .001. Results remained significant following Benjamini-Hochberg FDR correction.

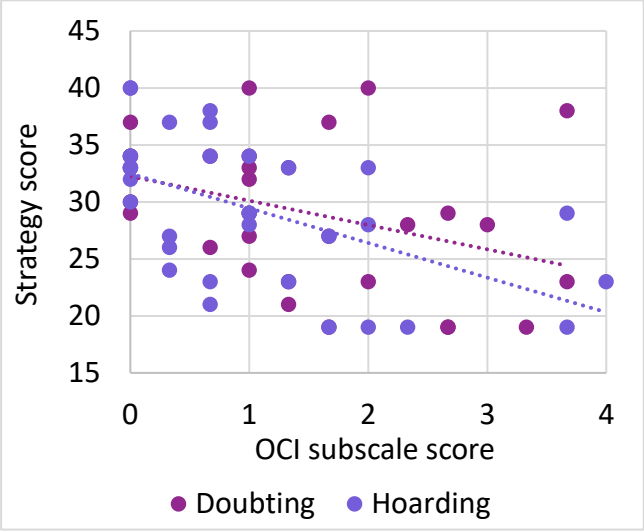


Figure 119. Relationship between SWM strategy and OCI subscale scores.

SST

OCD composite score was found to be significantly correlated with mean RT, r = -.371, p = .033 and median RTs, r = -.356, p = .042. Quicker RTs were associated with worse OCD symptoms. Significance remained following Benjamini-Hochberg FDR correction.

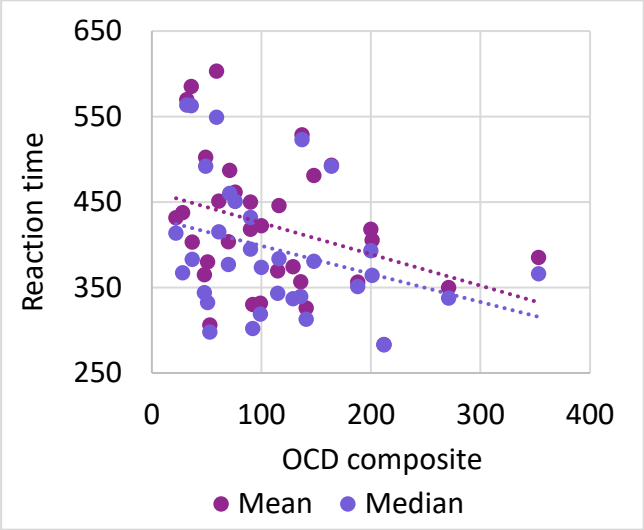


Figure 120. Relationship between OCD composite score and SST subtest mean and median reaction times

Investigation into the specific OCD symptoms that are related to RTs revealed significant relationships with the Padua-L urges and worries subscales, r_s = -.503, p = .003, and mean RT as well as median RT, r_s = -.526, p = .002; remaining significant following Benjamini-Hochberg FDR correction.

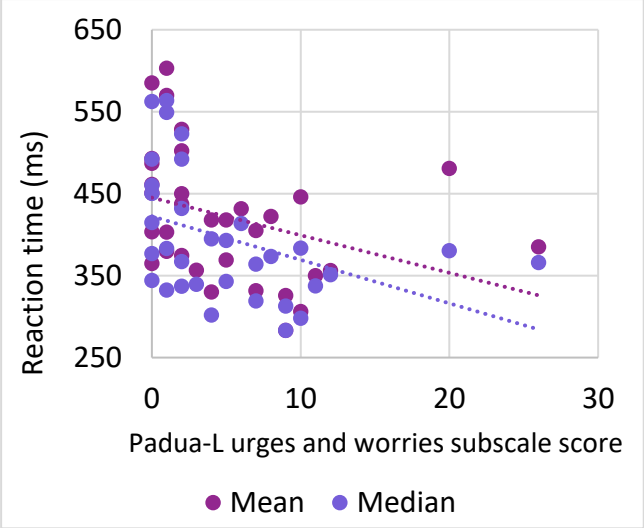


Figure 121. Relationship between Padua-L urges and worries subscale scores and SST subtest mean and median reaction times.

Similarly, the OCI obsessions subscales was significantly related to mean RT, r_s = -.365, p = .040 and median RT, r_s = -.385, p = .029; remaining significant following Benjamini-Hochberg FDR correction.

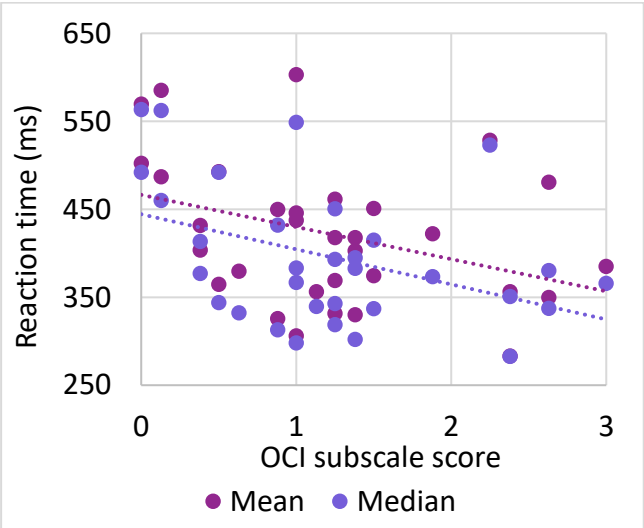


Figure 122. Relationship between OCI obsessions subscale score and SST subtest mean and median reaction times.

Interoceptive awareness

There was no significant difference in interoceptive awareness, t (31) = .439, p = .664, d = .174, and resting heart rate, t (31) = -.361, p = .720, d = -.134, amongst those with and without likely comorbid OCD. There was also no significant correlation between the OCD composite score and interoceptive awareness, r_s = .037, p = .836.

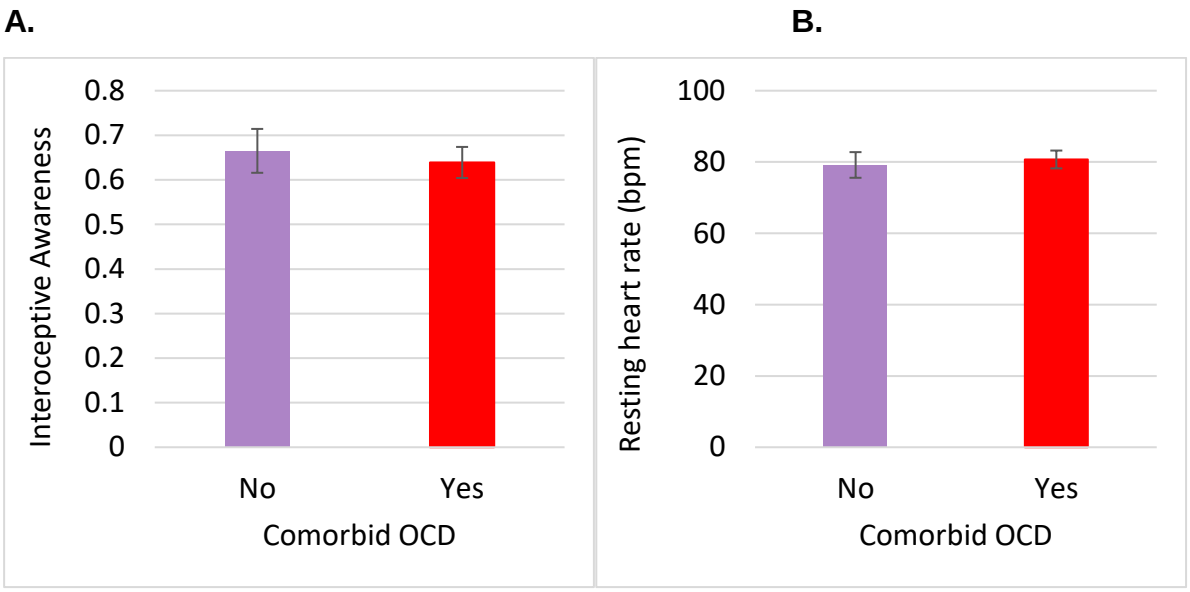


Figure 123. Mean A) interoceptive awareness and B) resting heart rate (bpm) for adult TS with and without comorbid OCD. Errors bars represent SEM.

Neurophysiology

Motor thresholds and OCD

Those with comorbid OCD needed significantly higher levels of stimulation than those without to evoke an MEP at rest, U = 73, z = -1.995, p = .046, r = -.35 and to evoke a 1mV peak-peak amplitude MEP, U = 66.5, z = -2.233, p = .026, r = -.39. There was no difference in the stimulation levels needed to elicit an MEP in the active target muscle, U = 88.5, z = -1.407, p = .159, r = -.24. Results remained significant following Benjamini-Hochberg FDR correction. There were no significant correlations between OCD composite and motor threshold intensities (all p > .05).

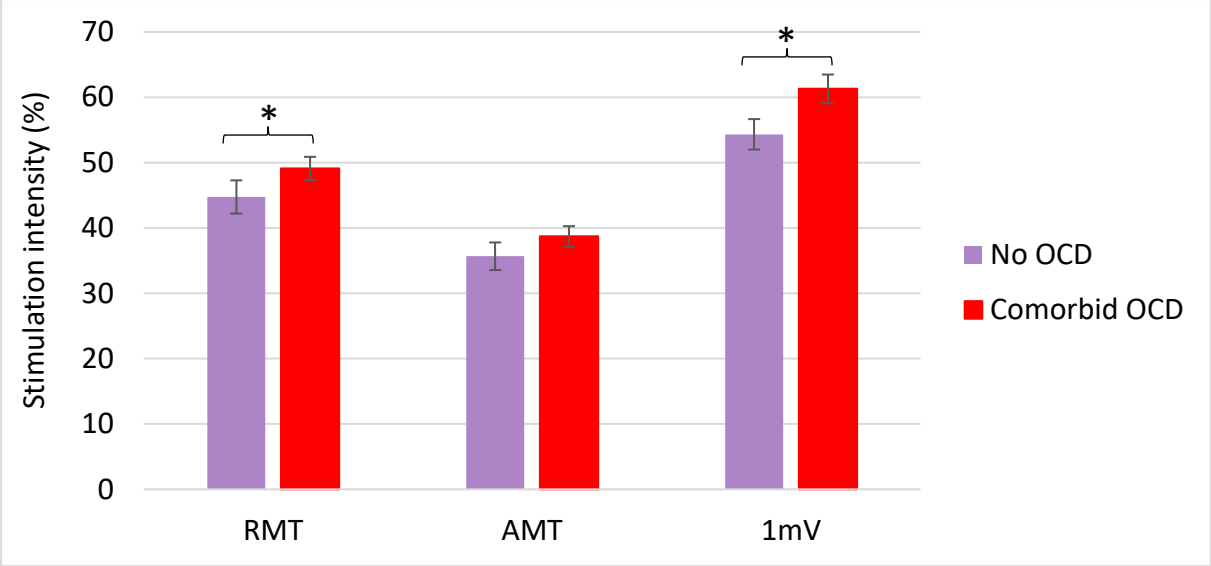


Figure 124. Stimulation intensity (percentage maximum output) needed to reach resting, active and 1mV motor thresholds for adult TS with and without comorbid OCD. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

SICI and OCD

There was a significant main effect of SICI condition on the size of the normalised MEP, F (2, 62) = 38.81, p = .000, r = .62. Planned contrast (repeated) revealed that there were no differences in the size of MEPs between 2ms and 3ms, F (1, 31) = .312, p = .581, r = .10, and a significant increased in the size of MEPs from 3ms to 12ms, F (1, 31) = 51.503, p = .000, r = .79. Results remained significant following Benjamini-Hochberg correction.

There was no significant interaction effect between SICI condition and OCD comorbidity status, F (2, 62) = .490, p = .615, r = .09, and no significant effect of OCD comorbidity on the size of the normalised MEPs, F (1, 31) = .627, p = .435, r = .14. Furthermore, the OCD composite measure was not significantly correlated to SICI or ICF measures (all p > .05).

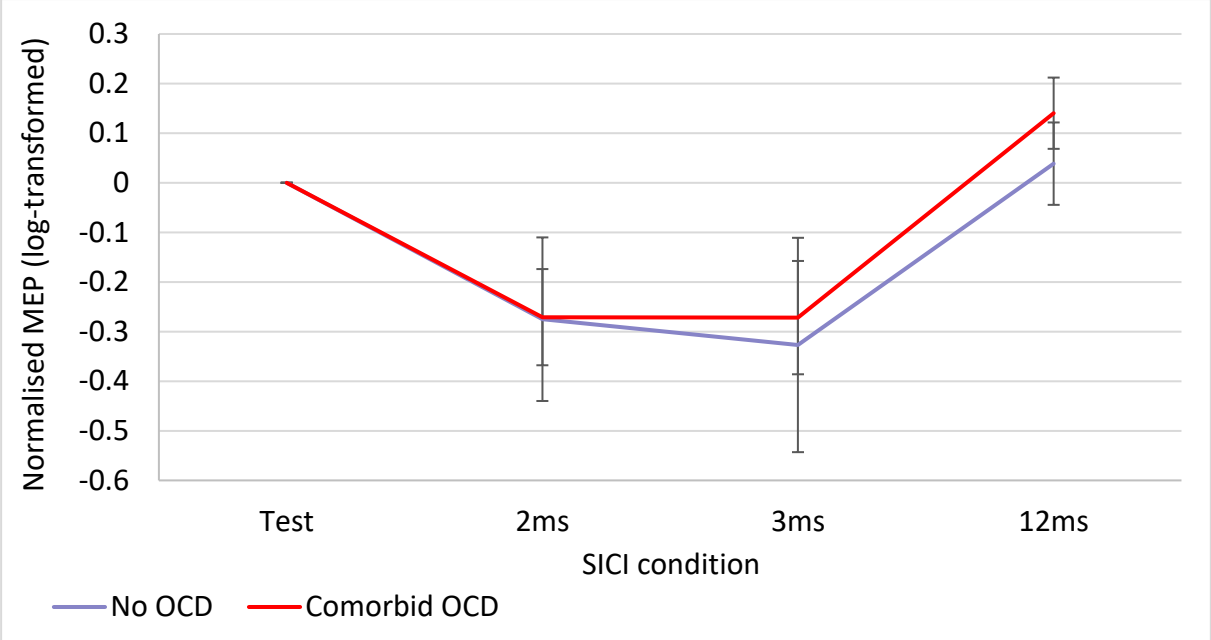


Figure 125. Mean normalised MEPs (log-transformed) elicited at test only and 2ms, 3ms or 12ms intervals, for adult TS with and without comorbid OCD. MEPs are normalised to test pulse condition, with negative values representing inhibition and positive facilitation. Error bars represent SEM.

SAI and OCD

There was no significant main effect of SAI condition on the size of the normalised MEP, F (3, 87) = 5.846, p = .492, r = .25, and no significant interaction effect between SAI condition and OCD comorbidity status, F (3, 87) = 1.674, p = .178, r = .14, and no significant effect of OCD comorbidity on the size of the normalised MEPs, F (1, 29) = .896, p = .352, r = .17. Furthermore, the OCD composite measure was not significantly correlated to SAI (all p > .05).

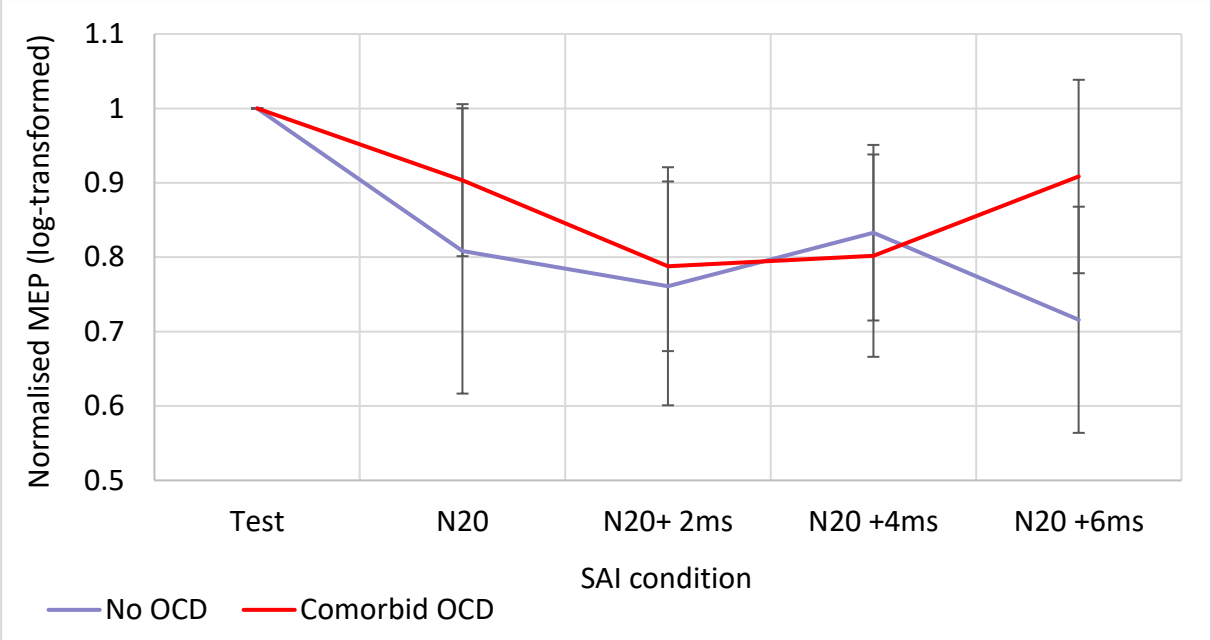


Figure 126. Mean normalised MEPs (log-transformed) elicited at test only and N20, $N20^{+2ms}$, $N20^{+4ms}$ and $N20^{+6ms}$ intervals, for adult TS with and without comorbid OCD. MEPs are normalised to test pulse condition, with negative values representing inhibition and positive facilitation. Error bars represent SEM.

Summary

Following assessment with the OCI, Padua-L and the Y-BOCS, twenty-one participants, 64% of our sample, were identified as having OCD symptom severity consistent with likely comorbid OCD. Individuals with more severe OCD symptoms, consistent with likelihood of comorbid OCD, had significantly worse urge and tic severity as indicated by higher PUTS, YGTSS and MRVS total scores.

On the CANTAB SWM task, worse OCD symptoms were associated with significantly better strategy utilisation. There was however, no significant difference in these cognitive abilities between those with and without likely comorbid OCD. Interestingly, worse OCD symptoms were associated with making significantly fewer EDS errors on the CANTAB IED task. Comorbid OCD was in this instance, associated with significantly fewer EDS errors than those without comorbid OCD.

Comorbid OCD was not related to interoceptive awareness. During TMS individuals with comorbid OCD required significantly more stimulation to reach RMT and 1mV thresholds. Furthermore, those with comorbid OCD appeared to have less SICI and

more ICF, but this was not significant; SAI levels in TS were also unaffected by comorbid OCD.

Table 17. Summary of Chapter 7 section Comorbidities OCD

Results Summary					Main Finding(s)
Cognition	**Interoceptive Awareness**	**Clinical Symptoms**	**Neurophysiology**	**Tic control**	
On the CANTAB IED, those with comorbid OCD made significantly fewer EDS errors on the IED task compared to those without comorbid OCD $p = .036$ Comorbid OCD found to be associated with higher PUTS scores and fewer EDS errors, $p = .033$. Controlling for OCD composite score, abolished this relationship, $p = .299$. OCD composite score significantly correlated with the number of EDS errors, $p = .017$, but not pre-EDS errors, $p = .413$. Number of EDS errors correlated significantly with Padua-L mental activities and urges and worries; OCI doubting and hoarding; Y-BOCS total, obsession and compulsion scores (all $p < .05$). On the CANTAB SWM task strategy score was significantly correlated with OCD composite, Padua-L mental activities, contamination and urges and worries; OCI doubting and hoarding (all $p < .05$). There was however, no significant difference in strategy scores between those with and without likely comorbid OCD ($p > .05$). On the CANTAB SST task mean and median RTs correlated with OCD composite score, Padua-L urges and worries and OCI obsessions (all $p < .05$). There was however, no significant difference in RTs between those with and without likely comorbid OCD ($p > .05$).	There was no significant difference in interoceptive awareness, $p = .664$, amongst those with and without likely comorbid OCD. There was no significant correlation between the OCD composite score and interoceptive awareness, $p = .836$.	Assessment with the OCI, Padua-L and the Y-BOCS revealed that twenty-one participants, 64% of our sample, were identified as having OCD symptom severity consistent with likely comorbid OCD. Those with comorbid OCD had significantly higher PUTS scores, $p = .013$, than those without comorbid OCD. PUTS scores correlated significantly with the OCD composite measures, $p = .002$, Comorbid OCD was associated with significantly higher YGTSS total scores, $p = .002$, and MRVS total scores, $p = .010$, than those without comorbid OCD. YGTSS total significantly correlated with the OCD composite, $p = .000$, as did the MRVS total score, $p = .001$.	Comorbid OCD was associated with requiring significantly higher levels of stimulation to evoke an MEP at rest, $p = .046$ and a 1mV peak-peak amplitude MEP, $p = .026$, There was no difference in the stimulation levels needed to elicit an MEP in the active target muscle, $p = .159$ in those with and without comorbid OCD. There were no significant correlations between OCD composite and motor threshold intensities (all $p > .05$). There was no significant effect of OCD comorbidity on the size of the normalised MEPs, $p = .435$. There was no significant relationship or interaction between SICI or SAI condition and OCD symptoms or comorbidity (all $p > .05$). There was no effect of OCD comorbidity on the size of the normalised MEPs, $p = .352$.	No relationship identified between OCD (comorbidity or composite score) and mechanisms of tic control (all $p > .05$)	64% of our sample, were identified as having OCD symptom severity consistent with likely comorbid OCD. Individuals with more severe OCD symptoms and comorbid OCD, had significantly worse urge and tic severity. Comorbid OCD was significantly related to making fewer EDS errors on the CANTAB IED task. Specifically, the following OCD symptoms were associated with fewer EDS errors: Padua-L mental activities, urges and worries, OCI doubting and hoarding and Y-BOCS scores. On the CANTAB SWM task, worse OCD symptoms were associated with significantly better strategy utilisation. Specifically, the following OCD symptoms were associated with better strategy utilisation, Padua-L mental activities, contamination and urges and worries; OCI doubting and hoarding. Despite this finding, comorbid OCD did not lead to better SWM strategy performance. On the CANTAB SST, quicker RTs were associated with worse OCD symptoms, specifically Padua-L urges and worries and OCI obsessions. Despite this, comorbid OCD was not associated with quicker RTs. OCD symptoms and comorbidity was not related to interoceptive awareness. During TMS individuals with comorbid OCD required significantly more stimulation to reach RMT and 1mV thresholds.

7.3. Discussion

During the third decade of life, tics are reported to reduce significantly, with 80% of cases reporting mild to non-existent tics (Byler et al., 2015; Hassan & Cavanna, 2012). Whilst the majority of TS cases are close to complete remission by 21 years of age (Novotny et al., 2018) between 10-20% cases have persistent tics throughout adulthood (Cath et al., 2011; Hirschtritt et al., 2015; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, Woods, Hariz, Mathews, Crncec, et al., 2017). Furthermore, more than 40% of cases report psychopathologies and comorbidities that persist into adulthood, even during episodes of remission (Byler et al., 2015; Hirschtritt et al., 2015).

Psychopathologies are common in TS and often arise after the onset of tics (Freeman et al., 2000; Robertson, 2015b). Dysregulation of emotions and mood, alongside disorders with personality are frequent, with individuals displaying disruptive behaviours and conduct disorder in childhood (Comings, 1987; Freeman et al., 2000; Hirschtritt et al., 2015; Piedad & Cavanna, 2016; Robertson, 2012, 2015b). For example, impulse control disorders are highly prevalent, affecting 74% of adults with TS, with compulsive buying, kleptomania and gambling behaviours being common (Budman, Rockmore, Stokes, & Sossin, 2003; Frank, Piedad, Rickards, & Cavanna, 2011; Wright, Rickards, & Cavanna, 2012). Furthermore, 5-30% cases have intermittent explosive disorder (Cravedi et al., 2017; Robertson, 2006), 30-60% cases experience non-obscene socially inappropriate or disruptive behaviours (Hirschtritt et al., 2015; Kurlan et al., 1996) and there is a 39% lifetime incidence of self-injurious behaviours (Sambrani et al., 2016). Affective symptoms, anxiety and impulsivity are also highly prevalent (Frank et al., 2011) with 29.8% cases having mood disorders (Hirschtritt et al., 2015) and 2-45% cases having anxiety disorders (Cath, 2013; Cravedi et al., 2017; Evans, Seri, & Cavanna, 2016; Frank et al., 2011; Hirschtritt et al., 2015; Robertson, 2003; Robertson, 2011, 2012). Whilst less common, there have also been reports in TS of psychotic disorders, affecting 0.8% of cases and substance abuse, affecting 6.2% of cases (Hirschtritt et al., 2015).

In TS, the most common psychopathology is depression, occurring in 11-76% cases (Cravedi et al., 2017; Robertson, 2006). Such prevalence is substantially higher than the general population and is due to a multitude of factors, both genetic and environmental (Pauls, Leckman, & Cohen, 1994; Robertson, 2006). Quality of life

(QOL) consistently declines overtime in TS (Evans et al., 2016) and typically, whilst severity reduces overtime, tics and urges remain. Distress and frustration caused by urges and tics coincides with pain and injury that hinders self-care, physical health and mobility; such functional impairment unsurprisingly coincides with a diagnosis of depression (Cavanna, David, et al., 2013; Cavanna, David, Orth, & Robertson, 2012; Conelea et al., 2013; Evans et al., 2016; Jalenques et al., 2012; Kano et al., 2015; Lewin et al., 2011; Parisi, 2010; Piedad & Cavanna, 2016).

ADHD is a common comorbidity in TS, occurring in 20-90% cases (Freeman & Consortium, 2007; Freeman et al., 2000; Hirschtritt et al., 2015; Robertson, 2015b). Typically, onset occurs in childhood between 2-6 years age, often prior to tic onset and is more predominant in males (Bloch & Leckman, 2009; Mol Debes, Hjalgrim, & Skov, 2008; O'Rourke et al., 2011; Spencer et al., 1998). In childhood, ADHD symptomology primarily involves impulsivity and inattentiveness, whilst in adulthood, despite being less disruptive, symptoms revolve around inattention (Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2006). In TS, comorbid ADHD is the largest determinant of problems with behaviour, cognition and the likelihood of other comorbidities and psychopathologies (Debes et al., 2008; Freeman & Consortium, 2007; Lebowitz et al., 2012; Specht et al., 2011). Impacting key stages of development, comorbid ADHD frequently results in mental fatigue and difficulty with concentration, with lasting interference of education and work life and negatively impacting on QOL (APA, 2013; Haddad et al., 2009; Rizzo, Gulisano, Cali, & Curatolo, 2013).

OCD is another common comorbidity in TS, occurring in 10-80% cases (Byler et al., 2015; Gadow, Nolan, Sprafkin, & Schwartz, 2002; Hirschtritt et al., 2015; Robertson, 2015b; Sambrani et al., 2016). Typically, onset of comorbid OCD occurs several years after tic onset, often in adolescence, and is more predominant in females (Bloch & Leckman, 2009; Gunduz & Okun, 2016; Hirschtritt et al., 2015; Robertson, 2012). Comorbid OCD involves the experience of clinically obtrusive, unwelcome and distressing intrusive thoughts known as obsessions and individuals feel driven to perform compulsions, that are repetitive behaviours or acts (Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989; Sukhodolsky et al., 2005). Compulsions appear to be more common in TS than obsessions (Debes, 2009). Similarly, in TS, obsessive-

compulsive behaviours occur in 60-90% of cases; these less intrusive behaviours include checking, counting, ordering, evening-up, maintaining symmetry and frequent obsessive thoughts (Bloch & Leckman, 2009; Eapen, Robertson, Alsobrook, & Pauls, 1997; Stern, 2018). Obsessive-compulsive symptoms relating to perfectionism, obsessions, and performance of lengthy compulsive acts can make daily life difficult, further affecting QOL (Conelea et al., 2013; Parisi, 2010).

Comorbid autism spectrum disorders (ASD) have also been reported to occur in 2.9-50% of cases of TS (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Burd, Fisher, Kerbeshian, & Arnold, 1987; Burd, Li, Kerbeshian, Klug, & Freeman, 2009; Canitano & Vivanti, 2007; Comings & Comings, 1991; Huisman-van Dijk, 2016; Khalifa & von Knorring, 2006; Marriage, Miles, Stokes, & Davey, 1993; Robertson, 2012; Simonoff et al., 2008; Sverd, Montero, & Gurevich, 1993). Large variability in the prevalence of ASD in TS likely arises due to differences across studies in diagnostic criteria and clinical heterogeneity (Martino, Ganos, & Pringsheim, 2017). Nevertheless, up to 40% of individuals with TS have difficulties with empathy and social interactions (Khalifa & von Knorring, 2006) with a recent review identifying impaired social cognition in TS (Morand-Beaulieu, Leclerc, et al., 2017).

The experiences of urges and tics in conjunction with the emotional and behavioural aspects of psychopathologies and comorbidities can have a drastic negative effect on social skills, can result in instances of stigma and bullying (Bawden et al., 1998; O'Hare et al., 2015; Swain et al., 2007) and can have a lasting impact on relationships and work life (Cavanna, Luoni, et al., 2013; Cavanna et al., 2008; Evans et al., 2016; Haddad et al., 2009; Jalenques et al., 2012). Consequently, in adult TS there are high rates of unemployment and poorer psychosocial standing (Elstner et al., 2001; Pappert et al., 2003). The presence of comorbidities has also been shown to impact the efficacy of CBIT therapies in children with TS (Piacentini et al., 2010) and may impact efficacy in adults. Furthermore, the majority of support networks and organisations in TS are child and adolescent orientated, contributing to adults feeling isolated from guidance and their peers (Kompoliti, 2015). Unfortunately, in adult TS there is a 9.7% prevalence of suicidality associated with the impact of tic and urge severity, treatment resistance, psychopathology and the presence of comorbid conditions (Davila, Berthier, Kulisevsky, & Jurado Chacon, 2010; Storch et al., 2015). Recently, there been reports of an elevated risk of death

in adults with TS (Meier, Dalsgaard, Mortensen, Leckman, & Plessen, 2017) and a 4-fold risk of attempted and completed suicide that was not related to the presence of comorbidity (Fernandez de la Cruz et al., 2017). Despite the dramatic effect of comorbidities and psychopathologies to treatment efficacy and QOL (Eapen, Cavanna, & Robertson, 2016; Piacentini et al., 2010) these features have not been the primary clinical or research focus in adult TS.

In our sample of adults with TS, the mean urge severity (24.52) corresponded to marked impairment (≥24 PUTS) and is slightly higher than previous samples of adults with TS (19.7 Ganos et al, 2015; 20.93 Ganos et al, 2018; 24 Misirsloy et al, 2015). Total tic severity (55.27 ± 18.1) and ratings of impairment (30.91 ± 9.48) corresponded to severe (>30 YGTSS) classifications (Bloch et al., 2006; Byler et al., 2015; Lewin et al., 2012; Tinaz et al., 2014) similar to previous samples of adults with TS and comorbidities (Total: 45.44 Orth et al, 2005; 48.6 Orth & Rothwell, 2009; 46.14 Ganos et al, 2018; 37.5 Ganos et al 2015) but higher in severity than adult TS samples with uncomplicated TS (29.05 Channon et al, 2009; 27 Channon et al, 2006; 26.69 Martino et al, 2017; 16.8 Misirlsoy et al, 2015; 22.9 Wilhmelm et al, 2012; 23.53 Yaniv 2018). Furthermore, none of our sample meet Yaniv and colleagues (2018) operational criteria of remission.

We found that worse experiences of premonitory urges was significantly related to worse tic severity, consistent with previous findings (Crossley et al., 2014; Eddy & Cavanna, 2014; Ganos, Garrido, Navalpotro-Gomez, et al., 2015; Reese et al., 2014; Woods et al., 2005). Furthermore, tic severity corresponded to significantly larger normalised MEPs when free to tic. Larger MEPs recorded with above threshold stimulation indicates that the components of the corticospinal system are equally excitable. We found evidence that altering the distribution of CSE may be a putative tic control mechanism (Draper et al., 2015; Orth, Munchau, et al., 2008), with significantly reduced MEPs observed during active tic suppression (Chapter 6). Worse tic severity likely requires extensive employment of tic control mechanisms. Subsequently, removal of tic control upon instruction to tic freely, may serve to restore the distribution of CSE resulting in significantly larger MEPs (Orth, 2009).

Additionally, worse tic severity corresponded to poorer sensitivity to targets and thus, more false alarms on the RVP task. Such results are consistent with more frequent and severe tics being distracting during tasks (Channon et al., 2006; Eddy &

Cavanna, 2017; Ozonoff et al., 1998). Conversely, we found that worse premonitory urge severity corresponded to quicker RTs on the RVP task and better cognitive flexibility for habitually learned behaviours on the IED task. Following a partial correlation, the relationship between urge severity and EDS errors was found to be accounted for by the relationship between OCD and EDS errors, which is discussed later.

Rates of depression in our sample were 13.33%, at the lower end of the 11-76% reported prevalence (Cravedi et al., 2017; Robertson, 2006). This might be explained by the fact that a third of our sample were currently taking antidepressant medication (see Chapter 8). The report of a previous manic episode was 23.33% in our sample, consistent with previous observations of 29.8% prevalence of mania and bipolar disorder (Hirschtritt et al., 2015). Current generalised anxiety disorders occurred in 36.66% of our sample, panic disorder in 13.33%, agoraphobia in 30% and social anxiety in 10%. Such observations are consistent with anxiety disorders being prevalent in 2-45% cases (Cath, 2013; Cravedi et al., 2017; Evans et al., 2016; Frank et al., 2011; Robertson, 2003; Robertson, 2011, 2012). In accordance with rates of psychotic disorders occurring in <1% cases (Hirschtritt et al., 2015), none of our sample presented with current psychotic disorders. Furthermore, 3.33% of our sample were dependent and 6.66% abusing psychoactive substances and 13.33% dependent and 10% abusing alcohol; such results are consistent with reports of substance abuse, in 6.2% of TS cases (Hirschtritt et al., 2015). Our sample of individuals with TS represent cases recruited from both clinical and community settings, thus our results demonstrate the existence and persistence of psychopathologies into adulthood in those with TS, advancing our understanding of the clinical features of adult TS.

Following dual assessment with the BAARS-IV and ASRS, 64% of our sample were identified as having ADHD, consistent with prevalence occurring in 20-90% cases (Freeman & Consortium, 2007; Freeman et al., 2000; Hirschtritt et al., 2015; Robertson, 2015b). Interestingly, in adulthood, there were no differences in scores across the BAARS-IV subscales in those with and without comorbid ADHD. Our results therefore identify that comorbid ADHD in adult TS is associated with global impairment in domains of inattention, hyperactivity, impulsivity and sluggish cognitive tempo, contrasting with observations that ADHD symptoms revolve around

inattention in adult TS (Biederman et al., 2000; Faraone et al., 2006). We also found that worse ADHD symptoms were associated with stronger premonitory urges, which has been seen previously (Eddy & Cavanna, 2014). However, there were no significant differences in PUTS scores between those with and without comorbid ADHD, consistent with previous observations in both adults (Reese et al., 2014) and children with TS (Gulisano, Cali, Palermo, Robertson, & Rizzo, 2015).

Severe ADHD symptoms were associated with significantly enhanced levels of ICF, consistent with previous findings that comorbid ADHD is associated with more extensive alterations to ICF (Orth & Rothwell, 2009). We did not find a relationship between ADHD symptoms and tic severity and comorbid ADHD did not further alter interoceptive awareness, mirroring previous results (Pile, Lau, Topor, Hedderly, & Robinson, 2018). Furthermore, worse ADHD symptoms corresponded to significantly fewer perseverative errors on the CPT task. However, there were no significant differences between those with and without comorbid ADHD.

Following assessment with the MINI, 46.66% of our sample were identified as having OCD. Additionally, following exploration of symptom severity with the Y-BOCS, OCI and Padua-L, 64% of our sample has OCD symptom severity that is consistent with the likelihood of comorbid OCD. Such observations are consistent with OCD being prevalent in 10-80% cases (Byler et al., 2015; Gadow et al., 2002; Hirschtritt et al., 2015; Robertson, 2015b; Sambrani et al., 2016). Furthermore, the MINI also identified 63.33% of our sample as having obsessions and 70% compulsions, in the absence of OCD, consistent with previous findings of obsessive-compulsive behaviours occurring in 60-90% of cases (Bloch & Leckman, 2009; Eapen et al., 1997; Stern, 2018), with compulsions being more common than obsessions (Debes, 2009). In our sample, the mean Y-BOCS score of 13.61 corresponded to previous samples of adults with TS and comorbidities (12.3 Ganos et al, 2015; 10.45 Ganos et al, 2018) but not with samples of uncomplicated TS (2.3 Misirlsoy et al, 2015).

Individuals with comorbid OCD were found to have significantly worse premonitory urges and tic severity, consistent with previous findings that worse tic severity corresponds to worse experience of premonitory urges (Crossley et al., 2014; Eddy & Cavanna, 2014; Ganos, Garrido, Navalpotro-Gomez, et al., 2015; Reese et al., 2014; Woods et al., 2005) and that the more severe the comorbid OCD, the more intense the experience of premonitory urges (Kano et al., 2015). In addition, individuals with

comorbid OCD are seen to experience more ‘not just right’ sensory experiences (Rajagopal & Cavanna, 2014; Rajagopal et al., 2013).

Furthermore, where a positive correlation was found between PUTS scores and OCD symptoms (Ganos, Garrido, Navalpotro-Gomez, et al., 2015) this did not remain significant after being entered into a regression model alongside interoceptive awareness. Nevertheless, such results implicate a link between comorbid OCD and altered sensory processing phenomena (Cox et al., 2018; Ganos, Garrido, Navalpotro-Gomez, et al., 2015); it is therefore unsurprising that our results have established a strong link between worse urge symptoms and comorbid OCD.

Worse OCD symptoms were also found to correspond to better strategy utilisation on the SWM task, and to quicker RTs on the SST. Whilst there are few studies investigating OCD symptom subtypes and cognition, worse performance has been reported in those with checking symptoms compared to washing symptoms for pattern recognition, planning, problem solving, and response inhibition (Leopold & Backenstrass, 2015; Nedeljkovic et al., 2009). Our results are consistent with this observation, as symptoms relating to checking were not associated with better performance on tasks assessing these domains. Whilst we did not find a significant difference in cognition between those with and without comorbid OCD, further investigation into comorbid OCD symptoms and cognition is warranted.

In our sample, those with comorbid OCD had significantly better cognitive flexibility for habitually learned behaviours on the IED. OCD is associated with hyperdopaminergic frontostriatal signalling (Denys, Zohar, & Westenberg, 2004; Klanker et al., 2013) that has been seen to result in a broad range of cognitive deficits (Benzina, Mallet, Burguiere, N'Diaye, & Pelissolo, 2016; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Suhas & Rao, 2019). The most consistent impairment is seen to cognitive flexibility, whereby the presence of comorbid OCD and the severity of obsessive-compulsive symptoms are related to worse performance on the WCST (Bornstein, 1991a; Gruner, & McKay, 2013; Matsuda et al., 2012). Subsequently, cognitive inflexibility was proposed as an endophenotype of OCD (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). Intriguingly, our results contradict a large body of evidence that OCD is associated with impaired cognitive flexibility (Chamberlain et al., 2007; Chamberlain et al., 2008; Gruner & Pittenger, 2017; Gu et al., 2008; Remijnse et al., 2006; Viswanath,

Janardhan Reddy, Kumar, Kandavel, & Chandrashekar, 2009); including those with a history of tics having more impairment (Gruner, & McKay, 2013). Whilst there is evidence that individuals with comorbid OCD, match uncomplicated TS on WCST performance (de Groot, Yeates, Baker, & Bornstein, 1997; Muller et al., 2003) there is little evidence to support our findings of comorbid OCD being beneficial to cognitive flexibility.

Finally, comorbid OCD was found to influence motor thresholding, with significantly more stimulation required to reach RMT and 1mV threshold. In accordance with those with comorbid OCD having worse urge and tic severity, employment of tic control mechanisms, that serves to alter the distribution of CSE, likely occurs to a stronger extent during rest, to reduce the likelihood of tic generation. Therefore, significantly more stimulation would be required during TMS protocols to recruit cortical propagating pyramidal tract neurons and synchronise spinal motor neuron firing (Day et al., 1989; Rossini et al., 2015). Conversely, similar AMTs were observed irrespective of comorbid OCD which is consistent with the role of voluntary action in regulating CSE (Orth, 2009). The presence of comorbidities in TS has been found to have overlapping and advanced pathology in CSTC circuity (Karagiannidis, 2016; Mathews & Grados, 2011) attributable to the cumulative load of additional genetic and environmental risk factors (Eapen & Robertson, 2015), compatible with TS being a neurodevelopmental continuum, ranging from uncomplicated to phenotypes with comorbidities (Cravedi et al., 2017). Our results have found evidence that in comorbid OCD, there is a requirement for enhanced tic control, likely to compensate for advanced CSTC pathology, achieved via extensive alteration to the distribution of CSE. Interestingly, as better cognition appears to correspond to comorbid OCD, it is plausible that such alterations to CSE may lead to better cognitive flexibility, especially so, as compensatory mechanisms have been seen to benefit task performance in individuals with TS previously (Jackson, Parkinson, Jung, et al., 2011; Mueller et al., 2006; Plessen et al., 2009; Plessen et al., 2004; Roessner et al., 2008).

Our results have confirmed that, alongside marked urge and severe tic severity, there are prevalent and persistent psychopathologies and comorbidities in adults with TS from clinical and community settings, advancing our understanding of the clinical profile. Interestingly, extensive compensatory alteration in the distribution of CSE is

employed as a tic control mechanisms in those with comorbid OCD, due to experiencing a more severe clinical profile. Furthermore, such compensation, employed to a larger extent in those with worse OCD symptom severity, may be beneficial and facilitate some aspects of cognition, such as cognitive flexibility.

Chapter 8. Comorbidity subgroups

8.1. Introduction

The aim was to explore the different comorbidity subgroups of adult TS to determine whether comorbidity presence is related to TS symptoms, interoceptive awareness, cognition, and motor neurophysiology; this will allow us to infer whether abnormalities associated with adult TS are inherent to TS or rather a consequence of comorbidity.

8.2. Results

Subgroup classification

Seven adults with TS were classified as having uncomplicated TS i.e. with no comorbidity, five as having comorbid ADHD only, five as having comorbid OCD only and sixteen having complicated TS i.e. with both comorbid ADHD and OCD.

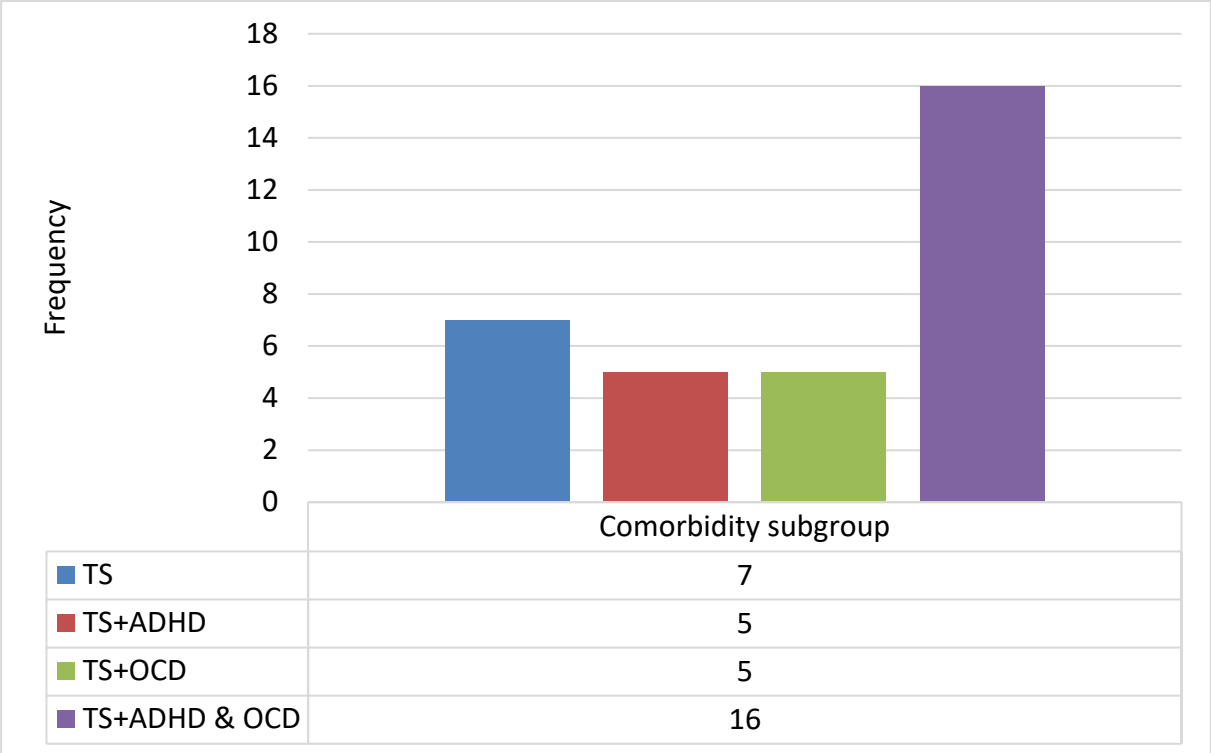
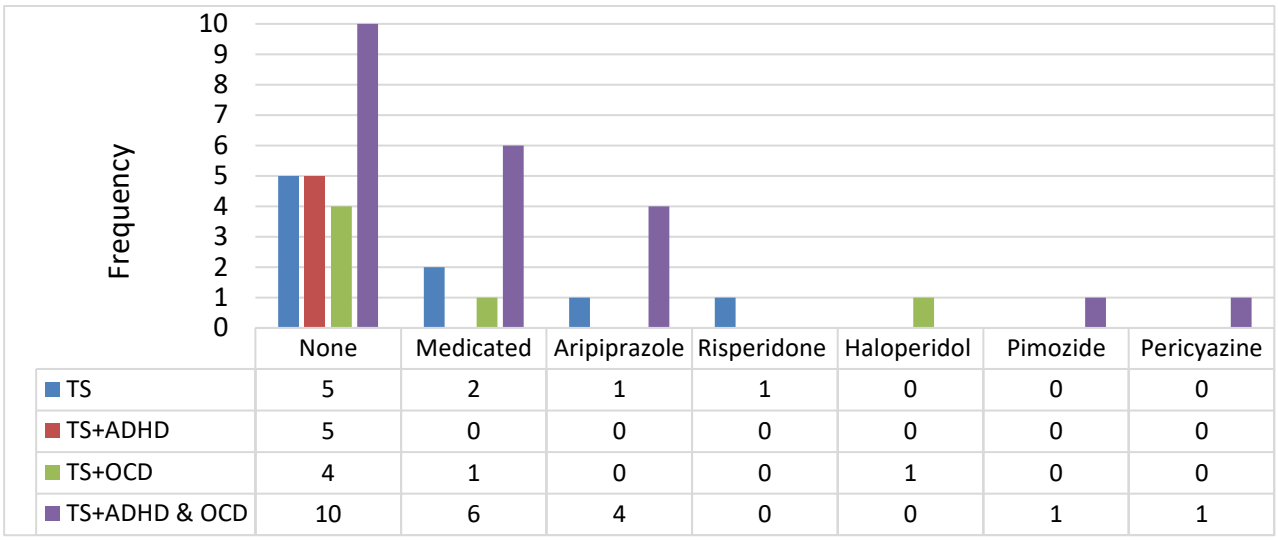


Figure 127. The number of adults with TS with no comorbidity, comorbid ADHD, comorbid OCD or both comorbid ADHD and OCD.

Medication

Antipsychotics

There were no significant differences in the distribution of those medicated with antipsychotics, X_2 (3) =2.858, p = .414, across comorbidity subgroups.

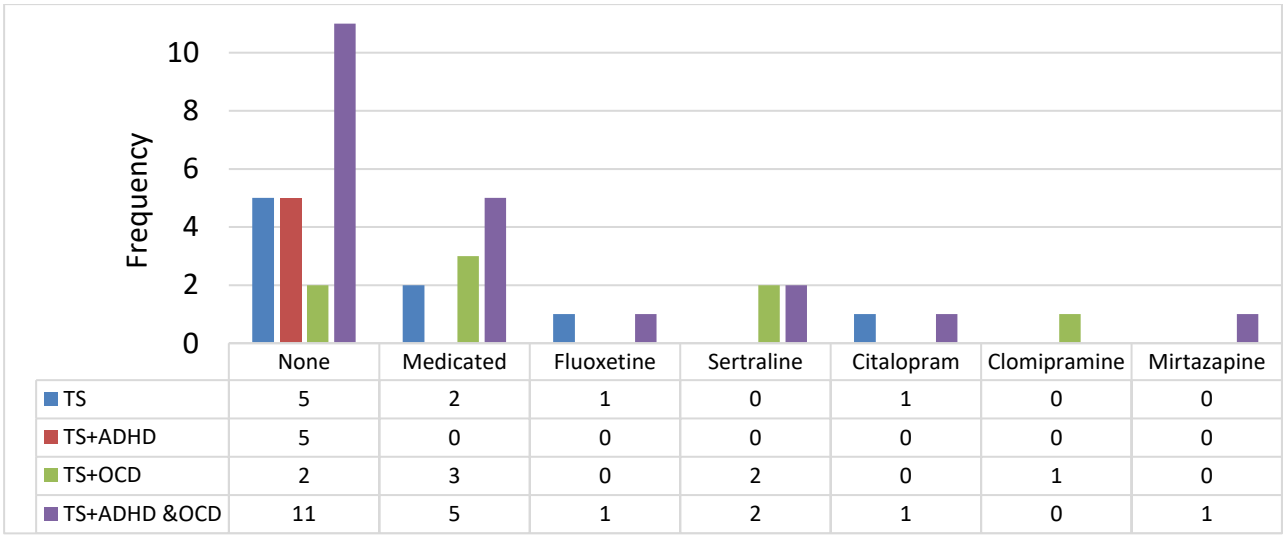


	None	Medicated	Aripiprazole	Risperidone	Haloperidol	Pimozide	Pericyazine
TS	5	2	1	1	0	0	0
TS+ADHD	5	0	0	0	0	0	0
TS+OCD	4	1	0	0	1	0	0
TS+ADHD & OCD	10	6	4	0	0	1	1

Figure 128. Frequency of adults with TS medicated with antipsychotics, alongside a breakdown of the various types of antipsychotics for each comorbidity subgroup.

Antidepressants

There were no significant differences in the distribution of those medicated with antidepressants, X_2 (3) =4.278 p = .233, across comorbidity subgroups.

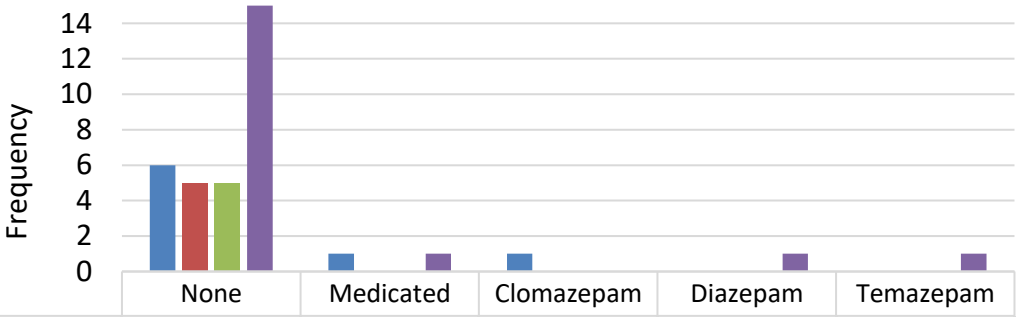


	None	Medicated	Fluoxetine	Sertraline	Citalopram	Clomipramine	Mirtazapine
TS	5	2	1	0	1	0	0
TS+ADHD	5	0	0	0	0	0	0
TS+OCD	2	3	0	2	0	1	0
TS+ADHD &OCD	11	5	1	2	1	0	1

Figure 129. Frequency of adults with TS medicated with antidepressants, alongside a breakdown of the various types of antidepressant for each comorbidity subgroup.

Benzodiazepines

There were no significant differences in the distribution of those medicated with benzodiazepines, X_2 (3) = 1.478 p = .687, across comorbidity subgroups.

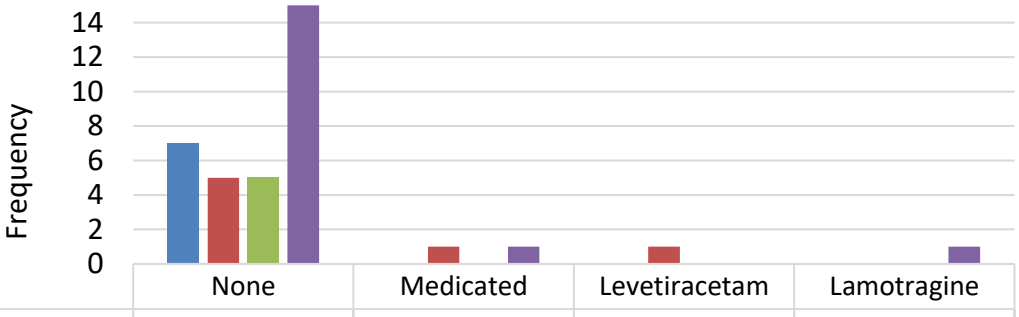


	None	Medicated	Clomazepam	Diazepam	Temazepam
TS	6	1	1	0	0
TS + ADHD	5	0	0	0	0
TS + OCD	5	0	0	0	0
TS + ADHD & OCD	15	1	0	1	1

Figure 130. Frequency of adults with TS medicated with benzodiazepines, alongside a breakdown of the various types of benzodiazepine for each comorbidity subgroup.

Antiepileptics

There was no significant differences in the distribution of those medicated with antiepileptics, X_2 (3) = 2.482, p = .479, across comorbidity subgroups.

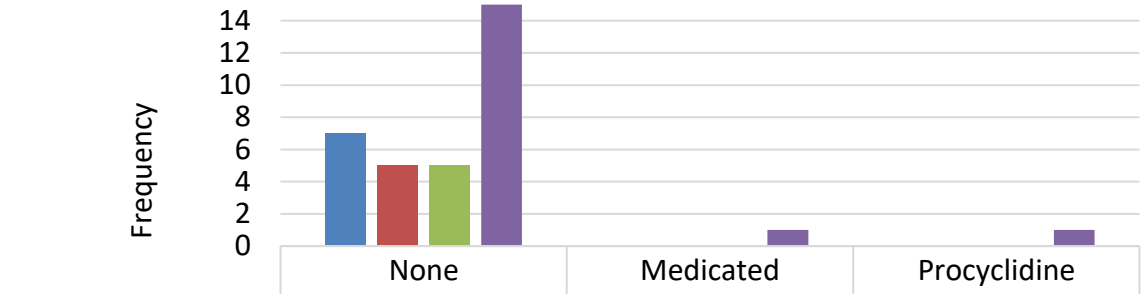


	None	Medicated	Levetiracetam	Lamotragine
TS	7	0	0	0
TS + ADHD	5	1	1	0
TS + OCD	5	0	0	0
TS + ADHD & OCD	15	1	0	1

Figure 131. Frequency of adults with TS medicated with antiepileptics, alongside a breakdown of the various types of antiepileptic for each comorbidity subgroup.

Anticholinergic

There was no significant differences in the distribution of those medicated with anticholinergics, X_2 (3) = 1.096, p = .778, across comorbidity subgroups.



	None	Medicated	Procyclidine
TS	7	0	0
TS + ADHD	5	0	0
TS + OCD	5	0	0
TS + ADHD & OCD	15	1	1

Figure 132. The frequency of adults with TS medicated with anticholinergics, alongside a breakdown of the type of anticholinergic for each comorbidity subgroup.

Medication Combinations

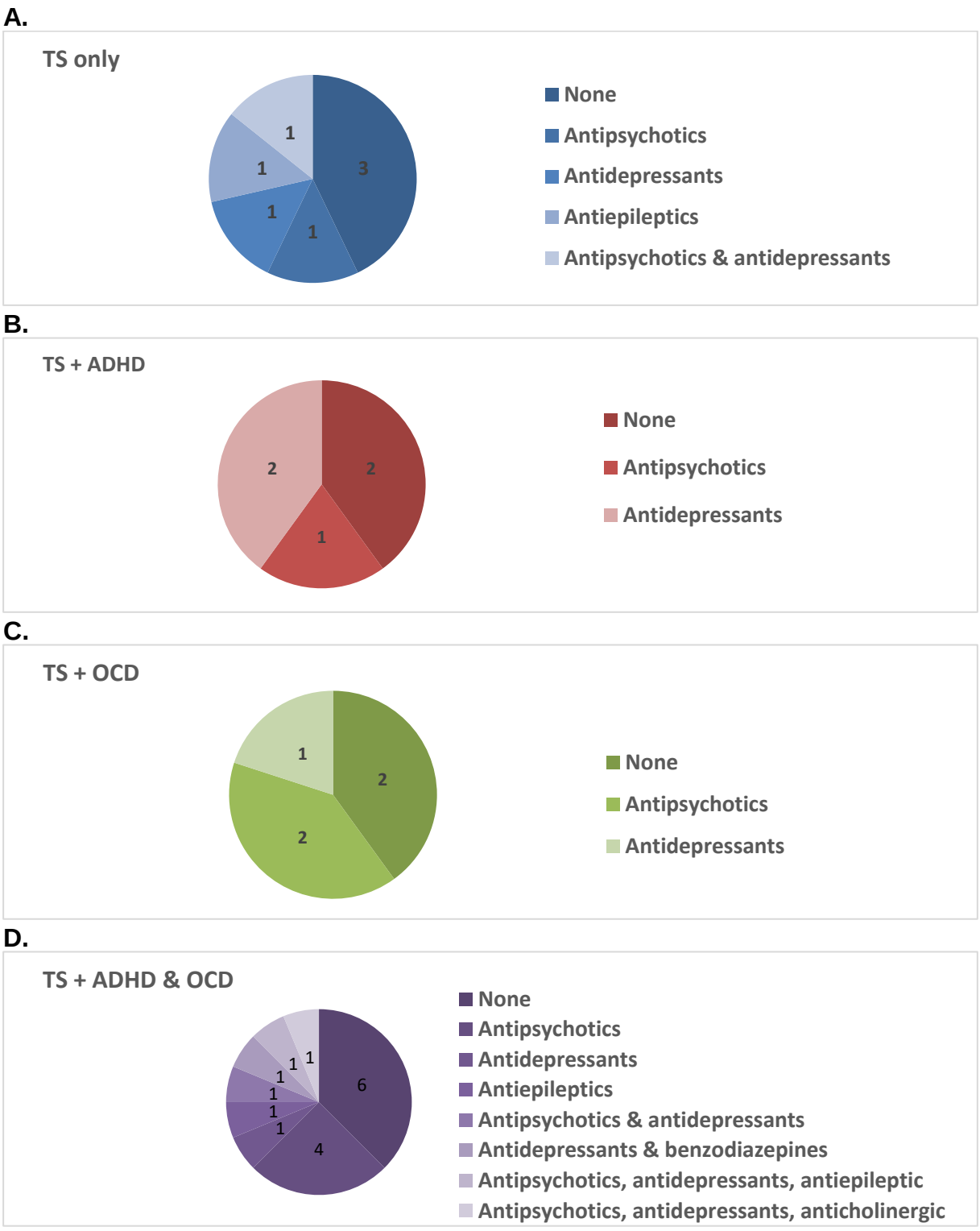


Figure 133. Different medication combinations received by adults with TS with A) uncomplicated, B) comorbid OCD, C) comorbid ADHD and D) complicated TS.

Summary

Only nine individuals were medicated with antipsychotics and there was no difference in the distribution of antipsychotic medicated and non-medicated individuals across comorbidity subgroups. Similarly, there were no differences in the distribution of those medicated with antidepressants, benzodiazepines or anti-epileptics, across comorbidity subgroups.

Clinical profile

Premonitory urges

Results

PUTS

There was a significant effect of comorbidity on PUTS scores, F (3, 29) = 3.756, p = .022, r = .34. Post-hoc analyses using Gabriel's procedure revealed that those with comorbid ADHD only had significantly lower PUTS scores than those with comorbid ADHD and OCD (p = .028).

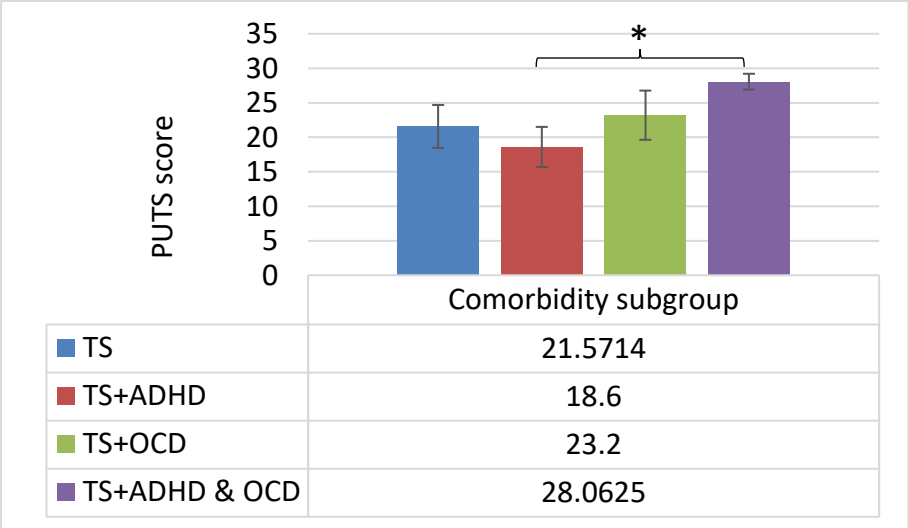


Figure 134. Mean PUTS score for each comorbidity subgroup. Errors bars represent SEM.*Significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to PUTS score, F (1, 28) = .356, p = .555, r = .11. There remained a significant effect of comorbidity subgroup on PUTS score after controlling for the effect of medication with antipsychotics, F (3, 28) = 3.104, p = .042, η^2 = .250; remaining significant following Benjamini-Hochberg FDR correction.

Summary

Participants with uncomplicated TS and lone comorbid OCD were observed to have intermediate PUTS scores; those with lone comorbid ADHD had significantly reduced urge severity than individuals with complicated comorbidity who had the worst urge severity of all subgroups. The effects of comorbidity subgroup were independent from the effects of medication with antipsychotics.

Tic severity

Results

YGTSS

There was a significant effect of comorbidity on YGTSS total score, F (3, 29) = 3.823, p = .020, r = .34. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS only had significantly lower scores compared to those with comorbid ADHD and OCD (p = .031).

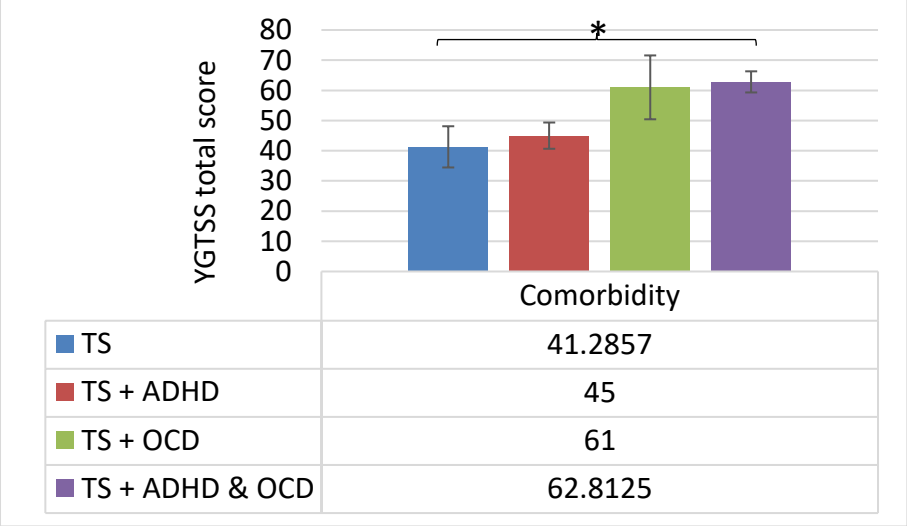
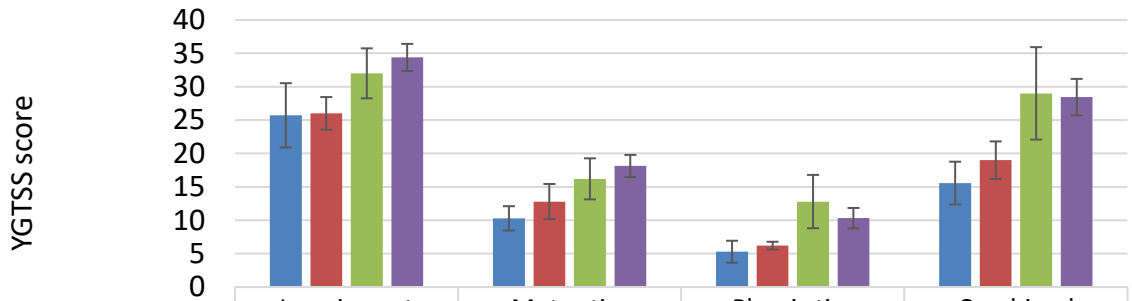


Figure 135. Mean total YGTSS scores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

There was no significant effect of comorbidity subgroup on YGTSS impairment score, F (3, 29) = 2.719, p = .063, r = .29, YGTSS phonic tic score, F (3, 29) = 2.276, p = .101, r = .27, or YGTSS motor tic score, F (3, 32) = 2.897 p = .052, r = .29. There was a significant effect of comorbidity subgroup on the YGTSS combined score, F (3, 32) = 3.068, p = .043 r = .30. Following Gabriel's post hoc analyses, the difference was observed between those with uncomplicated and complicated (>1 comorbidity), whereby more complex comorbidity was associated with higher combined scores at trend level significance (p = .064).



	Impairment	Motor tics	Phonic tics	Combined
TS	25.71	10.29	5.29	15.57
TS + ADHD	26.00	12.80	6.20	19.00
TS + OCD	32.00	16.20	12.80	29.00
TS + ADHD & OCD	34.38	18.13	10.31	28.44

Figure 136. Mean YGTSS subscale scores for each comorbidity subgroup. Error bars represent SEM.

Age onset

There was no main effect of comorbidity subgroup on age of onset for motor tics, H (3) = 5.802, p = .122, or age worst motor tic, H (3) = 2.781, p = .427. Similarly, there was no main effect of comorbidity subgroup on age of onset for vocal tics, H (3) = 3.14, p = .371, or age worst vocal tic, H (3) = 6.49, p = .090.

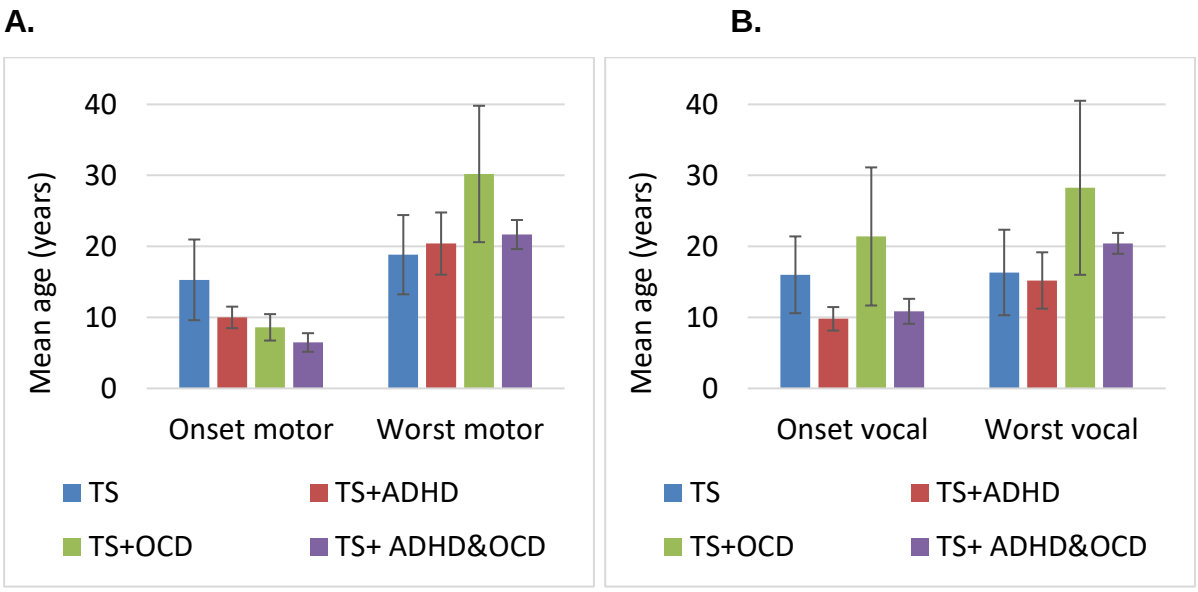


Figure 137. Mean age of onset and age of worst tics for A) motor tics and B) vocal tics, for each comorbidity subgroup. Error bars represent SEM.

MRVS

There was a trend towards a significant effect of comorbidity on MRVS total score, F (3, 29) = 2.719, p = .063, r = .29. Post-hoc analyses using Gabriel's procedure revealed that those with TS only had significantly lower scores than those with comorbid ADHD and OCD (p = .048).

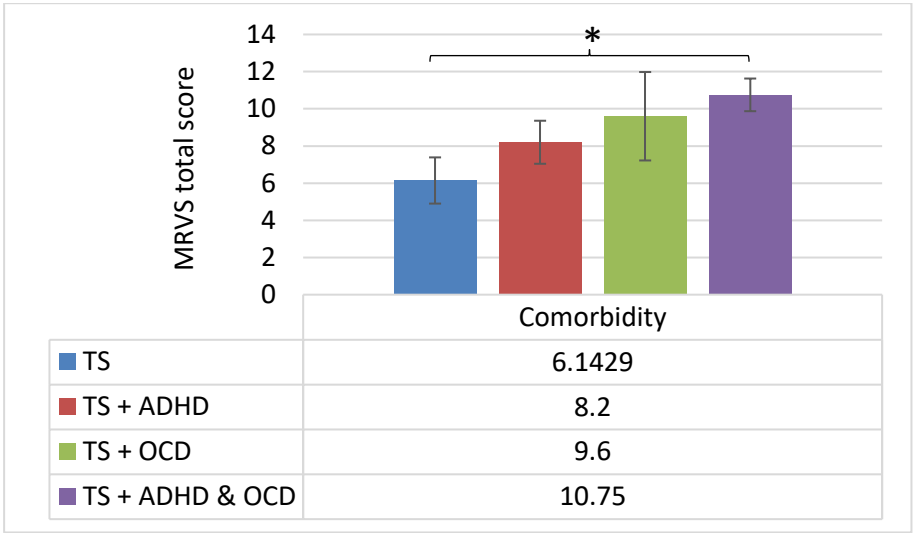
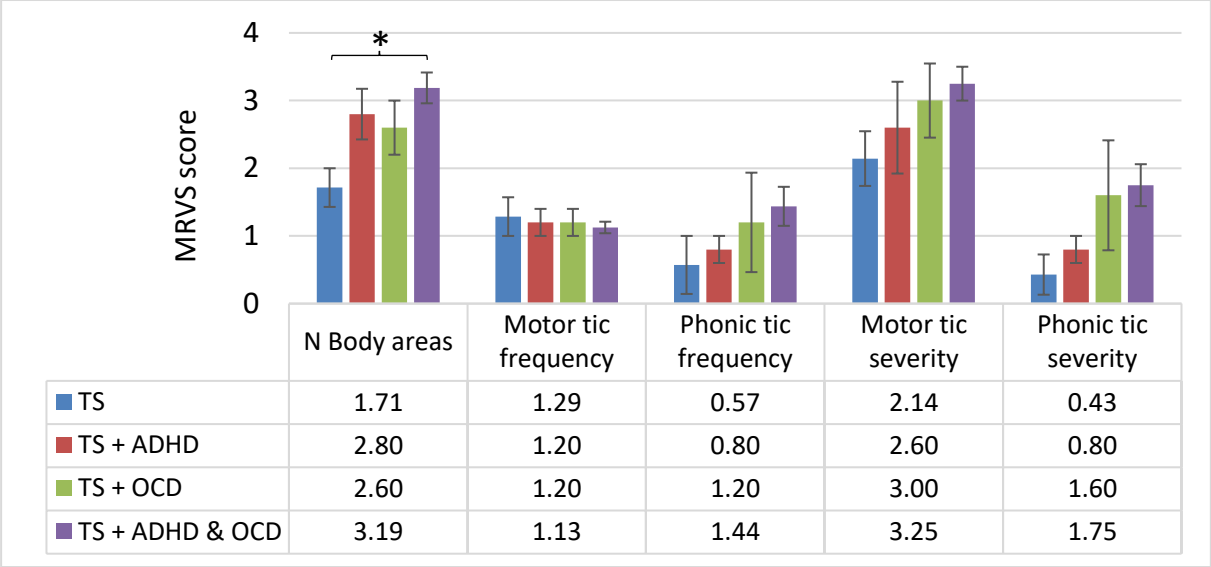


Figure 138. Mean MRVS scores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

There was a significant effect of comorbidity subgroup on the number of body areas, F (3, 29) = 4.721 p = .008, r = .37. Gabriel's post hoc analyses revealed a significant difference (p = .004) between those with uncomplicated TS and those with comorbid ADHD and OCD; with significantly more body areas affected with comorbidity. There were no significant effects of comorbidity subgroups on motor tic frequency, F (3, 29) = .186, p = .905, r = .08, or severity, F (3, 29) = 1.685, p = .192, r = .23 or on phonic tic frequency, F (3, 29) = 1.050, p = .385, r = .19, or severity, F (3, 29) = 2.435, p = .085, r = .28.



	N Body areas	Motor tic frequency	Phonic tic frequency	Motor tic severity	Phonic tic severity
TS	1.71	1.29	0.57	2.14	0.43
TS + ADHD	2.80	1.20	0.80	2.60	0.80
TS + OCD	2.60	1.20	1.20	3.00	1.60
TS + ADHD & OCD	3.19	1.13	1.44	3.25	1.75

Figure 139. Mean MRVS subscores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to YGTSS score, F (1, 28) = 1.235, p = .276, r = .21. There remained a significant effect of comorbidity subgroup on YGTSS score after controlling for the effect of medication with antipsychotics, F (3, 28) = 3.388, p = .032, η^2 = .266; remaining significant following Benjamini-Hochberg FDR correction.

Summary

Individuals with uncomplicated TS had the lowest YGTSS scores of all subgroups whilst those with comorbid ADHD and OCD had the highest YGTSS scores of all

subgroups. Individuals with lone comorbid ADHD or OCD were seen to have intermediate YGTSS scores, and the presence of OCD (lone and alongside ADHD) appeared to result in higher YGTSS scores. There was only a significant difference amongst tic severity for those with uncomplicated TS and those with more complicated (>1 comorbidity) TS. Exploration of the YGTSS subscale scores revealed that comorbidity subgroup was not associated with significant differences in impairment scores or motor and phonic tic severity. There was an effect of comorbidity subgroup on the combined score that mirrored the results of the YGTSS total score. Furthermore, there was no differences in the age of onset or age of worst motor or vocal tics across comorbidity subgroups.

Similarly, uncomplicated TS was associated with lower MRVS total score than those with complicated TS; this however only reach trend level significance. Exploration of MRVS subscale revealed that comorbidity subgroup was only associated with significant differences in the number of body areas subscore, whereby uncomplicated TS was associated with significantly fewer affected body areas than complicated TS. The effects of comorbidity subgroup were independent from the effects of medication with antipsychotics.

Comorbidity

Results

ADHD

BAARS-IV

There was a significant effect of comorbidity on BAARS-IV total score, F (3, 29) = 12.490, p = .000, r = .55. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower total score percentiles than those with comorbid ADHD (p =.001), comorbid OCD (p =.024) and complicated TS (p =.000).

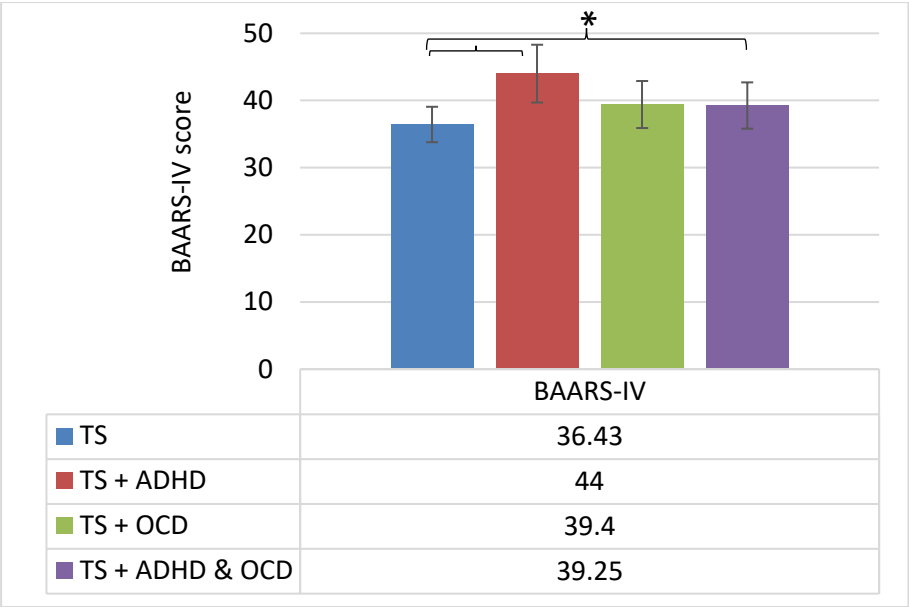


Figure 140. Total BAARS-IV percentile scores for each comorbidity subgroup in adult TS. *Significant following Benjamini-Hochberg FDR correction.

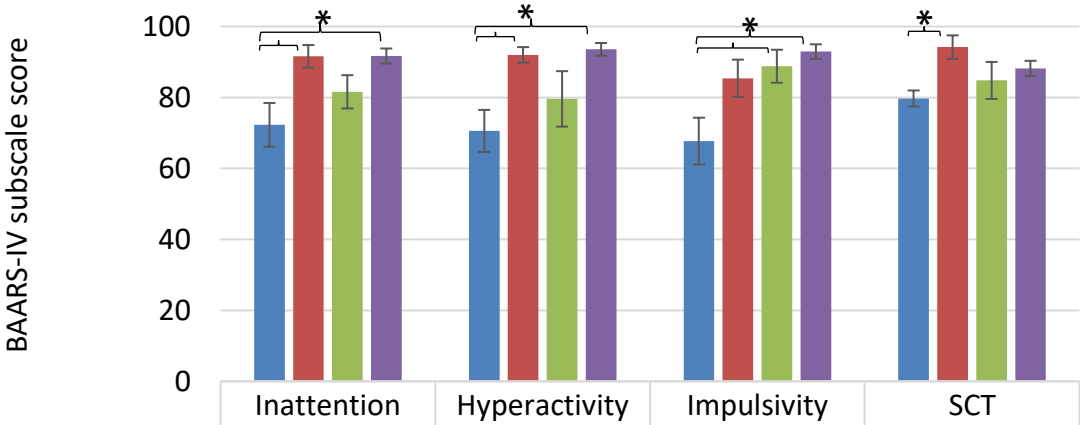
There was a significant effect of comorbidity on BAARS-IV inattention score, *F* (3, 29) = 6.106, *p* = .002, *r* = .42. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower inattention percentiles than those with comorbid ADHD (*p* =.025) and complicated TS (*p* =.002) but not those with comorbid OCD (*p* =.590).

There was a significant effect of comorbidity on BAARS-IV hyperactivity score, *F* (3, 29) = 8.033, *p* = .000, *r* = .47. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower hyperactivity percentiles than those with comorbid ADHD (*p* =.015) and complicated TS (*p* =.000) but not those with comorbid OCD (*p* =.659).

There was a significant effect of comorbidity on BAARS-IV impulsivity score, *F* (3, 29) = 7.993, *p* = .000, *r* = .46. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower impulsivity percentiles than those with comorbid OCD (*p* =.022) and those with complicated TS (*p* =.000) but not those with comorbid ADHD (*p* =.074). Subgroups with comorbidities did not differ from each other on impulsivity (*p* > .05).

There was a significant effect of comorbidity on BAARS-IV sluggish cognitive tempo score, *F* (3, 29) = 3.143, *p* = .040, *r* = .31. Post-hoc analyses using Gabriel's

procedure revealed that those with uncomplicated TS had significantly lower SCT percentiles than those with comorbid ADHD (*p* =.038) but not those with comorbid OCD (*p* =.880) and complicated TS (*p* =.170).



	Inattention	Hyperactivity	Impulsivity	SCT
TS	72.29	70.57	67.71	79.71
TS + ADHD	91.6	92	85.4	94.2
TS + OCD	81.6	79.6	88.8	84.8
TS + ADHD & OCD	91.69	93.56	92.94	88.19

Figure 141. BAARS-IV percentile scores for inattention, hyperactivity, impulsivity and sluggish cognitive tempo subscales amongst comorbidity subgroups in adults with TS. *Significant following Benjamini-Hochberg FDR correction.

ASRS

There was a significant effect of comorbidity on ASRS total score, *F* (3, 29) = 15.833, *p* = .000, *r* = .59. Post-hoc analyses using Gabriel's procedure revealed that there were no differences in ADHD composite scores amongst comorbidity subgroups with ADHD (*p* =.499). Furthermore, uncomplicated TS was found to have significantly lower scores than those with comorbid ADHD (*p* =.004) and complicated TS (*p* =.000) but not comorbid OCD (*p* =.224). Additionally, those with comorbid OCD had significantly lower total scores than those with complicated TS (*p* =.007) and did not differ from those with comorbid ADHD (*p* =.555).

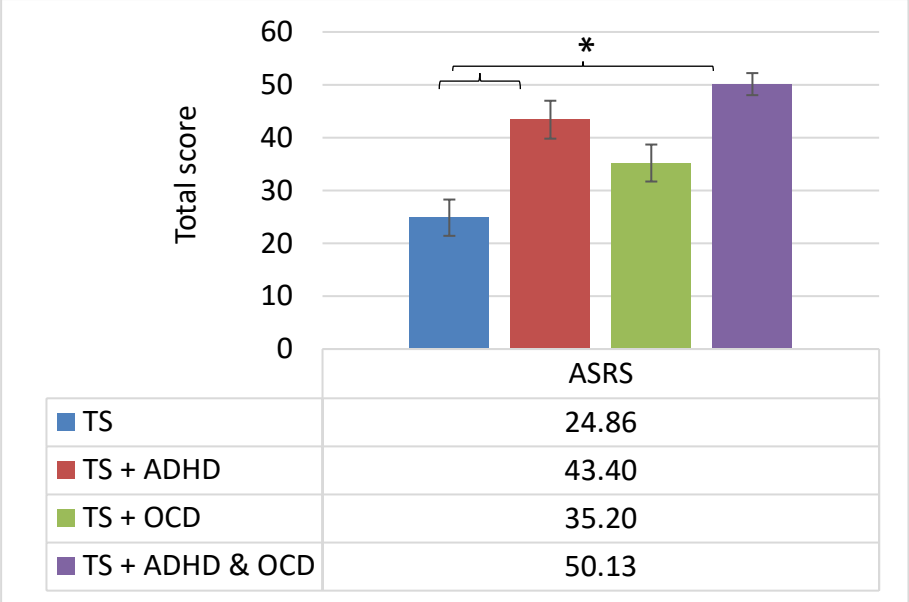


Figure 142. ASRS total scores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Composite

There was a significant effect of comorbidity on ADHD composite score, F (3, 29) = 22.141, p = .000, r = .66. Post-hoc analyses using Gabriel's procedure revealed that there were no differences in ADHD composite scores amongst comorbidity subgroups with ADHD (p =.833). Furthermore, uncomplicated TS was found to have significantly lower composite scores than those with comorbid ADHD (p =.000), comorbid OCD (p =.012) and complicated TS (p =.000). Additionally, those with comorbid OCD had significantly lower composite scores than those with complicated TS (p =.014) and did not differ from those with comorbid ADHD (p =.436).

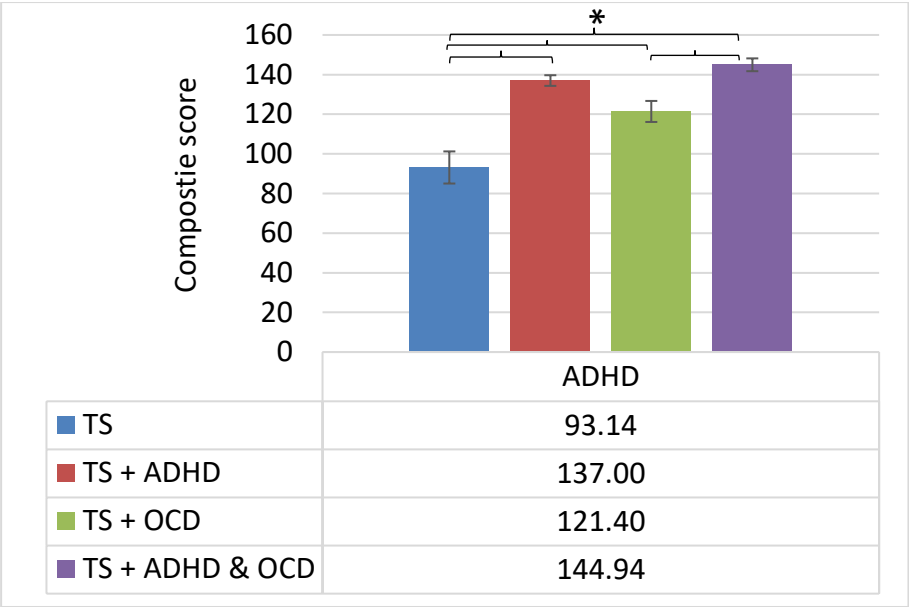


Figure 143. ADHD composite scores each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

OCD

Padua-L

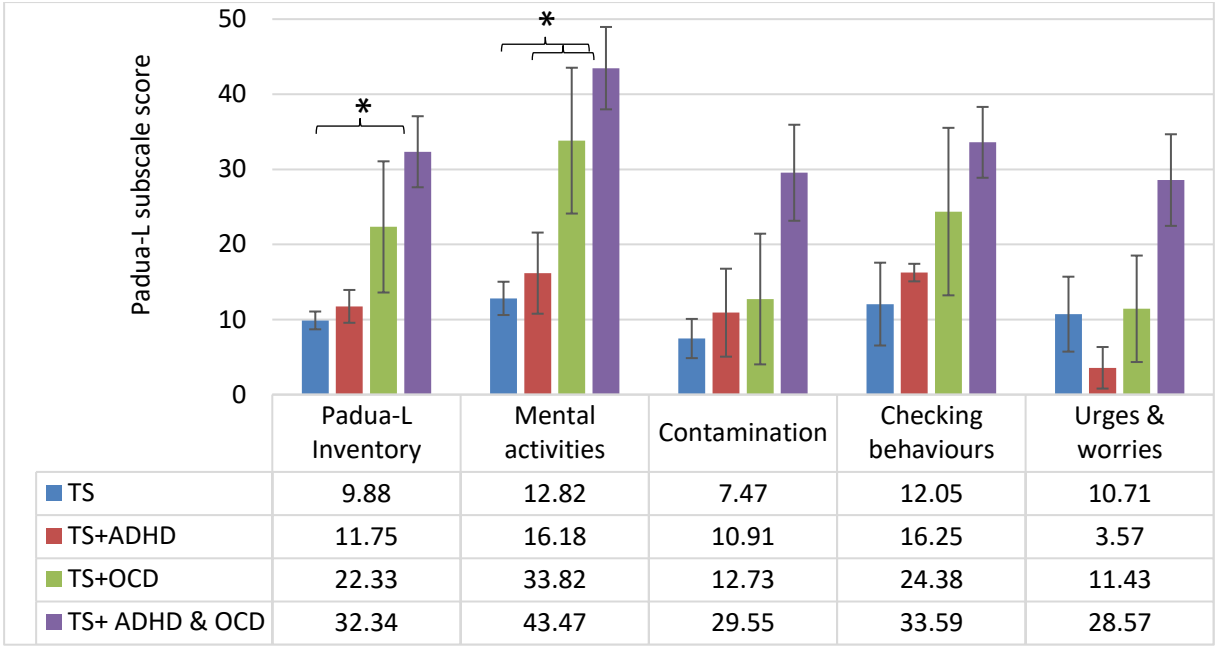
There was no significant effect of comorbidity subgroup on Padua-L contamination subscale, F (3, 29) = 2.535, p = .076, r = .28, or checking behaviours subscales, F (3, 29) = 2.899, p = .052, r = .30.

There was a significant effect of comorbidity on Padua-L inventory score, F (3, 29) = 4.437, p = .011, r = .36. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower inventory scores than those with complicated TS (p =.017).

There was a significant effect of comorbidity on Padua-L mental activities subscore, F (3, 29) = 5.799, p = .003, r = .41. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower mental activities subscores than those with complicated TS (p = .005). Furthermore, those with comorbid ADHD only also had significantly lower mental activities subscores than those with complicated TS (p = .032).

There was a significant effect of comorbidity on Padua-L urges and worries subscore, F (3, 29) = 2.899, p = .049, r = .30. Post-hoc analyses using Gabriel's

procedure revealed no significant differences amongst comorbidity subgroups on urges and worries subscores ($p > .05$).



	Padua-L Inventory	Mental activities	Contamination	Checking behaviours	Urges & worries
TS	9.88	12.82	7.47	12.05	10.71
TS+ADHD	11.75	16.18	10.91	16.25	3.57
TS+OCD	22.33	33.82	12.73	24.38	11.43
TS+ ADHD & OCD	32.34	43.47	29.55	33.59	28.57

Figure 144. Padua-L inventory and subscale scores (normalised to the number of items used in calculating each score) for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

OCI

There was a significant effect of comorbidity on OCI distress score, F (3, 29) = 4.721, p = .008, r = .37. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower inventory scores than those with complicated TS (p =.015).

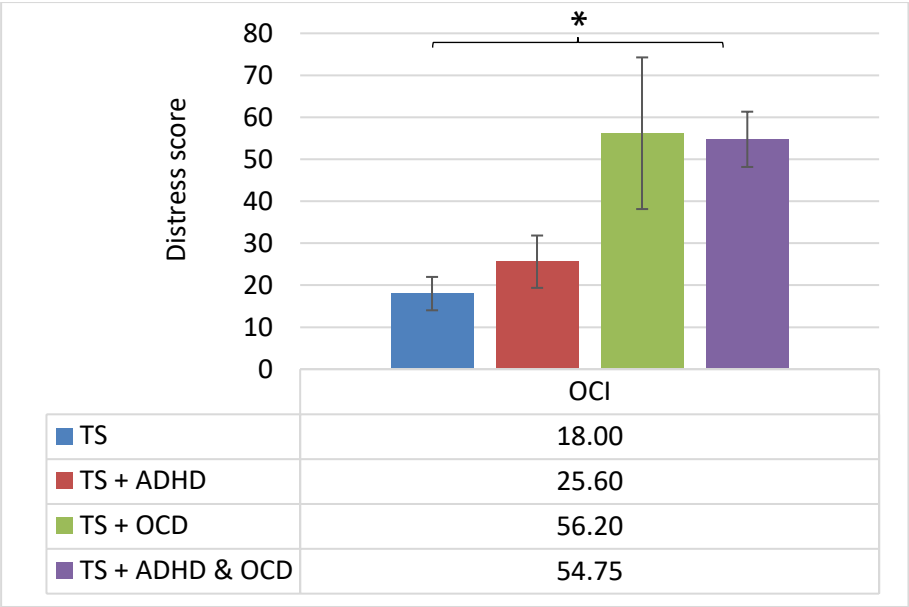


Figure 145. OCI distress score for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

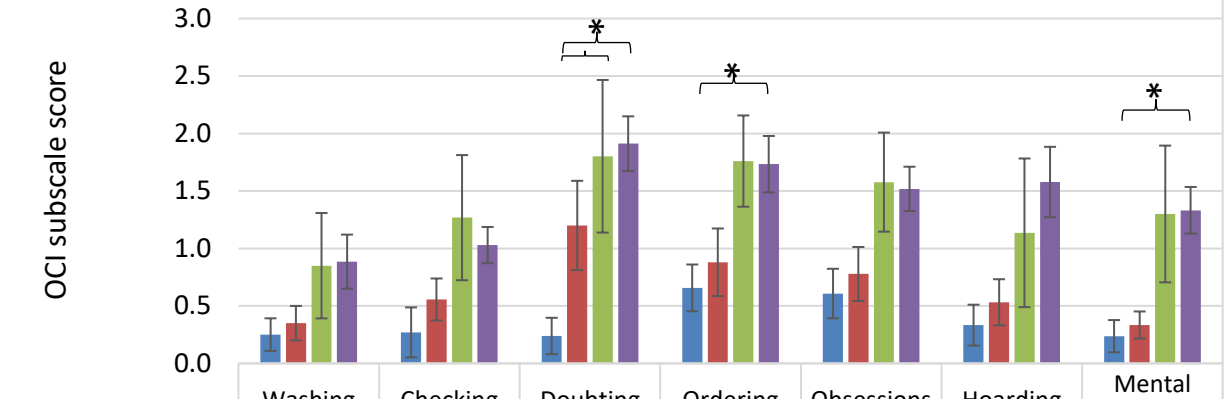
There was no significant effect of comorbidity subgroup on OCI washing subscale, *F* (3, 28) = 1.413, *p* = .260, *r* = .22, checking subscales, *F* (3, 28) = 2.790, *p* = .059, *r* = .30 or hoarding subscales, *F* (3, 28) = 2.829, *p* = .057, *r* = .31.

There was a significant effect of comorbidity on OCI doubting subscale, *F* (3, 28) = 5.410, *p* = .005, *r* = .40. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower doubting subscale scores than those with comorbid OCD (*p* =.047) and complicated TS (*p* =.003) but no difference compare to those with comorbid ADHD (*p* =.417).

There was a significant effect of comorbidity on OCI ordering subscale, *F* (3, 28) = 3.639, *p* = .025, *r* = .34. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower ordering subscale scores than those with complicated TS (*p* =.043).

There was a significant effect of comorbidity on OCI obsessions subscale, *F* (3, 28) = 3.567, *p* = .027, *r* = .34. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had lower obsession subscale scores than those with complicated TS at trend level significance (*p* =.051).

There was a significant effect of comorbidity on OCI mental neutralising subscale, F (3, 28) = 4.577, p = .010, r = .37. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower mental neutralising subscale scores than those with complicated TS (p =.023).



	Washing	Checking	Doubting	Ordering	Obsessions	Hoarding	Mental neutralising
TS	0.25	0.27	0.24	0.66	0.61	0.33	0.24
TS + ADHD	0.35	0.56	1.20	0.88	0.78	0.53	0.33
TS + OCD	0.85	1.27	1.80	1.76	1.58	1.14	1.30
TS + ADHD & OCD	0.89	1.03	1.91	1.73	1.52	1.58	1.33

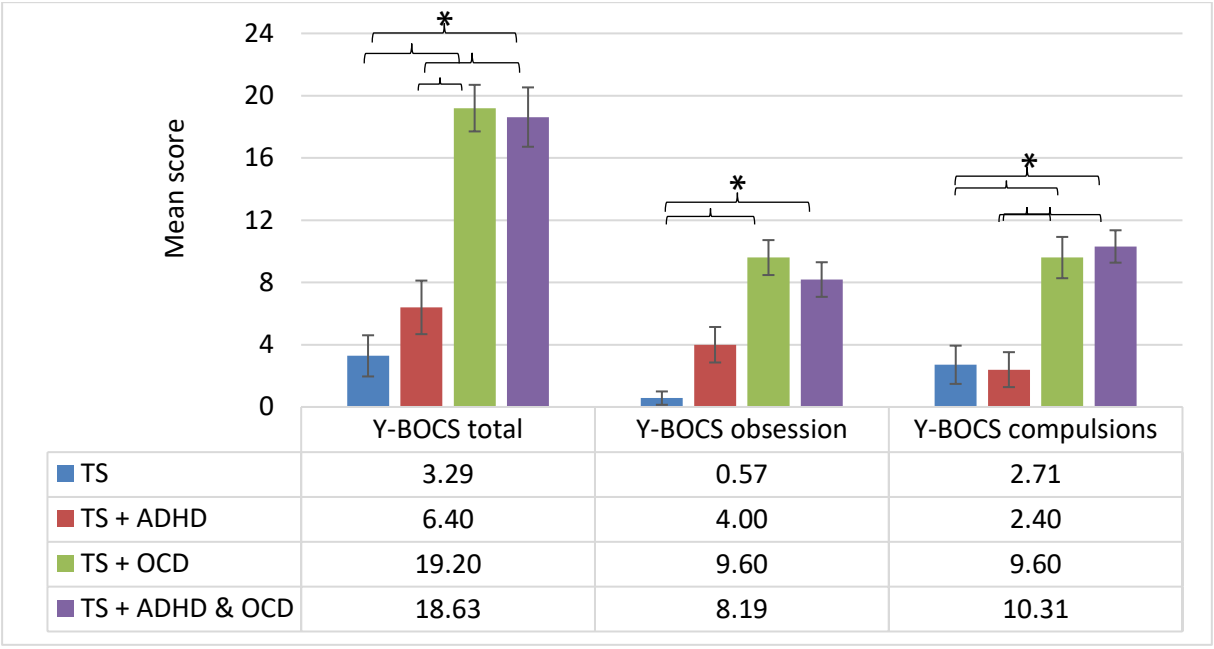
Figure 146. OCI subscale scores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Y-BOCS

There was a significant effect of comorbidity on Y-BOCS total score, F (3, 29) = 14.416, p = .000, r = .58. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower total scores than those with comorbid OCD (p =.001) and complicated TS (p =.000) but not compared to those with comorbid ADHD (p =.936). Similarly, those with comorbid ADHD had significantly lower total scores than those with comorbid OCD (p =.013) and complicated TS (p =.002).

There was a significant effect of comorbidity on Y-BOCS obsession score, F (3, 29) = 9.981, p = .000, r = .51. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower obsession scores than those with comorbid OCD (p =.001) and complicated TS (p =.000) but not compared to those with comorbid ADHD (p =.463).

There was a significant effect of comorbidity on Y-BOCS compulsion score, *F* (3, 29) = 11.063, *p* = .000, *r* = .53. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower obsession scores than those with comorbid OCD (*p* =.017) and complicated TS (*p* =.000) but not compared to those with comorbid ADHD (*p* =1.000). Similarly, those with comorbid ADHD had significantly lower total scores than those with comorbid OCD (*p* =.023) and complicated TS (*p* =.001).



	Y-BOCS total	Y-BOCS obsession	Y-BOCS compulsions
TS	3.29	0.57	2.71
TS + ADHD	6.40	4.00	2.40
TS + OCD	19.20	9.60	9.60
TS + ADHD & OCD	18.63	8.19	10.31

Figure 147. Y-BOCS total, obsession and compulsion scores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Composite

There was a significant effect of comorbidity on OCD composite score, *F* (3, 29) = 6.149, *p* = .002, *r* = .42. Post-hoc analyses using Gabriel's procedure revealed that those with uncomplicated TS had significantly lower composite scores than those with complicated TS (*p* =.003) but not compared to those with comorbid ADHD (*p* =.999) or comorbid OCD (*p* =.146). Similarly, those with comorbid ADHD had significantly lower total scores than those with complicated TS (*p* =.034). Subgroups with comorbid OCD did not differ from each other on Y-BOCS total scores (*p* = .976).

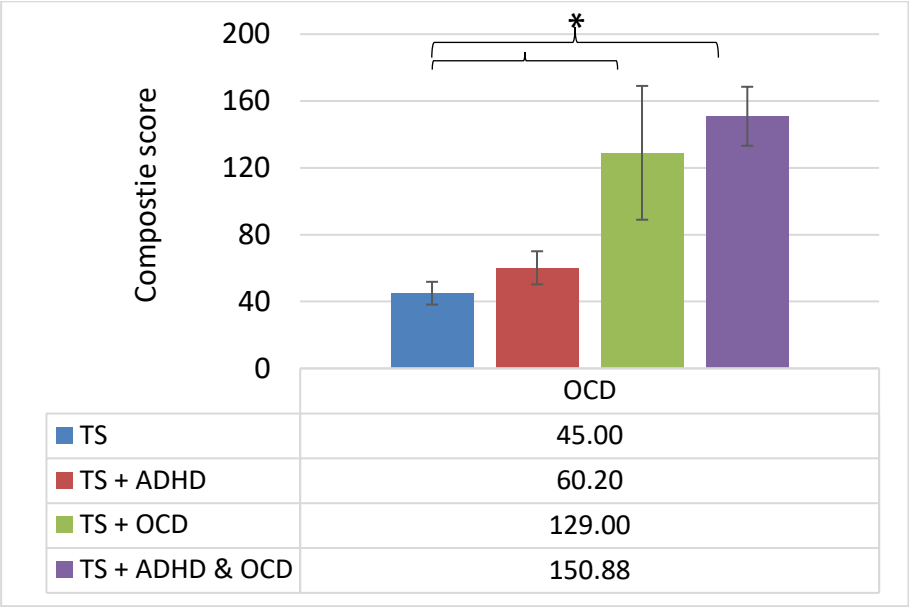


Figure 148. OCD composite scores for each comorbidity subgroup. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Summary

Individuals with uncomplicated TS naturally had the lowest scores on measures of ADHD and OCD symptomatology and it was observed that the more complicated the comorbidity, the more severe the clinical symptoms.

Specifically, the presence of likely comorbid ADHD was associated with the highest total and subscale scores on the ASRS and BAARS-IV. Aside from the total BAARS-IV and SCT subscale, where those with lone comorbid ADHD scored highest, complicated TS was associated with worse ADHD symptoms. Furthermore, the presence of likely comorbid OCD was associated with the highest total and subscale scores on the Padua-L, OCI and Y-BOCS. Aside from the OCI washing, checking, ordering and obsessions subscales and Y-BOCS total and obsessions, where lone comorbid OCD scored highest, complicated TS was associated with the highest scores on the doubting, ordering, hoarding and mental neutralising OCI subscales, Y-BOCS compulsions and all Padua-L subscales.

General cognition

Results

Intra-Extradimensional set-shift (IED)

There were no significant differences amongst comorbidity subgroups in the proportion of participants failing the EDS stage (stage 8) (2*i* = 2.621, *p* = .454) or EDR stage (stage 9) (2*i* = .101 *p* = .992). There were also no differences in the total trials completed amongst comorbidity subgroups, *H* (3) = 4.612, *p* = .203.

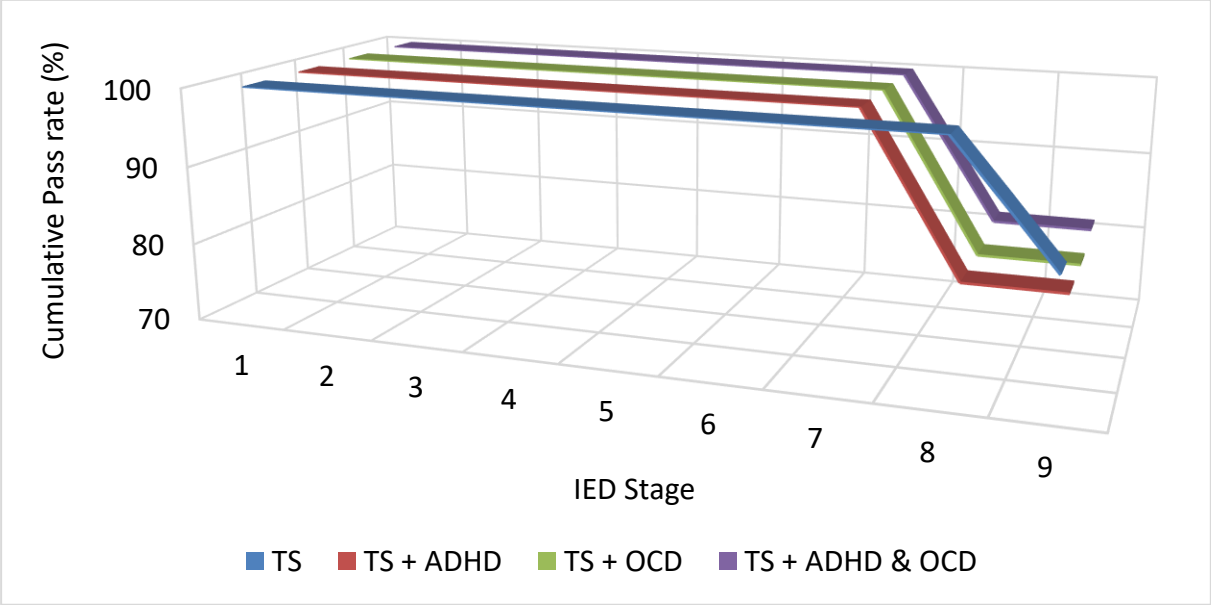


Figure 149. Cumulative pass rate (%), referring to the number of adults with TS that have completed previous and current stages, at each stage of the IED subtest for each comorbidity subgroup. *SD, simple discrimination; SR, simple reversal; C_D, compound discrimination; CD, compound discrimination; CR, compound reversal; IDS, intra-dimensional shift; IDR, intra-dimensional reversal; EDS, extra-dimensional shift; EDR, extra-dimensional reversal.*

There was a significant main effect of the IED stage on the number of errors made, *F* (3.866, 112.116) = 30.137, *p* = .000, *r* = .46. Planned contrasts (difference) comparing the number of errors made at the EDS stage to the mean effect of all previous IED stages revealed that significantly more errors were made at the EDS stage, *F* (1, 29) = 70.960, *p* = .000, *r* = .84. All differences remained following Benjamini-Hochberg FDR correction.

There was also a significant interaction effect between the IED stage and comorbidity subgroup, F (11.598, 112.116) = 2.575, p = .005, r = .15. Planned contrasts (difference) comparing the mean effect of all previous stages to the EDS stage revealed a significant difference in the number of errors made amongst comorbidity subgroups, F (3, 29) = 3.324, p = .033, r = .32, where participants with complicated TS make significantly fewer EDS errors.

There was no significant main effect of comorbidity subgroup on the number errors made at each stage of the total IED task, F (3, 29) = 1.254, p = .309, r = .20.

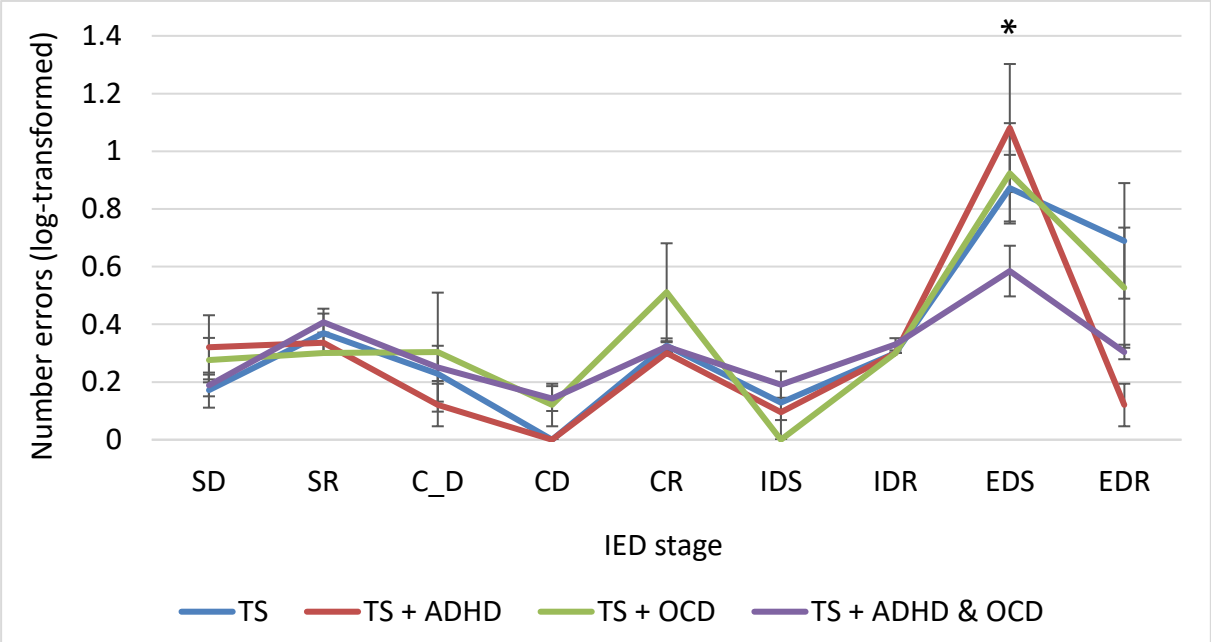


Figure 150. Mean number of errors made for each comorbidity subgroup at each IED stage. The data shown represents adults with TS that attempted the stage, having passed the previous stage. Error bars represent SEM. *Main effect of EDS stage and comorbidity subgroup on EDS errors significant following Benjamini-Hochberg FDR correction. *SD, simple discrimination; SR, simple reversal; C_D, compound discrimination; CD, compound discrimination; CR, compound reversal; IDS, intradimensional shift; IDR, intradimensional reversal; EDS, extradimensional shift; EDR, extradimensional reversal.*

Medication

Medication with antipsychotics was not significantly related to EDS errors (log-transformed), F (1, 28) = .293, p = .592, r = .10. There remained no significant effect of comorbidity subgroup on the number of EDS errors after controlling for the effect of medication with antipsychotics, F (3, 28) = 2.952, p = .05, η^2 = .240.

Stockings of Cambridge (SOC)

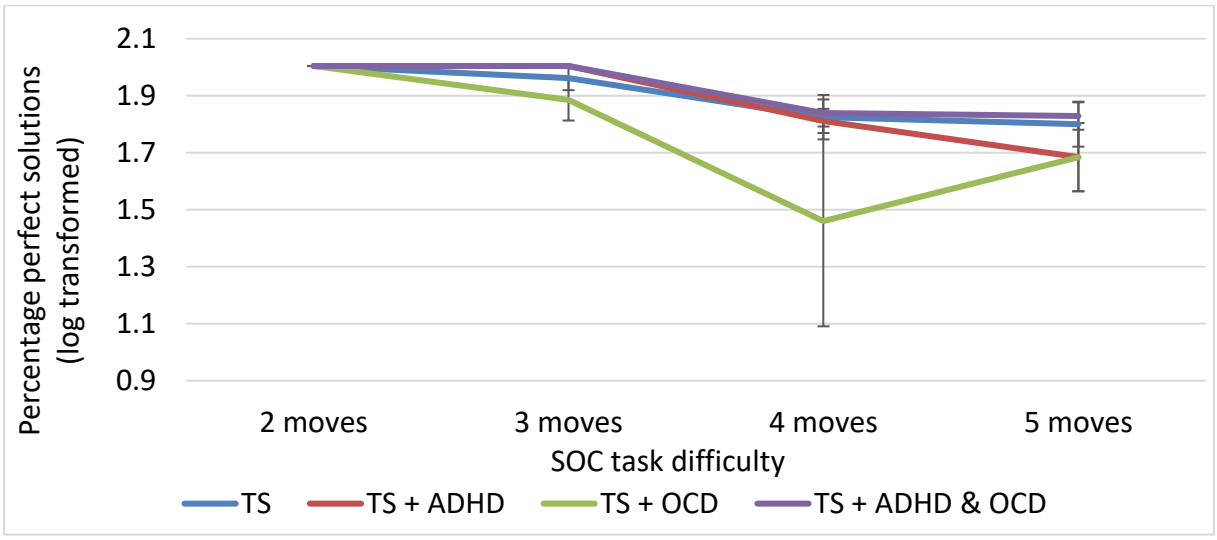
Perfect solutions

There was a significant main effect of task difficulty (number of moves a problem required to complete the task) on the percentage of problems solved perfectly, F (1.747, 50.667) = 11.858, p = .000, r = .44. Planned contrasts (simple) comparing the percentage of perfect solutions achieved at the highest level of difficulty (5 moves) found a significant increase in the percentage of perfect solutions achieved for 2 move, F (1, 29) = 35.767, p = .000, r = .74 and 3 move solutions, F (1, 29) = 18.598, p = .000, r = .63, but no difference to 4 move solutions, F (1, 29) = .043, p = .837, r = .04. All differences significant following Benjamini-Hochberg FDR correction.

There was no significant interaction between task difficulty (number of moves a problem required to complete the task) and comorbidity subgroup, F (5.241, 50.667) = .945, p = .463, r = .14.

There was a significant main effect of comorbidity on the percentage of perfect solutions achieved, F (3, 29) = 3.035, p = .045, r = .31. Post-hoc analyses using Gabriel's procedure, found that those with comorbid OCD solved fewer perfect solutions on the SOC task than those with comorbid ADHD and OCD (p = .024).

A.



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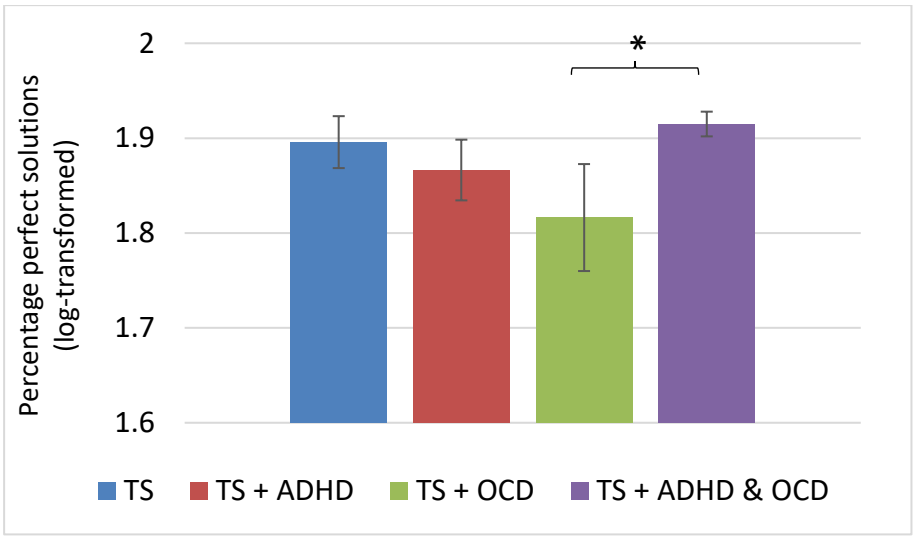


Figure 151. A) Percentage perfect solutions solved across varying levels of difficulty and B) percentage perfect solutions made on total SOC subtest for each comorbidity subgroup (all log-transformed). Errors bars represent the SEM. *Significant following Benjamini-Hochberg FDR correction.

Mean ITT

There was a significant main effect of task difficulty on the mean ITT, F (3, 87) = 69.042, p = .000, r = .67. Planned contrasts (simple) revealed that in comparison to 5 move solutions, participants took significantly less time to complete the first move of 2 move, F (1, 29) = 119.485, p = .000, r = .90, and 3 move solutions, F (1, 29) =

19.337, *p* = .000, *r* = .63, but not 4 move solutions, *F* (1, 29) = 1.751, *p* = .062, *r* = .24. Differences remained following Benjamini-Hochberg FDR correction.

There was no significant interaction effect between mean ITT at different levels of task difficulty and comorbidity subgroup, *F* (9, 87) = 1.564, *p* = .139, *r* = .13. Additionally, there was no main effect of comorbidity on mean ITT, *F* (3, 29) = .230, *p* = .875, *r* = .09. The time spent thinking (planning) about the moves to make in order to solve the task prior to attempting the first move, increases linearly with task difficulty and this effect is independent of participant comorbidity.

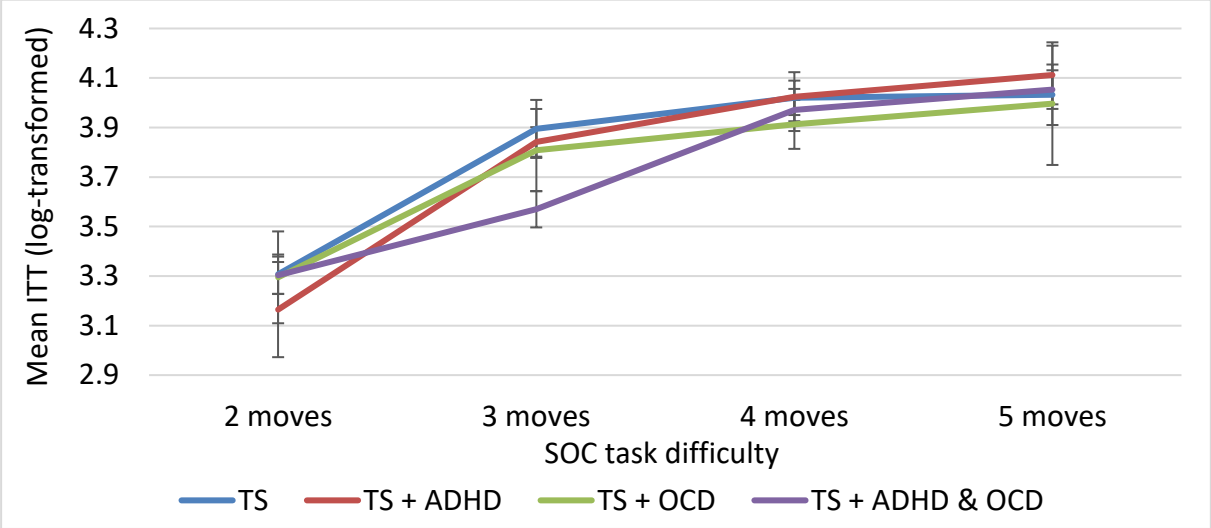


Figure 152. Mean initial thinking times across varying levels of difficulty on the SOC subtest for each comorbidity subgroup. Errors bars represent the SEM.

Mean STT

There was a significant main effect of task difficulty on the mean STT, *F* (3, 87) = 16.992, *p* = .000, *r* = .40. Planned contrasts revealed that subgroups did not differ in the time to complete subsequent moves for problems with 2 moves compared to 3 moves, *F* (1, 29) = .978, *p* = .331, *r* = .18, for 4 move problems compared to 5 moves, *F* (1, 29) = .405, *p* = .530, *r* = .12 and for 3 moves compared to 4 move difficulty, *F* (1, 53) = .074, *p* = .787, *r* = .66.

There was no significant interaction effect between mean STT at different levels of task difficulty and comorbidity, *F* (9, 87) = 1.612, *p* = .124, *r* = .13. Additionally, there was no main effect of comorbidity subgroup on mean STT, *F* (3, 29) = 1.923, *p* =

.148, *r* = .25. The time taken to complete subsequent moves of a problem following the first move, increases with task difficulty, an effect independent of comorbidity.

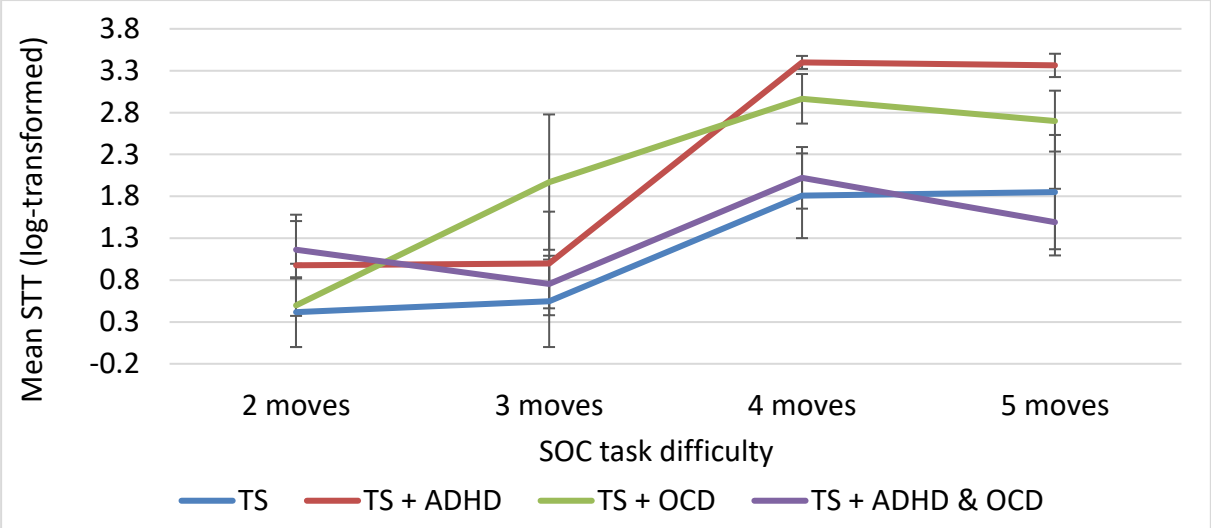


Figure 153. Mean subsequent thinking times across varying levels of difficulty on the SOC subtest for each comorbidity subgroup. Errors bars represent the SEM.

Medication

Medication with antipsychotics was not significantly related to the percentage perfect solutions (log-transformed), *F* (1, 28) = .1.012, *p* = .323, *r* = .19. There was no significant effect of comorbidity subgroup on percentage perfect solutions after controlling for the effect of medication with antipsychotics, *F* (3, 28) = 2.752, *p* = .061, η^2 = .228.

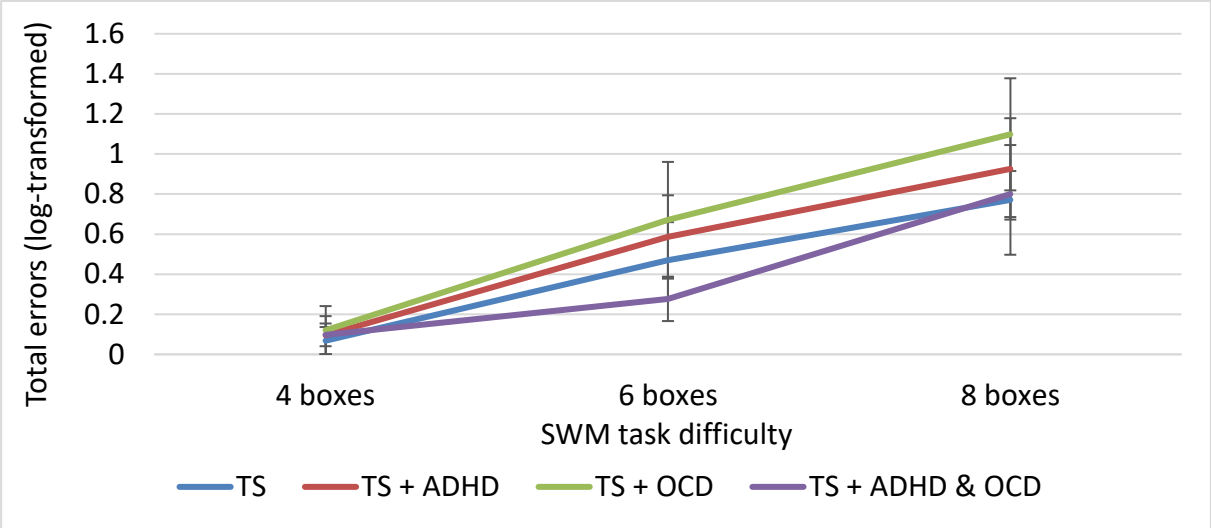
Spatial Working Memory (SWM)

Total Errors

There was a significant main effect of task difficulty (number of boxes) on mean total errors made, *F* (2, 58) = 32.284, *p* = .000, *r* = .60. Planned contrast (simple) revealed that participants made significantly more errors for problems with 8 boxes in comparison to 4 boxes, *F* (1, 29) = 55.527, *p* = .000, *r* = .81, and compared to 6 boxes, *F* (1, 29) = 15.056, *p* = .001, *r* = .58. Significant differences remained following Benjamini-Hochberg FDR correction.

There was no significant interaction effect between total errors made at different task levels of task difficulty and comorbidity subgroup, F (6, 58) = .590, p = .737, r = .10. Additionally, there was no main effect of comorbidity on total errors made, F (3, 29) = .736, p = .539, r = .16. The number of total errors made increases linearly with task difficulty irrespective of comorbidity subgroup.

A.



B.

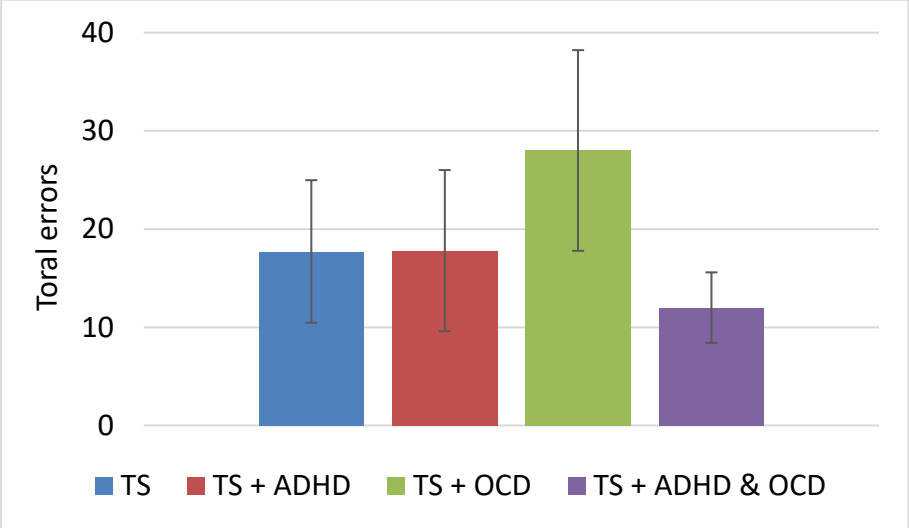


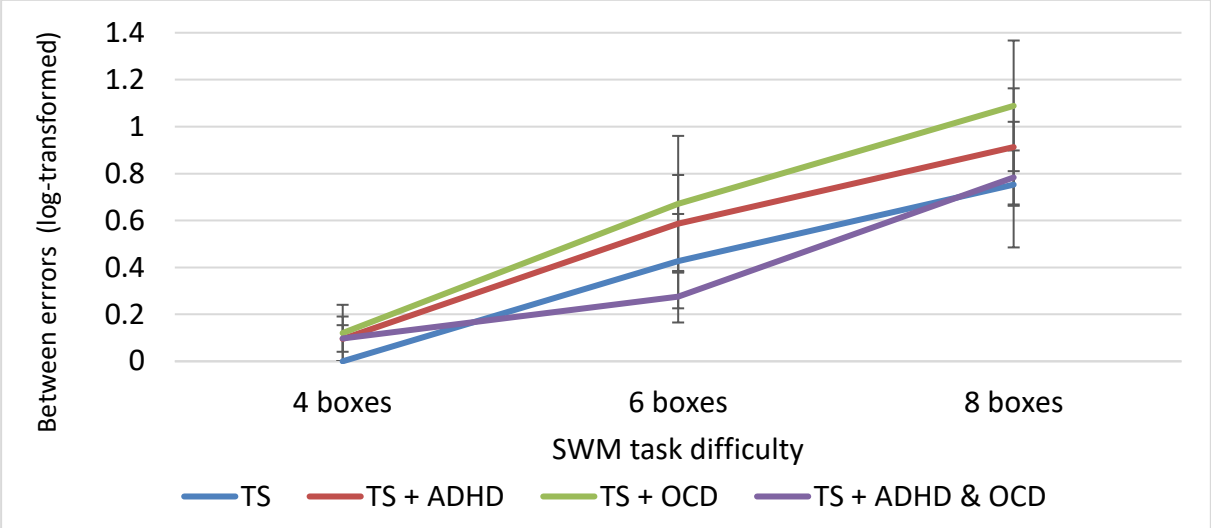
Figure 154. Mean number of total errors A) made at varying levels of task difficulty and B) for the total SWM subtest, for each comorbidity subgroup. Error bars represent SEM.

Between-errors

There was a significant main effect of task difficulty (number of boxes) on mean between-errors made, F (2, 58) = 35.969, p = .000, r = .62. Planned contrast (simple) revealed that subgroups made significantly more between-errors for problems with 8 boxes in comparison to 4 boxes, F (1, 29) = 64.020, p = .000, r = .83, and compared to 6 boxes, F (1, 29) = 16.302, p = .000, r = .60. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant interaction effect of between-errors made at different task levels of task difficulty and comorbidity subgroup, F (6, 58) = .625, p = .709, r = .10. Additionally, there was no main effect of comorbidity on between errors made on the SWM task, F (3, 29) = .776, p = .517, r = .16. The number of between-errors made increases linearly with task difficulty irrespective of comorbidity.

A.



B.

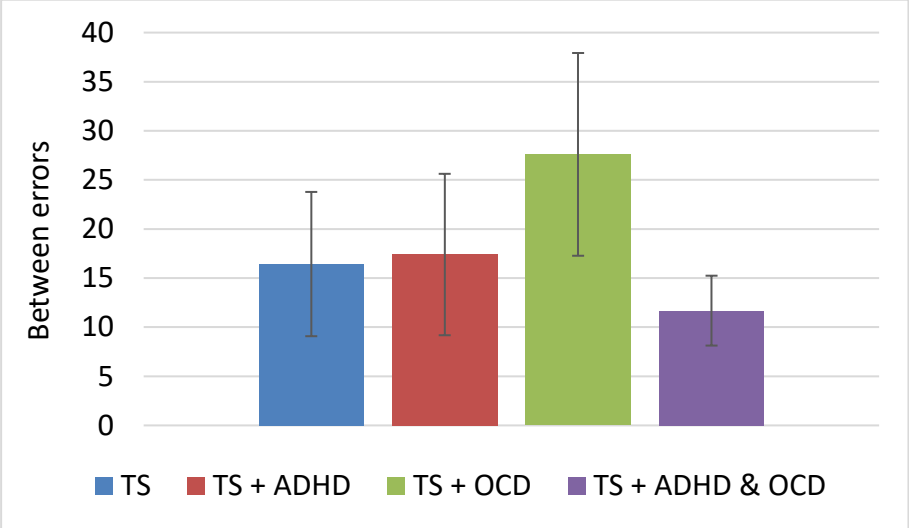
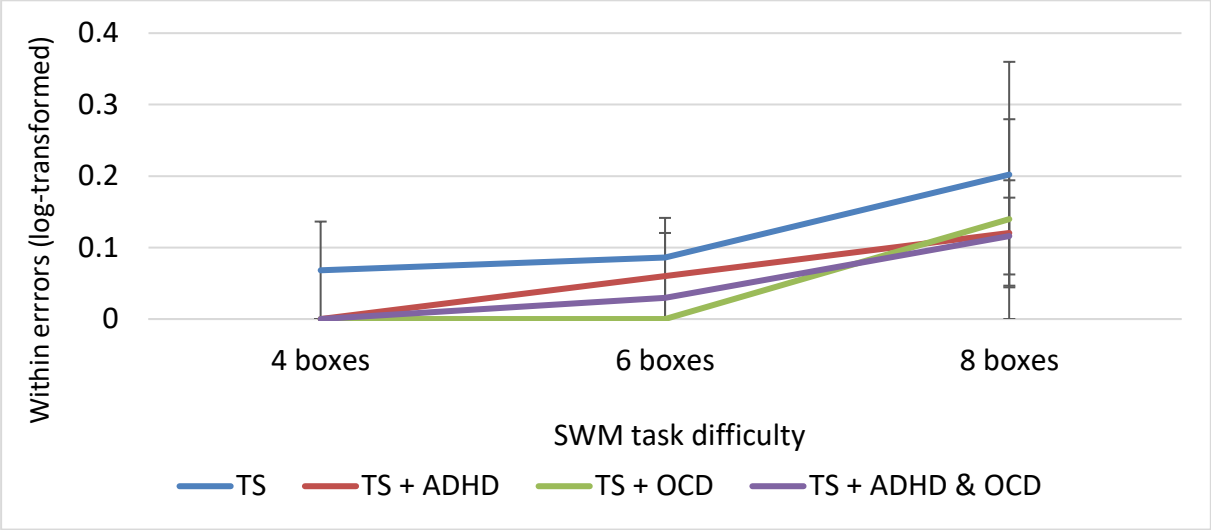


Figure 155. Mean between errors A) made at varying levels of task difficulty and B) for the total SWM subtest, for each comorbidity subgroup. Error bars represent SEM.

Within-errors

There was no significant main effect of task difficulty (number of boxes) on the number of within-errors made, F (1.206, 34.978) = 3.402, p = .06, r = .30 and no significant interaction between within-errors and comorbidity subgroup, F (3.618, 34.978) = .053, p = .992, r = .04. Additionally, there was no main effect of comorbidity, F (3, 29) = .941, p = .433, r = .18.

A.



B.

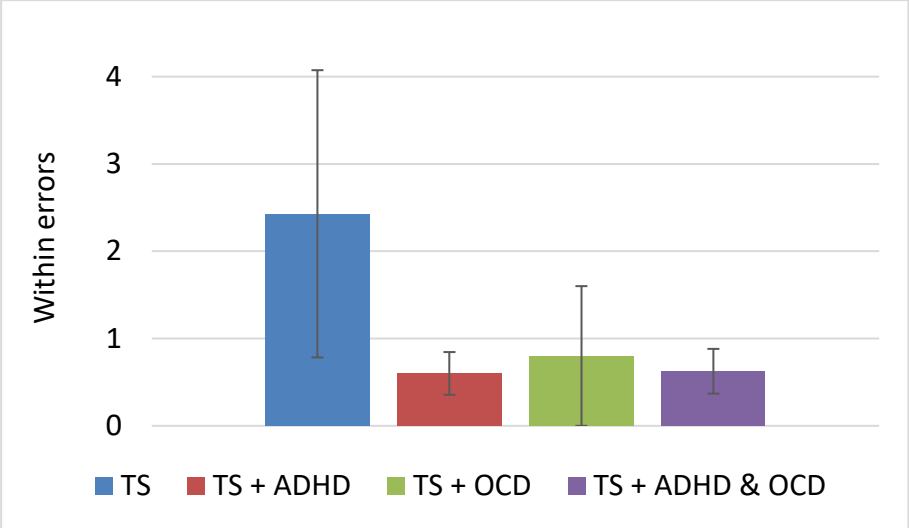
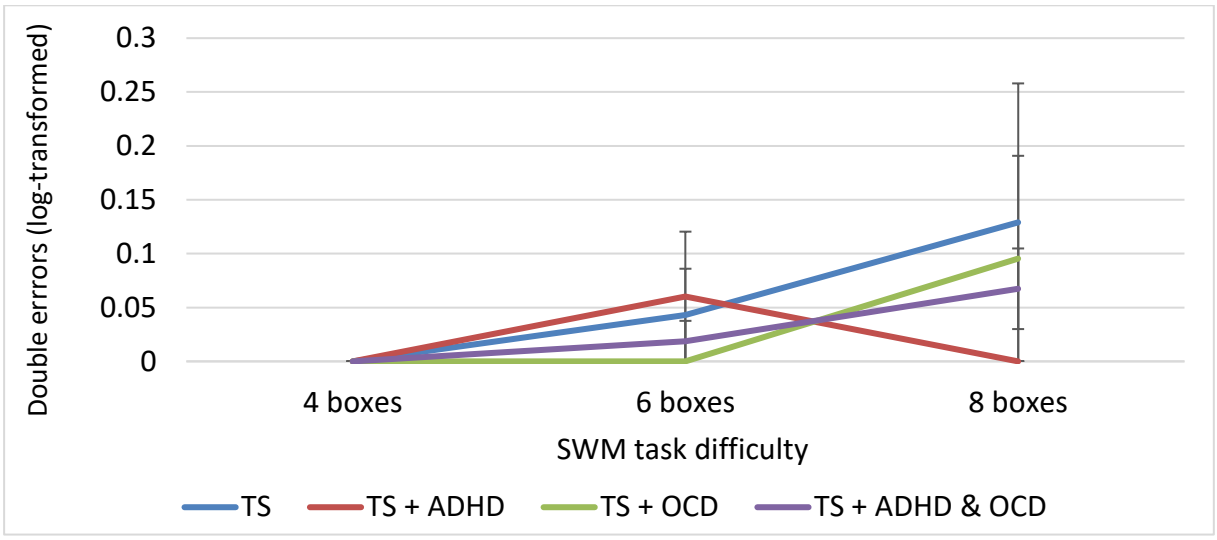


Figure 156. Mean number of within errors A) made at varying levels of task difficulty and B) for the total SWM subtest, for each comorbidity subgroup. Error bars represent SEM.

Double errors

There was no significant effect of task difficulty on mean double errors made, F (1.228, 35.609) = 2.043, p = .159, r = .23 and no significant interaction effect of task difficulty and comorbidity subgroup, F (3.684, 35.609) = .459, p = .751, r = .11. There was no main effect of comorbidity on double errors, F (3, 29) = .342, p = .795, r = .11. The number of double errors made did not differ with task difficulty or comorbidity.

A.



B.

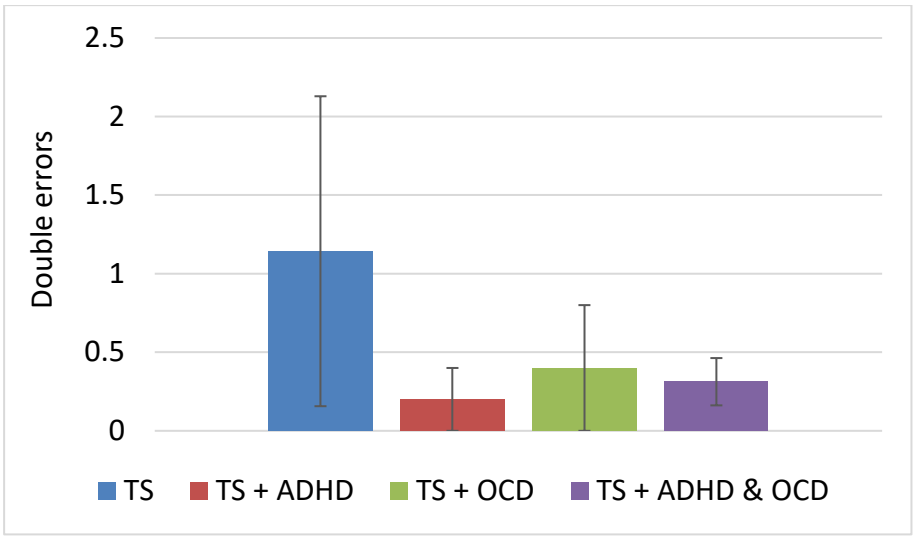


Figure 157. Mean number of double errors A) made at varying levels of task difficulty and B) for the total SWM subtest, for each comorbidity subgroup. Error bars SEM.

Strategy

There was a significant effect of comorbidity on SWM strategy score, F (3, 29) = 5.386, p = .005, r = .39. Post-hoc analyses using Gabriel's procedure revealed that those with lone comorbid OCD had significantly higher strategy scores than those with complicated TS (p = .004). A higher score is indicative of poorer strategic ability and a lower score indicative of better utility of strategy.

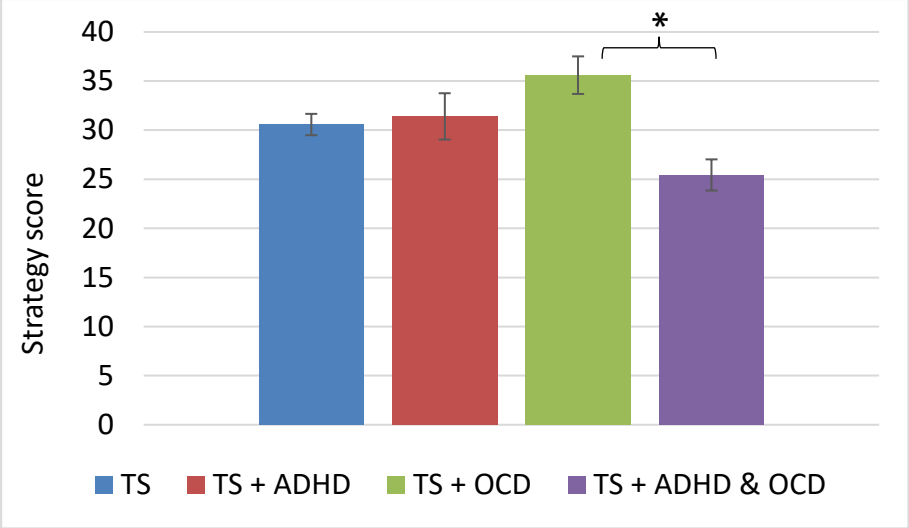


Figure 158. Mean task strategy score for participants from different comorbidity subgroups. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to SWM strategy score, F (1, 28) = .015, p = .904, r = .02. There remained a significant effect of comorbidity subgroup on SWM strategy score after controlling for the effect of medication with antipsychotics, F (3, 28) = 5.047, p = .006, η^2 = .351; remaining significant following Benjamini-Hochberg FDR correction.

Rapid Visual Information Processing (RVP)

A'

There were no significant differences amongst comorbidity subgroups on RVP *A'*, F (3, 29) = 1.487, p = .238, r = .22.

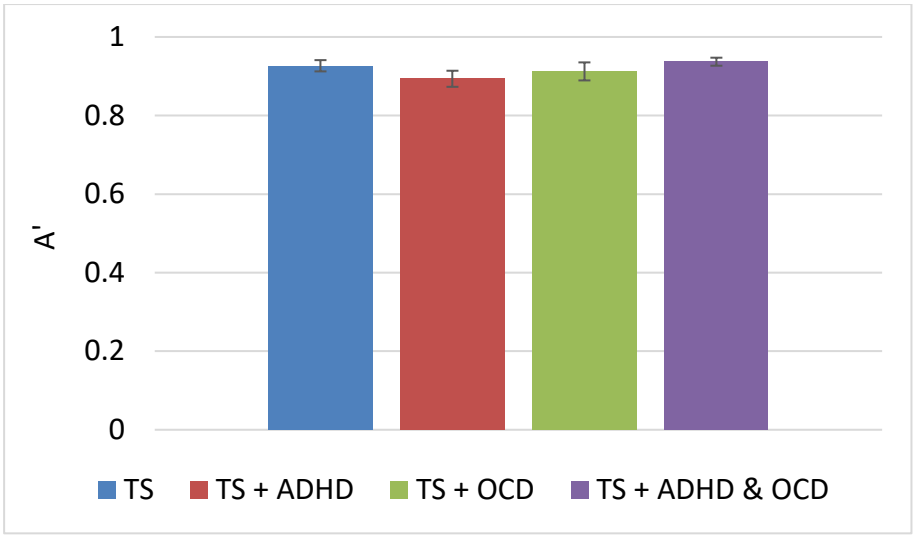


Figure 159. Mean *A'* score, a signal detection measure of sensitivity to the target, of the RVP subtest for each comorbidity subgroup. Error bars represent SEM.

B'

There were no significant differences amongst comorbidity subgroups on RVP *B'*, $F(3, 29) = .712$, $p = .553$, $r = .15$.

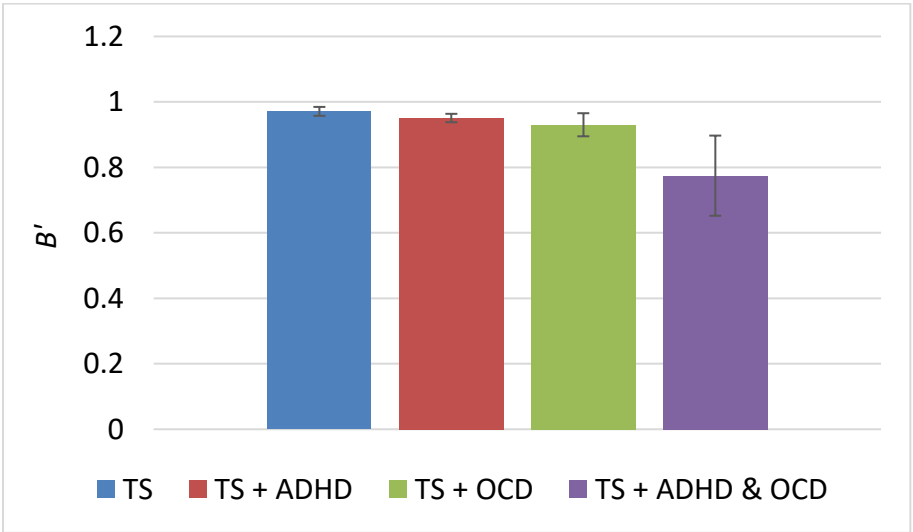


Figure 160. Mean *B'* score, a signal detection measure of the bias to respond i.e. false alarms, for each comorbidity subgroup. Error bars represent SEM.

Mean latency

There was a trend towards significant differences amongst comorbidity subgroups in mean latency, F (3, 29) = 2.841, p = .055, r = .30. Those with no comorbidity appear to have quicker RTs than those with comorbidity.

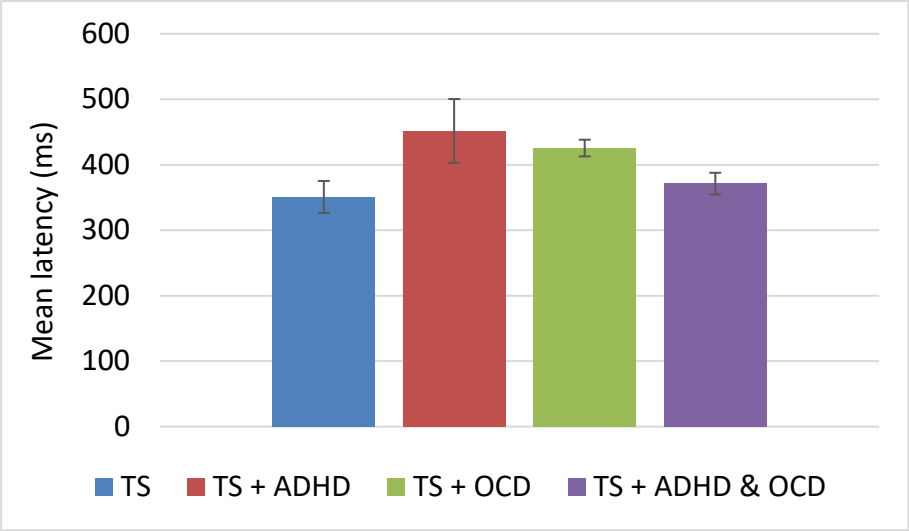


Figure 161. Mean latency (ms) of the RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Total hits

There were no significant differences amongst comorbidity subgroups on total hits, F (3, 29) = 1.610, p = .209, r = .23.

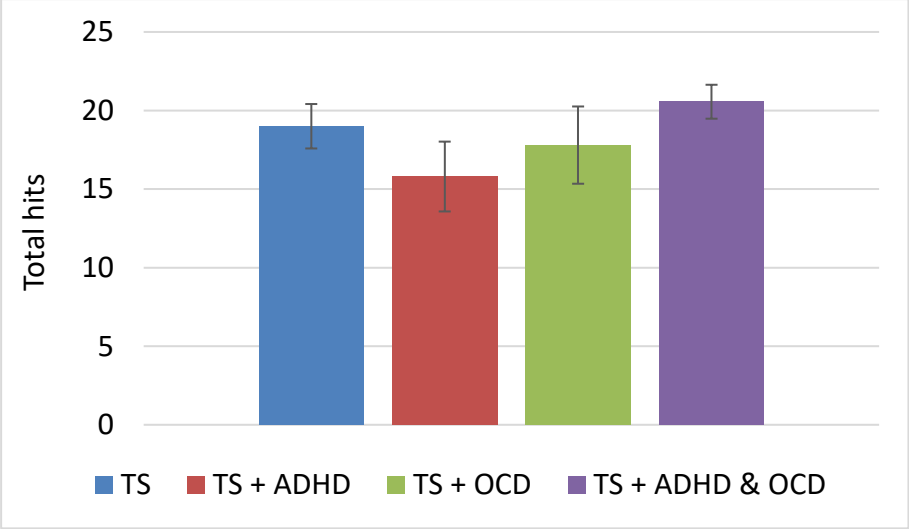


Figure 162. Mean number of total hits on the RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Total misses

There were no significant differences amongst comorbidity subgroups on total misses, F (3, 29) = 1.580, p = .215, r = .23.

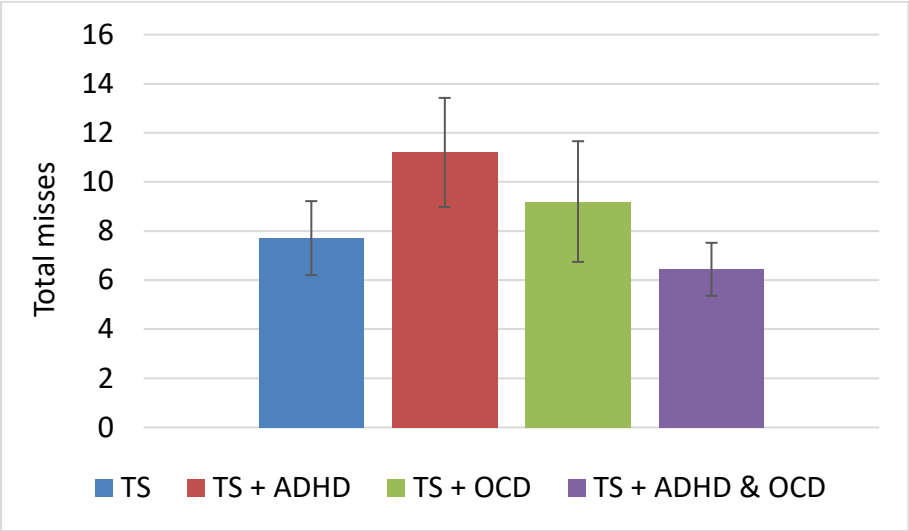


Figure 163. Mean number of total misses on the RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Total false alarms

There were no significant differences amongst comorbidity subgroups on total false alarms, F (3, 29) = .819, p = .494, r = .17.

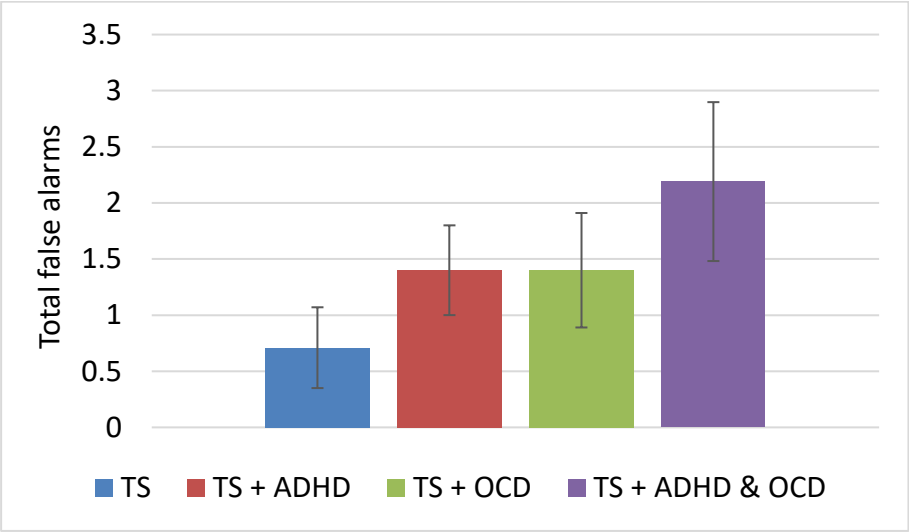


Figure 164. Mean number of false alarms on RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Total correct rejections

There were no significant differences amongst comorbidity subgroups on total correct rejections, F (3, 29) = 1.441, p = .251, r = .22.

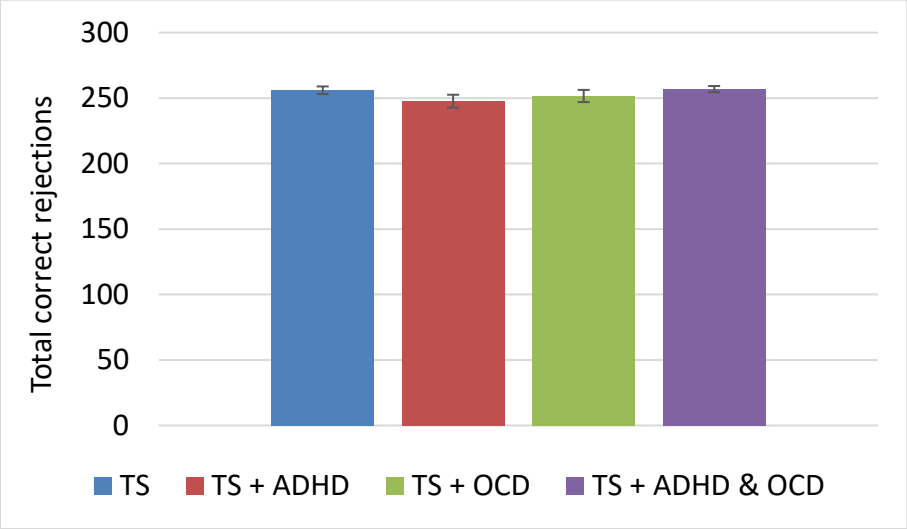


Figure 165. Mean number of correct rejections on RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Probability hit

There were no significant differences amongst comorbidity subgroups on probability of a hit, F (3, 29) = 1.584, p = .215, r = .23.

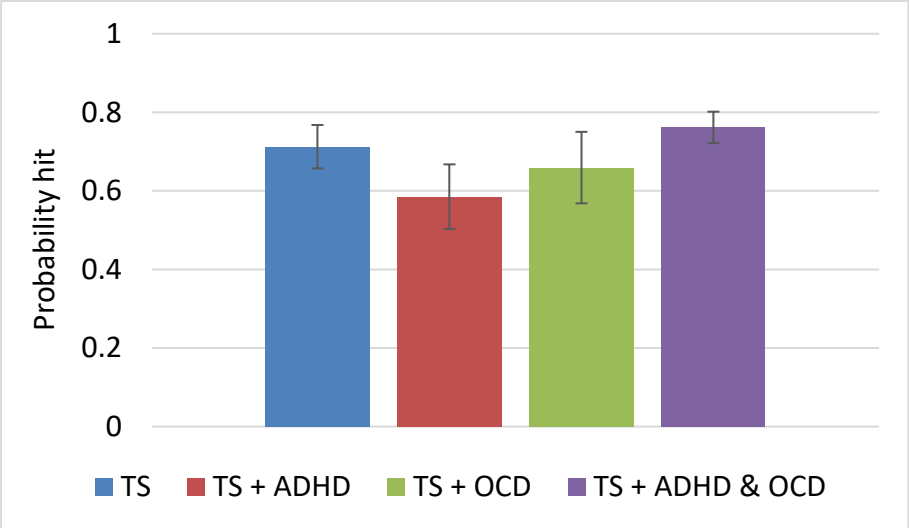


Figure 166. Mean probability of hits on RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Probability false alarm

There were no significant differences amongst comorbidity subgroups on probability of a false alarm, F (3, 29) = .785, p = .512, r = .16.

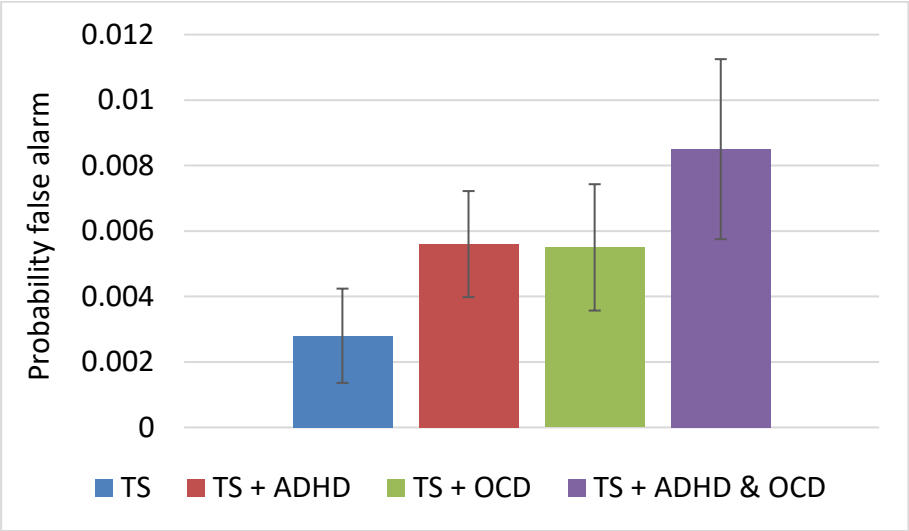


Figure 167. Mean probability of false alarms on RVP subtest for each comorbidity subgroup. Error bars represent SEM.

Stop-signal Test (SST)

Reaction time

Mean

There was no effect of comorbidity on mean RT, F (3, 29) = .546, p = .654, r = .14.

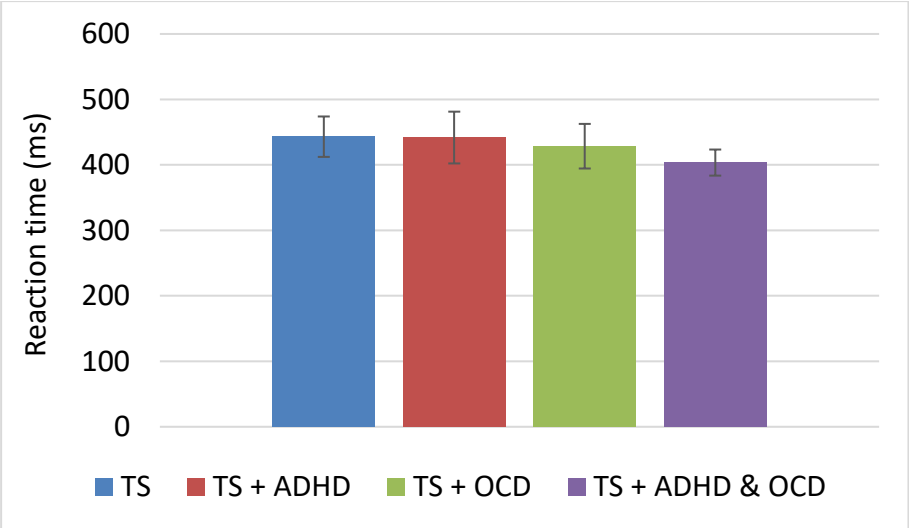


Figure 168. Mean reaction times (ms) on SST subtest for each comorbidity subgroup. Error bars represent SEM.

Median

There was no significant effect of comorbidity on median RT, F (3, 29) = .758, p = .527, r = .16.

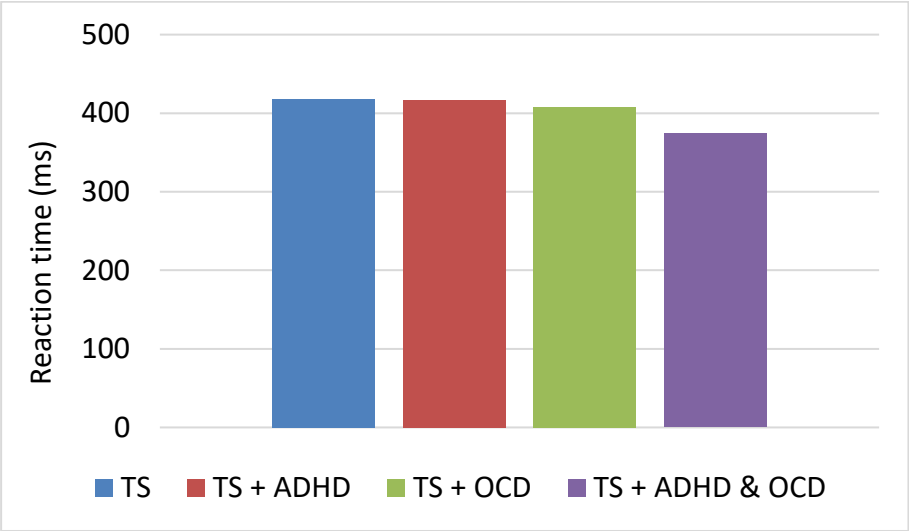


Figure 169. Mean median reaction times (ms) on SST subtest for each comorbidity subgroup.

Minimum

There was no significant effect of comorbidity on minimum RT, F (3, 29) = 1.060, p = .381, r = .19.

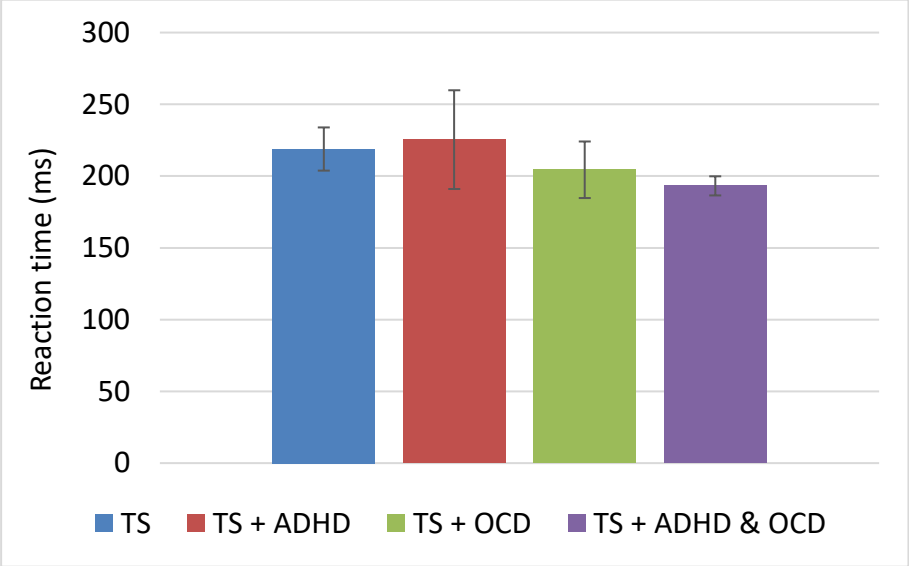


Figure 170. Mean minimum reaction times (ms) for SST subtest for each comorbidity subgroup. Error bars represent SEM.

Maximum

There was no significant effect of comorbidity on maximum RT, F (3, 29) = 1.331, p = .284, r = .21.

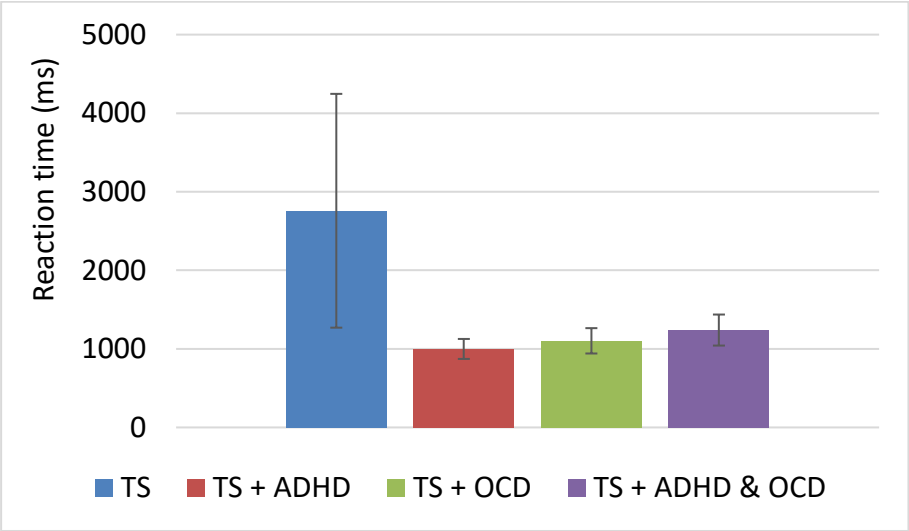


Figure 171. Mean maximum reaction times (ms) for SST subtest for each comorbidity subgroup. Error bars represent SEM.

Standard deviation

There was no significant effect of comorbidity on SST SD RT, F (3, 29) = .891, p = .458, r = .17.

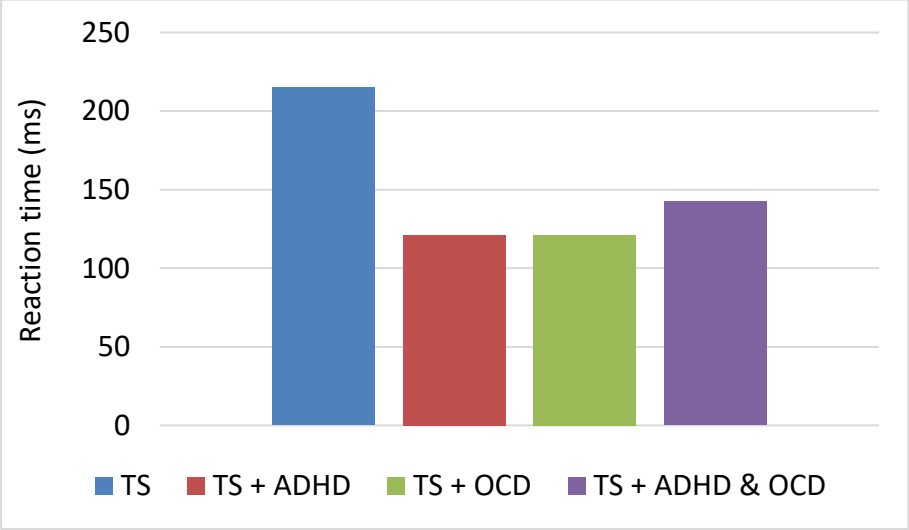


Figure 172. Mean variance (standard deviation) in reaction times (ms) for SST subtest for each comorbidity subgroup.

Direction errors

There was no significant effect of comorbidity on direction errors, F (3, 29) = .132, p = .940, r = .07.

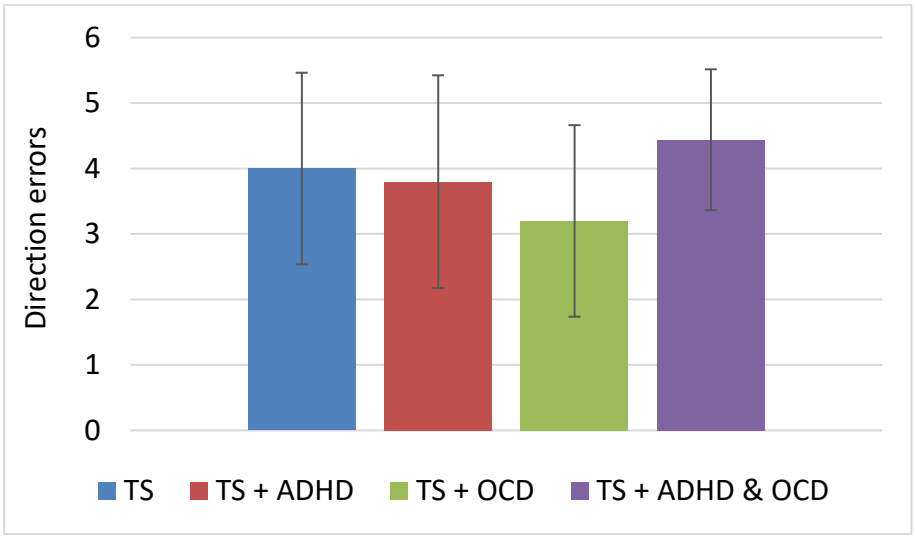


Figure 173. Mean number of direction errors for SST subtest for each comorbidity subgroup. Error bars represent SEM.

Proportion successful stops

There was no significant effect of comorbidity on the proportion of successful stops, F (3, 29) = 1.094, p = .367, r = .19.

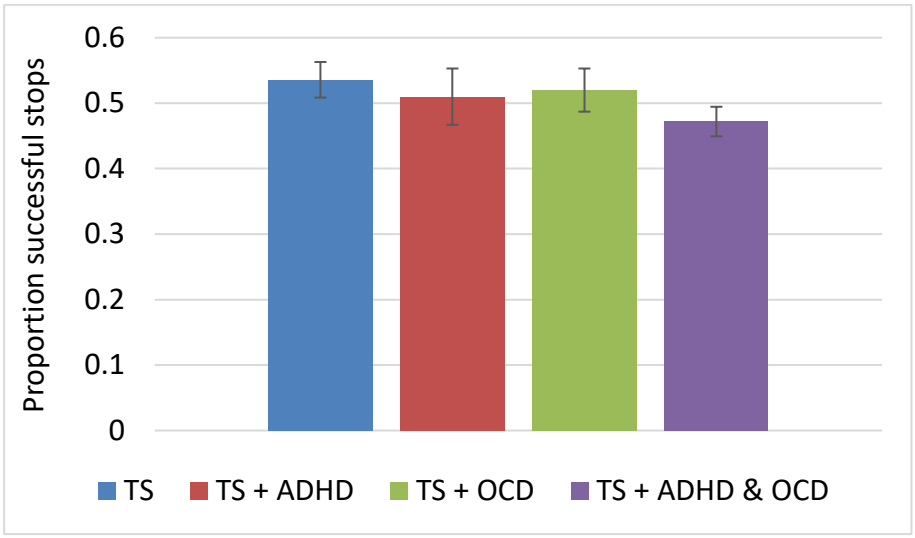


Figure 174. Proportion of successful stops on SST subtest for each comorbidity subgroup. Error bars represent SEM.

Stop signal delay (SSD)

There was no significant effect of comorbidity on the SSD, F (3, 29) = 1.076, p = .375, r = .19.

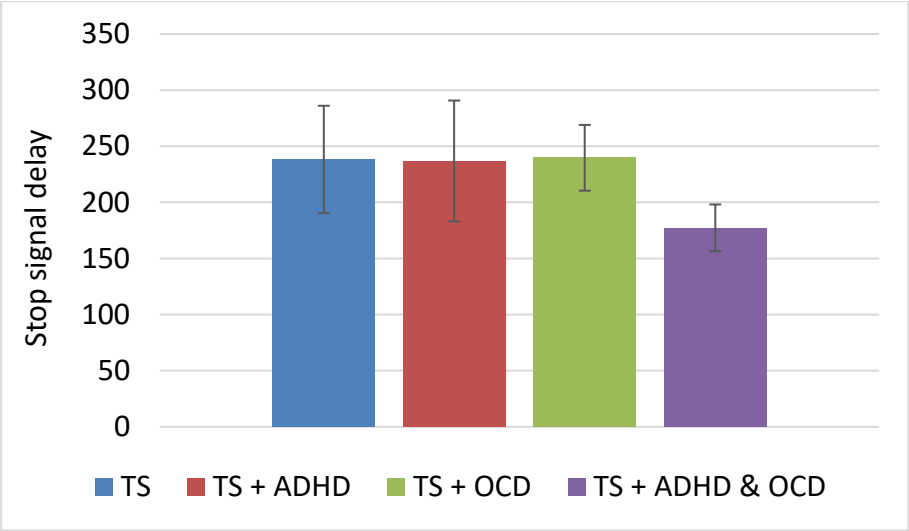


Figure 175. Mean stop signal delay (ms) on SST subtest for each comorbidity subgroup. Error bars represent SEM.

Stop signal reaction time (SSRT)

There was no significant effect of comorbidity on the SSRT, F (3, 29) = .435, p = .729, r = .12.

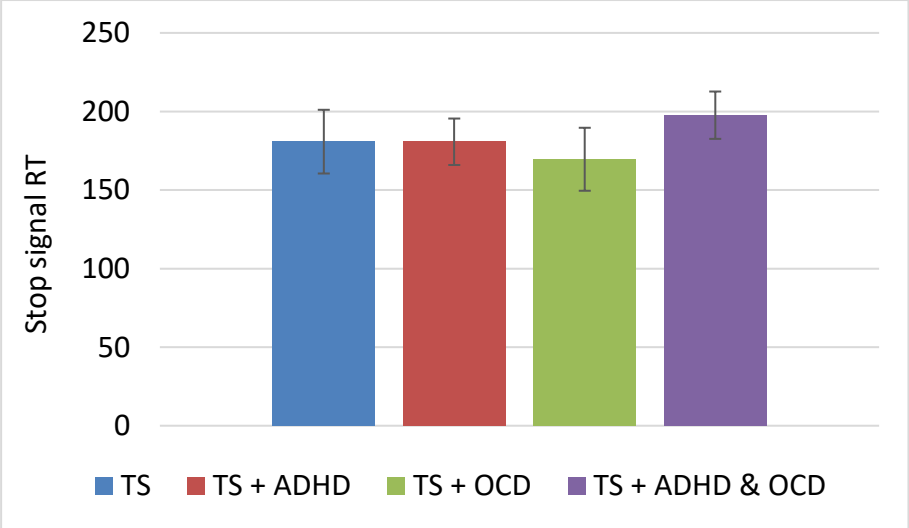


Figure 176. Mean stop signal reaction time (ms) on SST subtest for each comorbidity subgroup. Error bars represent SEM.

Summary

During performance on the IED task, there was a significant interaction between IED stage and comorbidity subgroup. Those with complicated TS made significantly fewer EDS errors than other comorbidity subgroups. There was no significant effect of comorbidity subgroup on the number of errors made at each stage of the IED task, including IDS and EDS stages.

During performance on the SOC task, there was a significant main effect of comorbidity on the percentage perfect solution achieved. Significantly fewer perfect solutions were achieved by those with lone comorbid OCD compared to those with complicated TS; this observation was reduced to trend level significance (p =.061) after controlling for medication with antipsychotics. No other differences existed amongst other comorbidity subgroups groups.

During performance on the SWM task, there was a significant effect of comorbidity on strategy score whereby lone comorbid OCD had significantly higher strategy scores, indicative of poorer strategy utilisation, than those with complex TS; no differences existed amongst other comorbidity subgroups. The effects of comorbidity subgroup on strategy score were independent from the effects of medication with antipsychotics. Finally, there were no significant effects of comorbidity subgroups found on the RVP or SST tasks.

Attention and inhibition

Continuous Performance Task (CPT)

Hit reaction time (HRT)

Target set-size

There was a significant main effect of target set-size on HRT, F (3, 84) = 56.182, p = .000, r = .63. Planned contrast (Helmert) comparing HRTs when only one target occurs to the mean effect on HRT of all subsequent set sizes revealed significantly quicker HRTs for fewer targets, F (1, 28) = 165.327, p = .000, r = .92. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant interaction effect between target set-size and comorbidity, F (9, 84) = .977, p = .465, r = .11 and no significant main effect of comorbidity, F (3, 28) = .312, p = .817, r = .10.

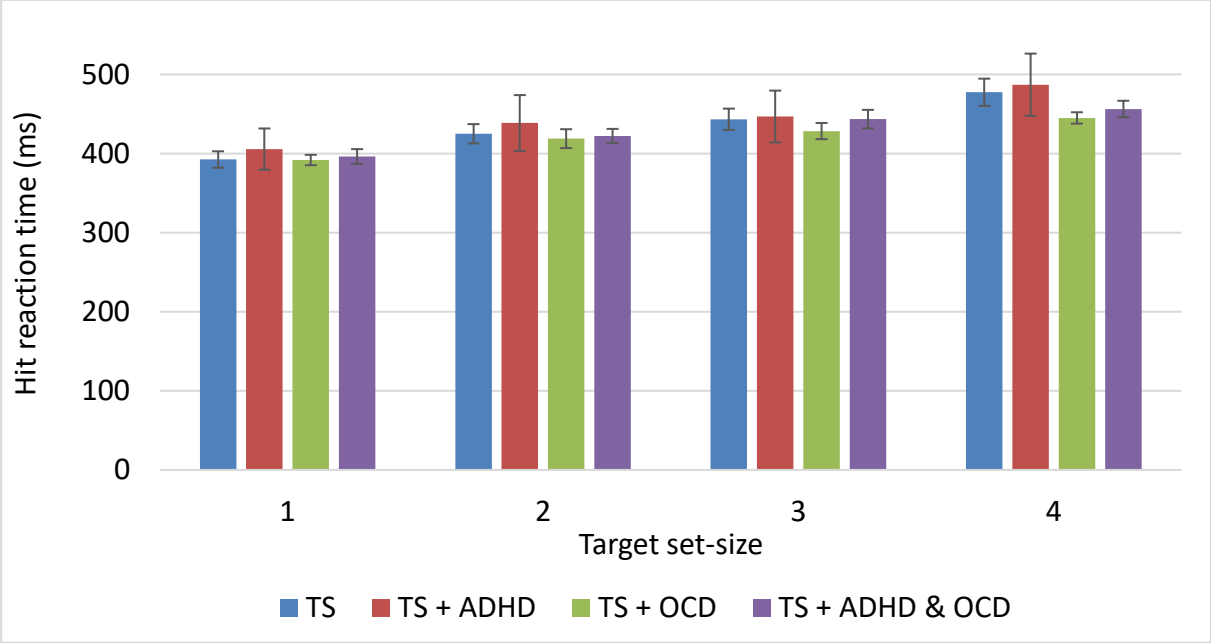


Figure 177. Mean hit reaction times (ms, log-transformed) on the CPT task at different target set-sizes for each comorbidity subgroup. Error bars represent SEM.

Experimental block

There was a significant main effect of experimental block on RT for correct trials, F (4.776, `33.721) = 11.310, p = .000, r = .28. Planned contrasts (Helmert) comparing the mean effect of the first block to the mean effect of all subsequent blocks, shows that participants were significantly quicker for the first block vs the remaining blocks, F (1, 28) = 57.326, p = .000, r = .82. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no difference between the second block and remaining blocks, F (1, 28) = .003, p = .954, r = .01. There was no significant interaction effect between block and comorbidity, F (14.327, 133.721) = .744, p = .729, r = .07 and no significant main effect of comorbidity, F (3, 28) = .295, p = .829, r = .10.

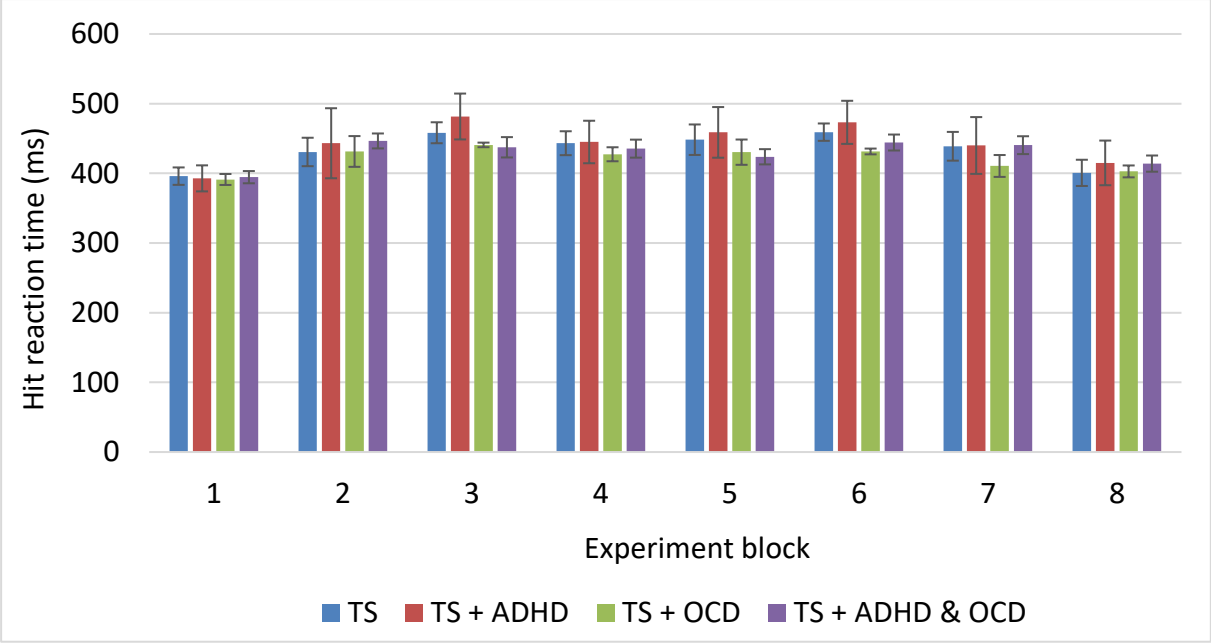


Figure 178. Mean hit reaction times (ms, log-transformed) on the CPT task at each experimental block for each comorbidity subgroup. Error bars represent SEM.

Accuracy

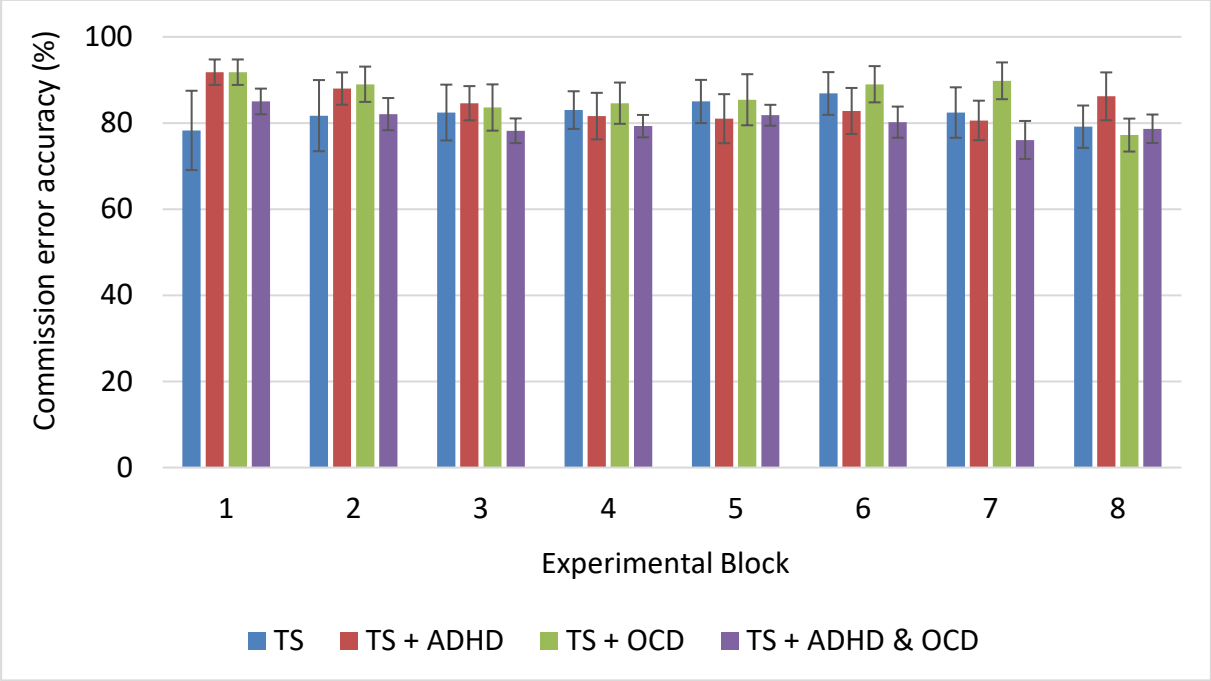
Experimental block

There was no effect of block on task accuracy, F (4.844, 135.642) = 1.776, p = .124, r = .11, and no interaction between block and comorbidity on task accuracy, F (14.533, 135.642) = 1.379, p = .169, r = .10.

There was a significant effect of error type on task accuracy, F (1, 3) = 21.667, p = .000, r = .66, with more commission errors than omission errors being made; but no interaction between error type and comorbidity, F (3, 28) = 2.100, p = .123, r = .26. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant interaction between block and error type, F (4.409, 123.450) = .836, p = .514, r = .08, or blocks, error type and comorbidity subgroup, F (13.227, 123.450) = .406, p = .967, r = .06. There was no significant main effect of comorbidity subgroup on task accuracy, F (3, 28) = .239, p = .868, r = .09.

A.



B.

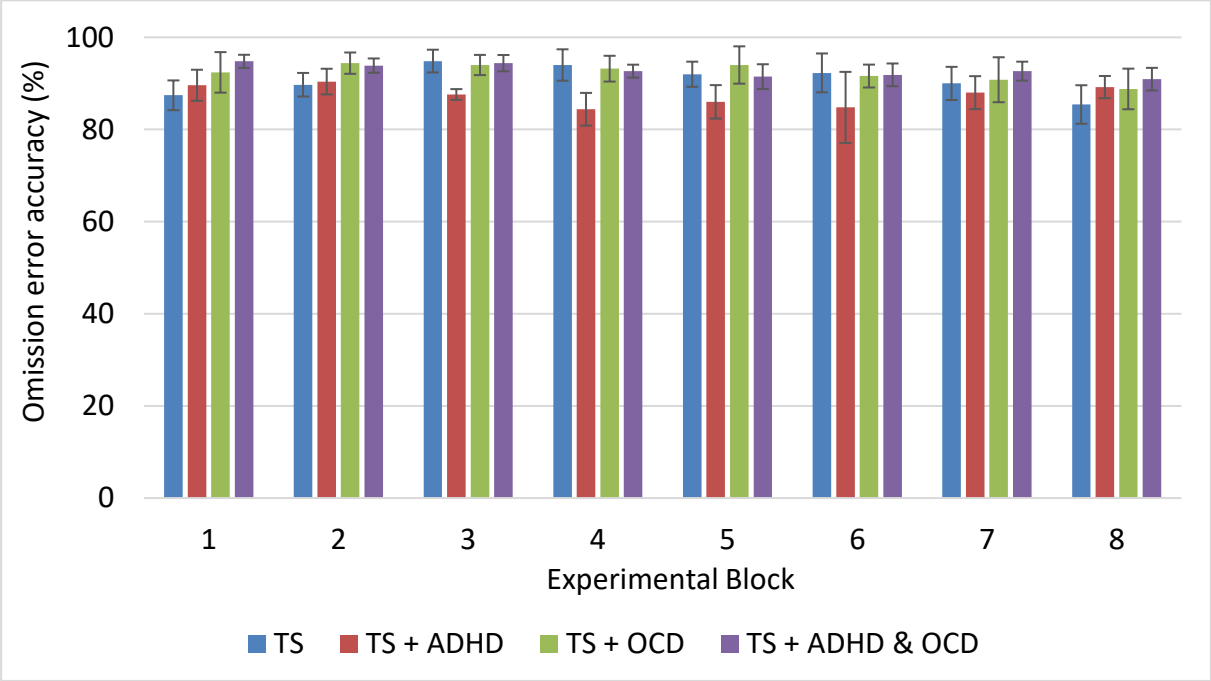


Figure 179. Mean percentage accuracy of A) commission and B) omission errors on the CPT task at each experimental block for each comorbidity subgroup. Error bars represent SEM.

Target set-size

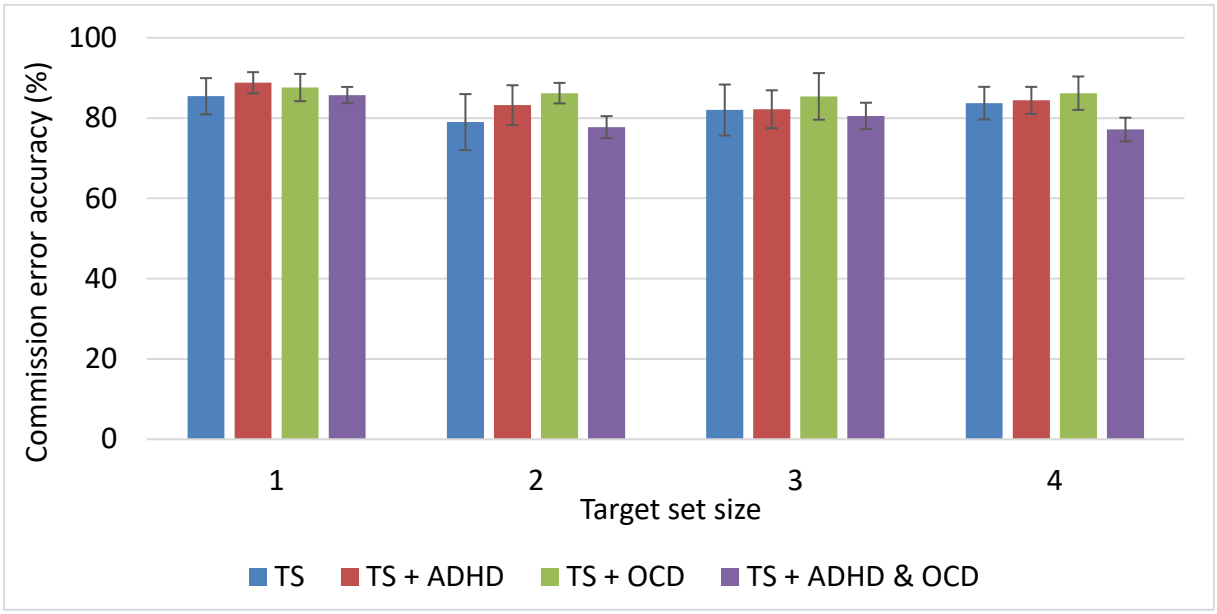
There was a significant main effect of error type on task accuracy, F (1, 28) = 20.952, p = .000, r = .65, where significantly more omission errors are made than commission. There was no interaction between error type and comorbidity subgroup, F (3, 28) = 2.067, p = .127, r = .26. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant effect of target set-size on task accuracy, F (3, 84) = 1.179, p = .323, r = .12, and no interaction between target set-size and comorbidity subgroup, F (9, 84) = 1.141, p = .344, r = .12.

There was a significant interaction between error type and target set-size, F (3, 84) = 5.584, p = .002, r = .25, occurring between omission and commission errors at target set-size 1, F (1, 28) = 1.179, p = .323, r = .06. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no interaction between error type, target set-size and comorbidity subgroup, F (9, 84) = .565, p = .822, r = .08. Furthermore, there was no significant effect of comorbidity subgroup on task accuracy, F (3, 28) = .231, p = .874, r = .05.

A.



B.

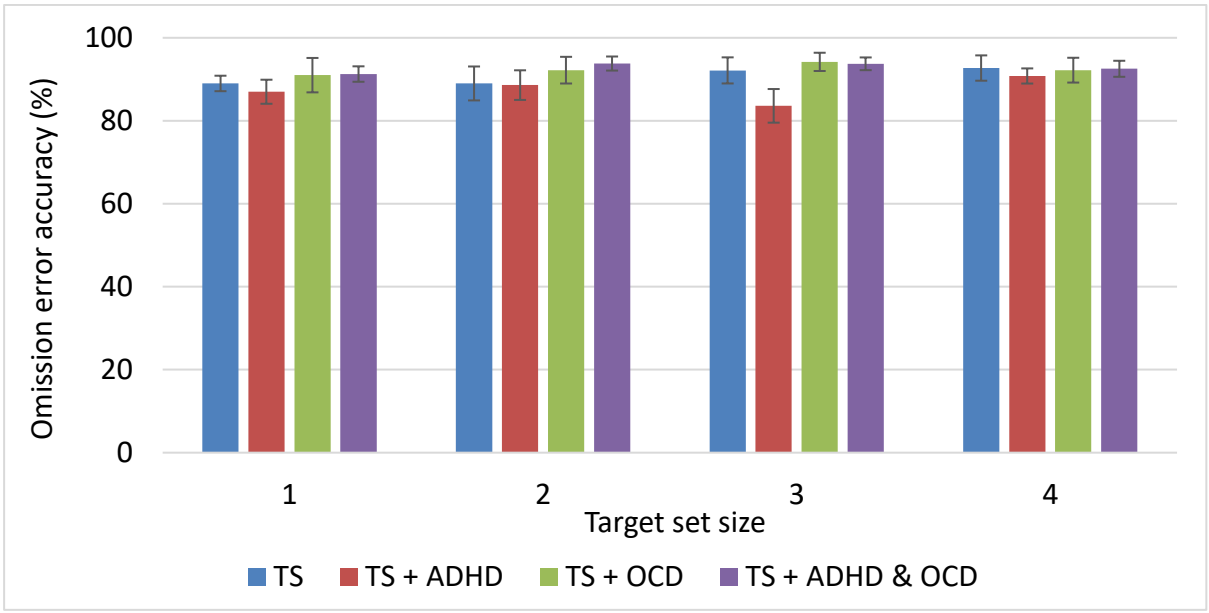
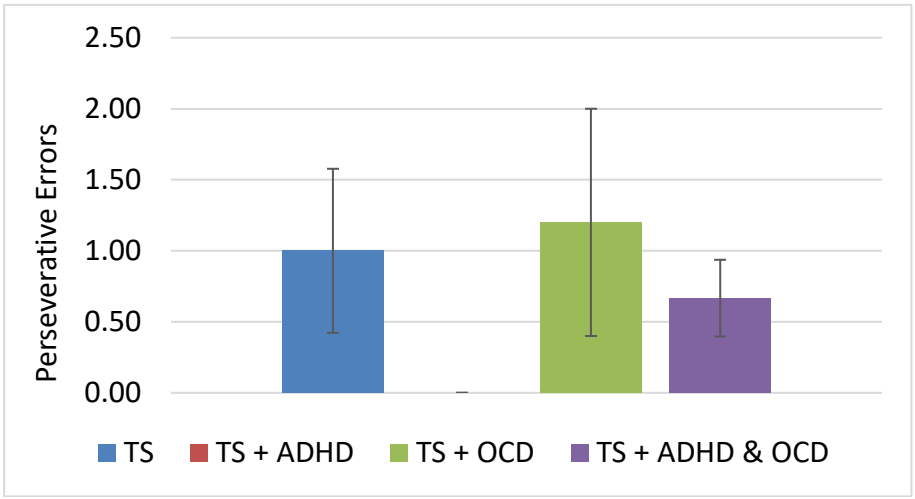


Figure 180. Mean percentage accuracy of A) commission and B) omission errors at different target set-sizes made on the CPT task for each comorbidity subgroup.

Perseverative errors and multiple responding

There was no significant effect of comorbidity subgroup on mean perseverative errors, F (3, 28) = .960, p = .425, r = .18 or on mean multiple responses, F (3, 28) = .554, p = .650, r = .14.

A.



B.

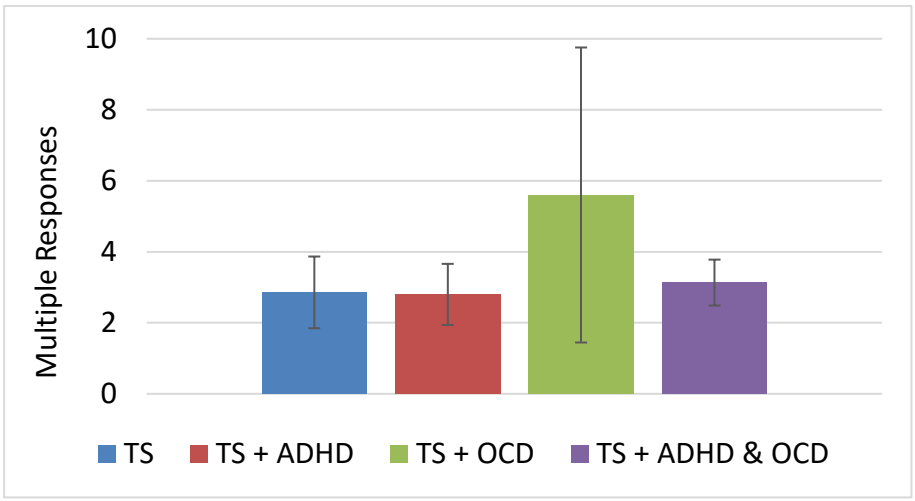


Figure 181. Mean A) perseverative errors and B) number of multiple responses made on the CPT task for each comorbidity subgroup. Error bars represent SEM.

Detectability *d'*

There was no significant effect of comorbidity on total task detectability *d*, F (3, 28) = .441, p = .725, r = .12.

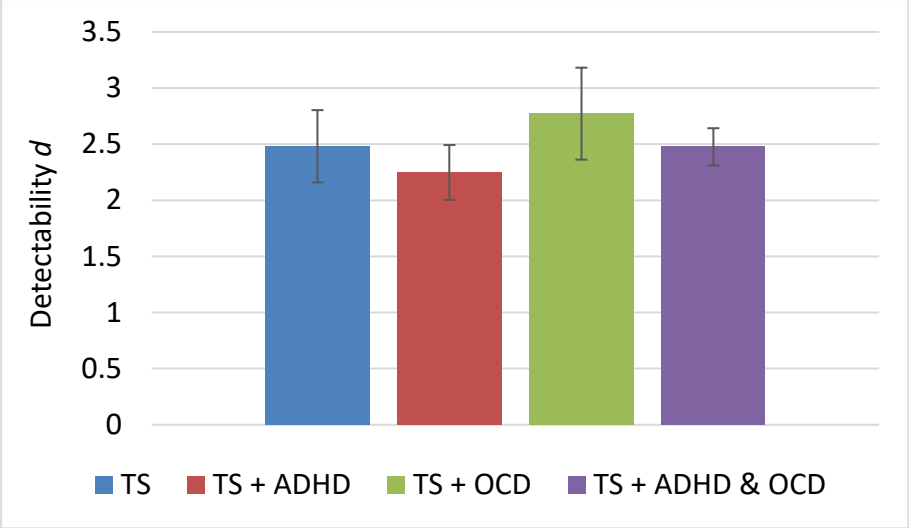


Figure 182. Mean total task detectability *d*' on the CPT task for each comorbidity subgroup. Error bars represent SEM.

Response style *c*

There was no significant effect of comorbidity on total task response style *c*, F (3, 28) = 2.30, p = .099, r = .28.

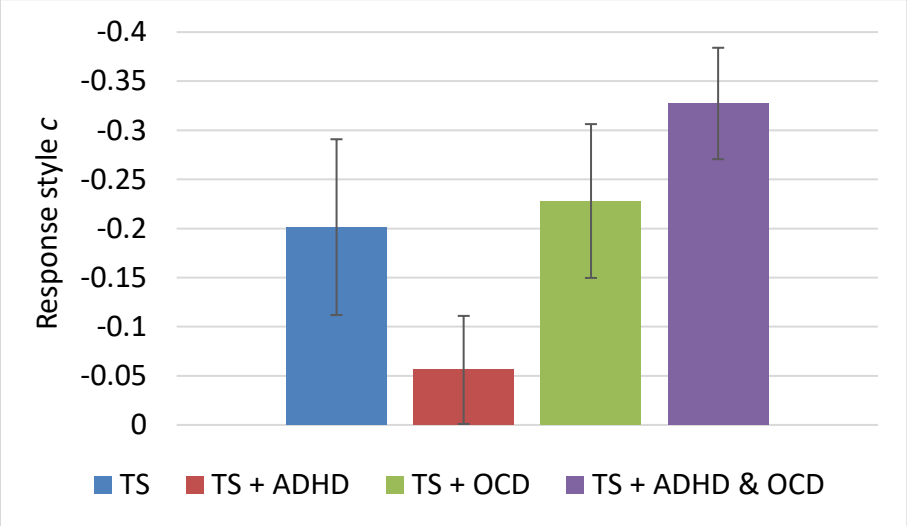


Figure 183. Mean total task response style *c*' on the CPT task for each comorbidity subgroup. Error bars represent SEM.

Response Conflict Flanker (RCF)

Accuracy

There was a significant main effect of flanker type on the number of errors made on RCF task, F (1.041, 30.194) = 19.785, p = .000, r = .63. Planned contrast (simple) revealed that in comparison to neutral flankers participants make fewer errors for congruent flankers, F (1, 29) = 6.446, p = .017, r = .43, and significantly more errors when incongruent flankers, F (1, 29) = 20.673, p = .000, r = .65. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant interaction between flanker type and comorbidity subgroup, F (3.124, 30.194) = 2.002, p = .133, r = .25 and no main effect of comorbidity on the number of errors made during the RCF task, F (3, 29) = 1.636, p = .203, r = .23.

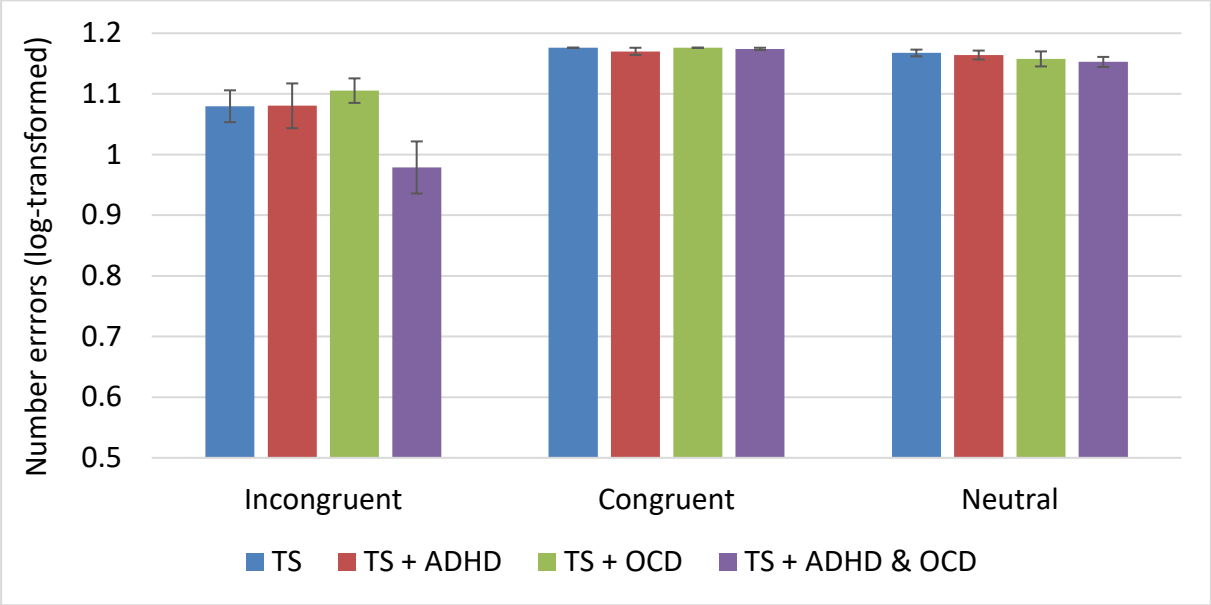


Figure 184. Mean number of errors (log-transformed) made on the RCF task in response to each flanker type (incongruent, congruent or neutral) for each comorbidity subgroup. Error bars represent SEM.

Reaction time

There was a significant main effect of flanker type on RTs, F (2, 58) = 236.604, p = .000, r = .90. Planned contrast (simple) revealed that in comparison to neutral flankers participants are significantly quicker for congruent flankers, F (1, 29) =

40.381, *p* = .000, *r* = .76, and significantly slower for incongruent flankers, *F* (1, 29) = 234.031, *p* = .000, *r* = .94. Differences remained significant following Benjamini-Hochberg FDR correction.

There was no interaction between flanker type and comorbidity subgroup, *F* (6, 58) = .265, *p* = .951, *r* = .10 and no main effect of comorbidity on RCF task RTs, *F* (3, 29) = .584, *p* = .630, *r* = .14.

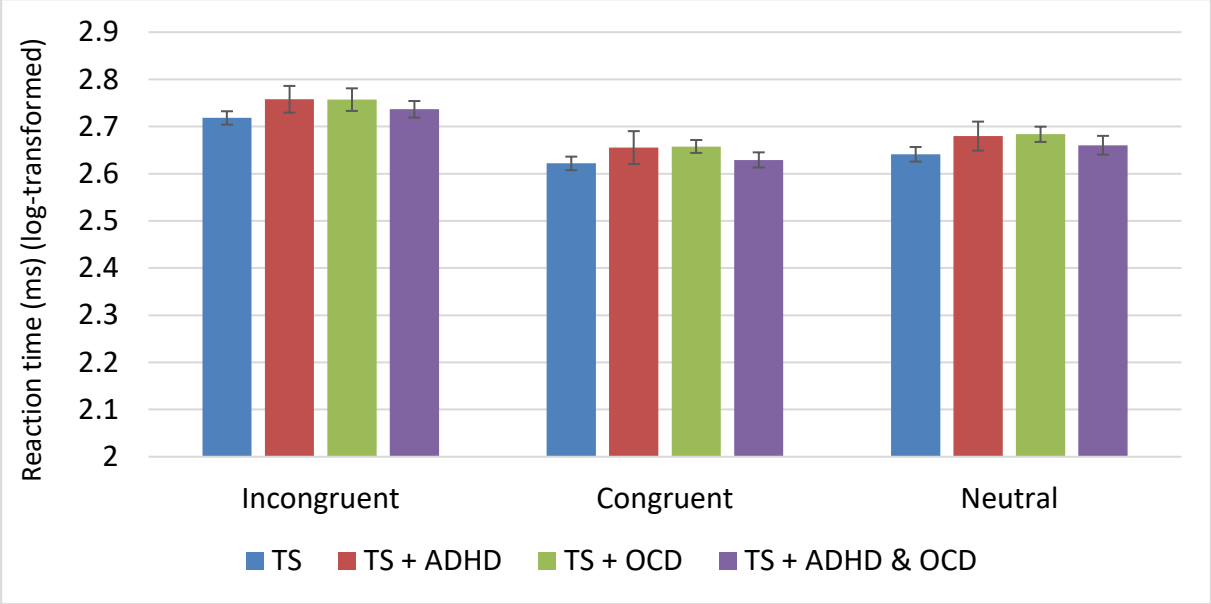


Figure 185. Mean reaction time (log-transformed) on the RCF task for each flanker type (incongruent, congruent or neutral) for each comorbidity subgroup. Error bars represent SEM.

Flanker effects

In Chapter 4, it was established that the RCF variant was not suitable for the assessment of conflict detection. Therefore, comparisons amongst comorbidity subgroups was not undertaken.

Summary

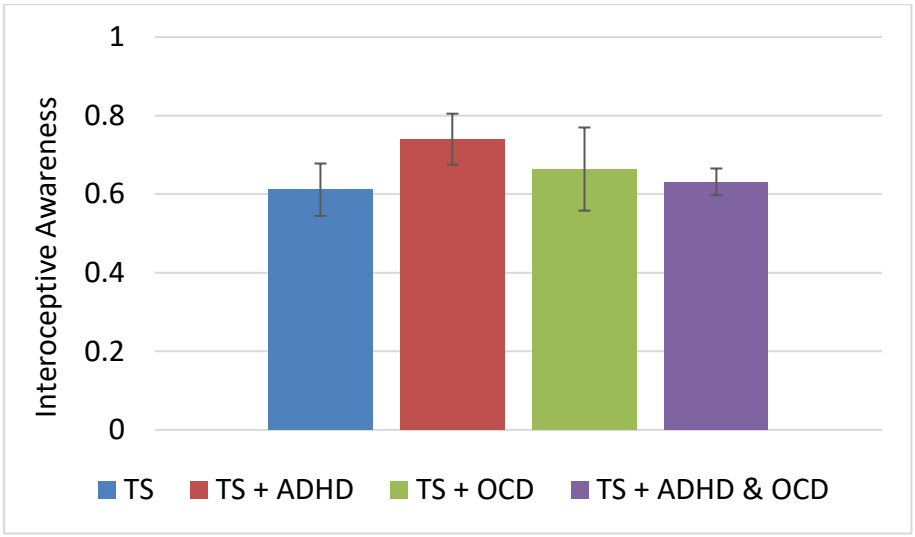
There were no significant main effects or interaction effects of comorbidity subgroups on any of the CPT or RCF task measures. All participants performed similarly, irrespective of comorbidity.

Interoceptive awareness

Results

There was no significant differences in interoceptive awareness, F (3, 29) = .715, p = .551, r = .16 or resting heart rate, F (3, 29) = .655, p = .586, r = .15, amongst comorbidity subgroups.

A.



B.

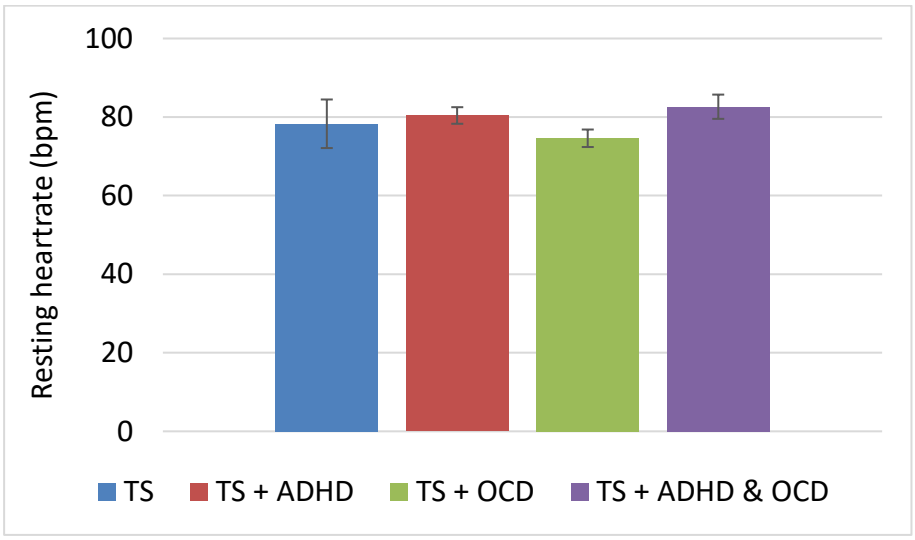


Figure 186 . Mean A) interoceptive awareess and B) resting heart rate (bpm) for each comorbidity subgroup. Error bars represent SEM.

Summary

There was no significant main effect of comorbidity subgroup on interoceptive awareness or resting heart rate.

Neurophysiology

Motor thresholds

There were no significant differences amongst comorbidity subgroups in the stimulation intensity (percentage of maximum output) needed to reach resting motor threshold, F (3, 29) = 1.126, p = .355, r = .19; active motor threshold, F (3, 29) = .515, p = .675, r = .13; or 1mV threshold, F (3, 29) = 1.648, p = .200, r = .23.

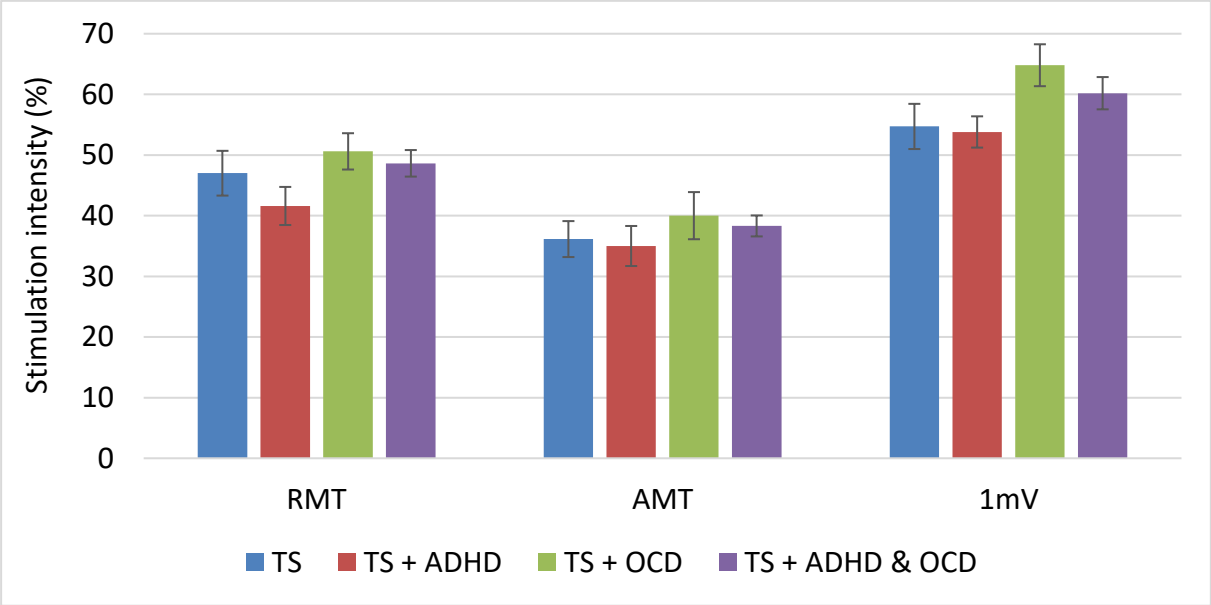


Figure 187. Stimulation intensity (percentage maximum output) needed to reach resting, active and 1mV thresholds for each comorbidity subgroup. Error bars represent SEM.

Short-interval Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF)

There was a significant main effect of SICI condition on the size of the normalised MEP, F (1.503, 43.573) = 20.892, p = .000, r = .57. Planned contrasts (repeated) revealed that there was no difference in MEP size at 2ms and 3ms, F (1, 29) = .073, p = .789, r = .05, and significantly larger MEPs at 12ms compared to 3ms, F (1, 29) =

24.144, *p* = .000, *r* = .67. All differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant interaction effect between SICI condition and comorbidity subgroup, *F* (4.508, 43.573) = 1.190, *p* = .325, *r* = .16, and no significant effect of comorbidity subgroup on the size of the normalised MEPs, *F* (3, 29) = 486, *p* = .695, *r* = .13.

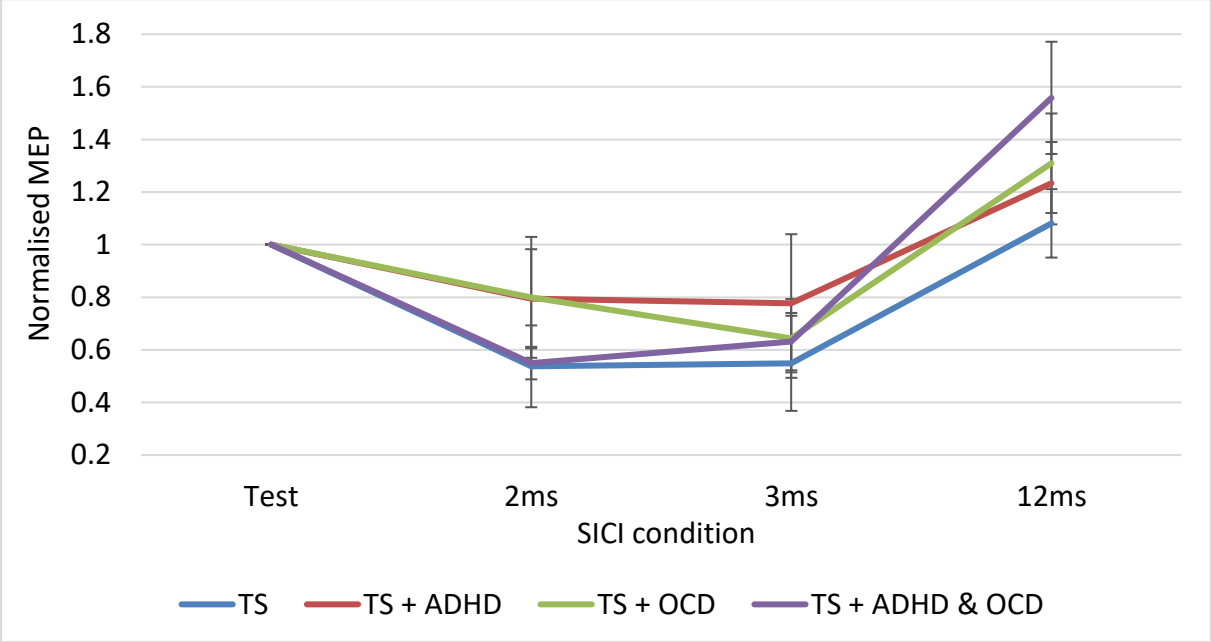


Figure 188. Mean normalised MEPs elicited at test only and 2ms, 3ms or 12ms intervals, for each comorbidity subgroup. MEPs are normalised to test pulse condition, with values below one representing inhibition and above one positive facilitation. Error bars represent SEM.

Short-latency Afferent Inhibition (SAI)

There was no significant main effect of SAI condition on the size of the normalised MEP, *F* (3, 81) = 1.164, *p* = .329, *r* = .12. There was no significant interaction effect between SAI condition and comorbidity subgroup, *F* (9, 81) = 1.426, *p* = .191, *r* = .13, and no significant effect of comorbidity on the size of the normalised MEPs, *F* (3, 27) = .358, *p* = .784, *r* = .11.

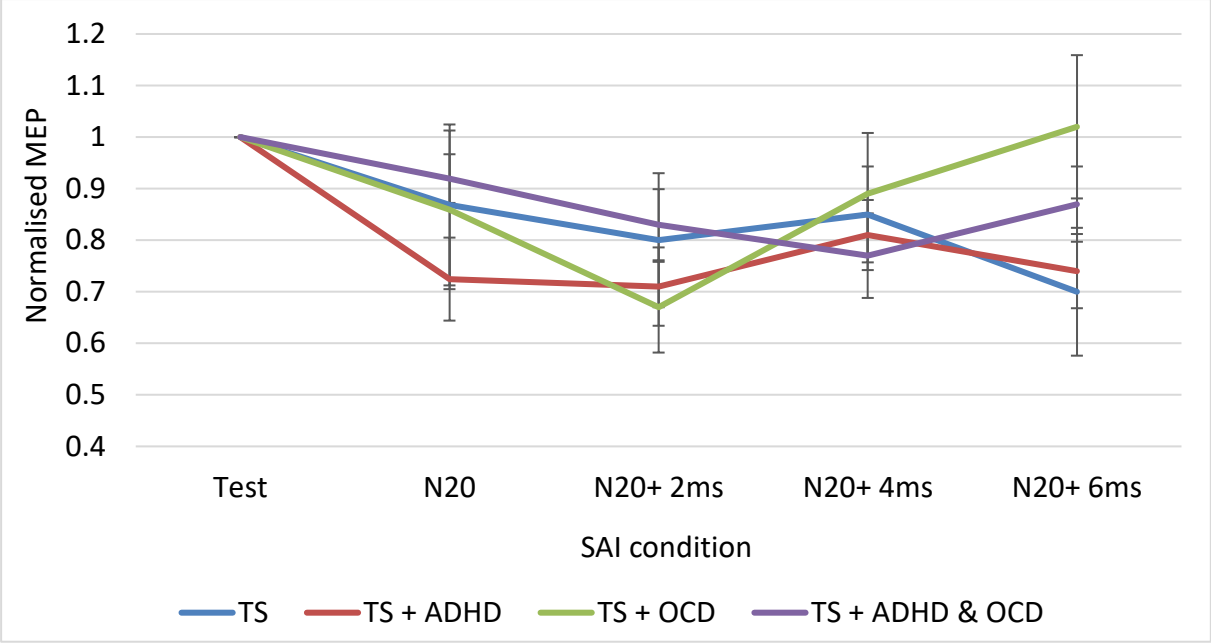


Figure 189. Mean normalised MEPs elicited at test only and N20, N20^{+2ms}, N20^{+4ms} and N20+^{6ms} intervals, for each comorbidity subgroup. MEPs are normalised to test pulse condition, with values below one representing inhibition and above one facilitation. Error bars represent SEM.

Tic control

There was a significant main effect of tic instruction on the size of normalised MEPs (log-transformed), F (2, 58) = 8.360, p = .001, r = .35. Planned contrast (simple) revealed that in comparison to baseline (no tic-related instructions), MEPs recorded under instruction to inhibit tics were significantly smaller, F (1, 29) = 8.381, p = .007, r = .47. MEPs recorded under instruction to allow tics however, did not differ from baseline MEPs, F (1, 29) = 2.228, p = .146, r = .27. All differences remained significant following Benjamini-Hochberg FDR correction.

There was no significant interaction between tic instruction and comorbidity subgroup interaction, F (6, 58) = .422, p = .861, r = .08 and no main effect of comorbidity on the size of normalised MEPs, F (3, 29) = .056, p = .982, r = .04.

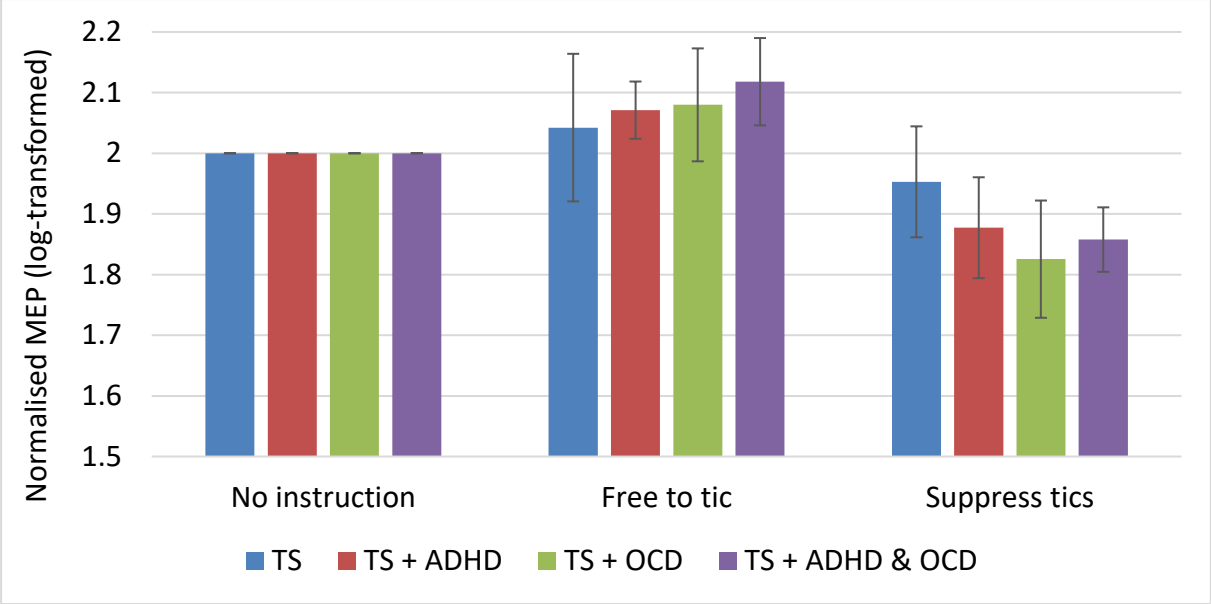


Figure 190. Mean normalised MEPs (log-transformed) recorded under no tic-related instructions (baseline), instruction to tic freely and instruction to suppress tics for each comorbidity subgroups. Error bars represent SEM.

Summary

There were no significant main effects or interaction effects of comorbidity subgroup on motor thresholds, SICI, ICF or SAI. Furthermore, there was no effect of comorbidity subgroup on the changes to CSE after allowing tics to occur and active tic suppression.

8.3. Discussion

TS pathology is associated with widespread neurodevelopmental abnormalities and alteration in neural functioning (Huang et al., 2017; Minzer, Lee, Hong, & Singer, 2004; Nag et al., 2013; Penagarikano et al., 2011; Verkerk et al., 2003). Such pathology likely arises due to cumulative mechanisms involving inherited polygenic vulnerabilities that are triggered by environmental risk factors, including both prenatal and postnatal infection, inflammation and psychosocial stress (Madhusudan, 2013; Martino et al., 2015; Mathews et al., 2014; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, et al., 2017). Consequently, in TS, there is disruption in CSTC circuitry. Thus, the typical clinical profile of TS, encompassing aberrant sensation, movement and behaviour, can be explained by alterations in limbic,

associative and motor circuits (Bohlhalter et al., 2006; Cortese, 2012; Kalanithi et al., 2005; Mink, 2001b; Parent & Hazrati, 1995; Peterson et al., 2003; Tisch et al., 2004; Worbe et al., 2012).

Neurodevelopmental disorders are observed to share similar genetic and environmental risk factors, resulting in overlapping neural pathology amongst those with TS and comorbidities including OCD, ADHD and ASD (Bloch et al., 2011; Canitano & Vivanti, 2007; Cukier et al., 2014; Davis et al., 2013; Karagiannidis, 2016; Kern et al., 2015; Mathews & Grados, 2011; Paschou et al., 2013; Peterson et al., 2001; Yu et al., 2015). Similar genetic mechanisms in TS and comorbid conditions can cause widespread alteration to synaptic functioning (Huang et al., 2017; Minzer et al., 2004; Penagarikano et al., 2011; Verkerk et al., 2003). For example, genes identified result in abnormality to synapses, neurexins, neuroligins, cell adhesion molecules, neurite outgrowth as well as histamine biosynthesis (Abelson et al., 2005; Clarke, Lee, & Eapen, 2012; Ercan-Sencicek et al., 2010; Nag et al., 2013; Sundaram, Huq, Wilson, & Chugani, 2010; Zilhao et al., 2015). Furthermore, similar brain connectivity patterns are observed across TS, OCD and ADHD (Worbe, 2015; Worbe, Marrakchi-Kacem, et al., 2015) with phenotypic similarity in TS corresponding to comparable genetic backgrounds (Huisman-van Dijk, 2016).

TS therefore represents a continuum ranging from cases with ‘pure’ TS to phenotypes that include comorbid neurodevelopmental conditions (Cravedi et al., 2017). Individual variability in environmental factors, polygenic burden and inherited de novo mutations can account for the clinical heterogeneity in TS severity, phenotypes, treatment response and clinical outcome (Biederman et al., 2000; Bloch et al., 2006; Faraone et al., 2006; Groth, 2018; Hirschtritt et al., 2015; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, et al., 2017). Furthermore, comorbidity corresponds to extensive abnormality within CSTC circuitry, due to the cumulative load of additional genetic and environmental risk factors (Eapen & Robertson, 2015). It has been proposed that worse clinical and functional outcomes in TS is associated with the presence of comorbidity (Rizzo, Gulisano, Cali, & Curatolo, 2012). Accordingly, comorbidities are observed to have a drastic impact to QOL (APA, 2013; Bawden et al., 1998; Cavanna, Luoni, et al., 2013; Cavanna et al., 2008; Conelea et al., 2013; Eapen, Cavanna, et al., 2016; Evans et al., 2016;

Haddad et al., 2009; Jalenques et al., 2012; O'Hare et al., 2015; Parisi, 2010; Piacentini et al., 2010; Rizzo et al., 2013; Swain et al., 2007).

Abnormalities of cognition have been associated with comorbidities (Abramovitch et al., 2017; Buse et al., 2012; Drury et al., 2012; Eddy et al., 2009; Johannes, Wieringa, Nager, et al., 2001; Lavoie et al., 2007; Ozonoff et al., 1998; Rizzo, Gulisano, Pellico, Cali, & Curatolo, 2014; Shin et al., 2001; Yeates, 1994). The degree to which cognitive deficits are inherent to 'pure' TS has yet to be elucidated (Morand-Beaulieu, Leclerc, et al., 2017). Comorbid ADHD has been identified as the largest determinant of problems with executive functioning in TS (Rizzo et al., 2013) and is seen to account for a proportion of deficits in inhibitory control, planning, working memory and, crucially, domains of attention (Barkley, 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Channon, Pratt, et al., 2003; de Groot et al., 1997; De Monte, 2007; Drury et al., 2012; Eddy et al., 2009; Freeman & Tourette Syndrome International Database, 2007; Harris et al., 1995; Roessner, Becker, Banaschewski, & Rothenberger, 2007; Sallee et al., 1994; Scharf, Miller, Mathews, & Ben-Shlomo, 2012; Schuerholz et al., 1996; Sherman et al., 1998; Shin et al., 2001; Termine et al., 2016). Similarly, comorbid OCD has been found to account for a proportion of the cognitive deficits in attention, planning and organising, verbal and non-verbal memory, response inhibition, visuo-motor integration and, crucially, cognitive flexibility (Bornstein, 1991a; Gruner, 2009; Gruner, & McKay, 2013; Gu et al., 2008; Harkin & Kessler, 2011; Lucke et al., 2015; Matsuda et al., 2012; Muller et al., 2003; Savage et al., 2000).

Despite evidence that comorbidities cause cognitive deficits in TS, there is evidence that comorbid ADHD (Cirino, Chapieski, & Massman, 2000; de Groot et al., 1997; Greimel et al., 2011; Mahone et al., 2002; Rothenberger et al., 2000; Schultz et al., 1998) and comorbid OCD does not confer neuropsychological disadvantage (Aukrust et al., 2003; de Groot et al., 1997; Lee et al., 2009; Milliery et al., 2000; Muller et al., 2003). Furthermore, there is evidence that deficits in cognition may be inherent to the presence of TS, as uncomplicated TS has been associated with impairment in attention (Sherman et al., 1998), executive functioning (Channon, Flynn, & Robertson, 1992; Eddy & Cavanna, 2015; Eddy, Rickards, et al., 2012; Goudriaan et al., 2006; Jeter et al., 2015) and response inhibition (Eddy, Rickards, et al., 2012; Eddy et al., 2014).

Alongside cognitive dysfunction, there is evidence that comorbidity may correlate with alterations in corticospinal excitability. For instance, comorbid ADHD has been associated with more extensive abnormalities in both SAI and ICF (Orth & Rothwell, 2009). Conversely, comorbid ADHD and OCD had no additional influence on ICF (Gilbert, Sallee, Zhang, Lipps, & Wassermann, 2005). Alternatively, typical levels of ICF have been observed in adults TS with comorbid ADHD (Richter, Ehlis, Jacob, & Fallgatter, 2007). However, results are mixed as reduced SICI has been observed across comorbidity subgroups (Orth & Rothwell, 2009).

Comorbidities are noted to be more problematic than tics and urges, causing substantially more psychosocial and functional impairment (Roessner et al., 2011), with evidence of a significant impact on cognition (Barkley, 1997; Channon, Pratt, et al., 2003; de Groot et al., 1997; Eddy et al., 2009; Freeman & Tourette Syndrome International Database, 2007; Gruner, 2009; Matsuda et al., 2012; Roessner et al., 2007) and the structure and functional balance of inhibition and excitation of CSTC circuitry (Bloch et al., 2011; Karagiannidis, 2016; Kern et al., 2015; Paschou et al., 2013; Peterson et al., 2001; Worbe, 2015). The impact of comorbidities in adult TS still remains unexplored (Johannes, Wieringa, Nager, et al., 2001). Thus, advancing our understanding of the causes, clinical features and outcomes of a comorbid diagnosis in adult TS will lead to better understanding, with important implications to the development of personalised treatment interventions and better psychological and educational support (Cravedi et al., 2017; Debes et al., 2010; Eapen, Snedden, et al., 2016; Martino, Ganos, et al., 2017).

Recently, longitudinal studies have provided insight into the developmental course of comorbidities in TS. For example, it has been observed that over time, 42% of individuals with a diagnosis of a comorbidity at baseline were found to have uncomplicated TS at follow-up, suggesting that typically, there is a decline in comorbidity severity, so that by late adolescence the majority of individuals have uncomplicated TS (Groth, 2018). Similarly, another study found that in children and adolescents with TS, over a period of 6 years, whilst tic severity remained severe, symptoms of OCD and ADHD reduced in severity (Hartmann, Worbe, & Black, 2018); supporting the idea that overtime there could be a shift towards uncomplicated TS. Intriguingly, 27% of individuals with uncomplicated TS at baseline

had developed a comorbidity by follow-up and interestingly, the oldest subgroup with baseline comorbidity were likely to retain these at follow-up (Groth, 2018).

Despite evidence that comorbidity presence and severity may decrease overtime, uncomplicated TS is seen to occur in only 8-24% of cases from clinical (Cavanna, Critchley, et al., 2011; Freeman & Consortium, 2007; Rizzo et al., 2012; Robertson, 2015b) and community samples (Freeman et al., 2000; Hirschtritt et al., 2015; Khalifa & von Knorring, 2006; Peterson et al., 2001; Robertson, 2012). There is a lifetime prevalence of comorbidity in 36-90% of TS cases (Eddy, Cavanna, et al., 2012; Robertson, 2012) with approximately 58% of these individuals experiencing multiple comorbid diagnoses (Hirschtritt et al., 2015; Khalifa & von Knorring, 2006).

In our sample of adults with TS, 21% were classified as having uncomplicated TS, 15% as having comorbid ADHD, 15% as having comorbid OCD and 49% as having complicated TS (comorbid ADHD and OCD). Our results therefore support that in adulthood, the majority of cases, 79%, experience comorbidity, with 62% of these cases experiencing multiple comorbid diagnoses. Our results are therefore consistent with previous observations and extend our understanding of adult TS, whereby uncomplicated TS is uncommon (Cavanna, Critchley, et al., 2011; Freeman & Consortium, 2007; Freeman et al., 2000; Hirschtritt et al., 2015; Khalifa & von Knorring, 2006; Peterson et al., 2001; Rizzo et al., 2012; Robertson, 2012, 2015b) and phenotypes with comorbidities highly prevalent (Eddy, Cavanna, et al., 2012; Hirschtritt et al., 2015; Khalifa & von Knorring, 2006; Robertson, 2012).

Exploration of comorbid symptoms amongst our subgroups revealed, as expected, that following classification, the highest ADHD symptom scores (inattention, hyperactivity, impulsivity) were distributed similarly amongst subgroups with comorbid ADHD. Furthermore, aside from total BAARS-IV and sluggish cognitive tempo subscale, where lone comorbid ADHD scored highest, complicated TS was associated with worse symptoms. Similarly, as expected, comorbid OCD was associated with the highest OCD symptom scores and interestingly, lone comorbid OCD and complicated TS subgroups scored similarly across subscale dimensions. Individuals with uncomplicated TS naturally had the lowest scores on measures of ADHD and OCD symptomatology. As observed previously, we found that the more complex the comorbidity, the more severe the clinical symptom ratings of comorbid ADHD and OCD.

The effects of comorbidity on urges was explored and compared to lone comorbid ADHD, complicated TS was associated with significantly worse premonitory experiences; there were no differences amongst other subgroups. Following classification of comorbidity subgroups, the highest OCD symptom scores were distributed amongst subgroups with comorbid OCD, with complicated TS associated with the most severe symptoms. Previously, in Chapter 7, comorbid OCD corresponded to worse urge severity, consistent with previous findings (Ganos, Garrido, Navalpotro-Gomez, et al., 2015; Kano et al., 2015) and with OCD being associated with altered sensory phenomena (Cox et al., 2018; Ganos, Garrido, Navalpotro-Gomez, et al., 2015; Rajagopal & Cavanna, 2014; Rajagopal et al., 2013). Worse premonitory urges in complicated TS is therefore consistent with the effects of severe OCD symptoms on urge severity.

Similarly, exploration of the effects of comorbidity subgroup on tic severity revealed that the presence of OCD coincided with the highest YGTSS total scores. These results are again consistent with the previously identified link between OCD and worse premonitory urges, that corresponds to worse tic severity (Crossley et al., 2014; Eddy & Cavanna, 2014; Ganos, Garrido, Navalpotro-Gomez, et al., 2015; Reese et al., 2014; Woods et al., 2005). Therefore, complicated TS with more severe OCD symptom ratings were found to have significantly worse total YGTSS and MRVS scores and significantly more body areas affected by tics, than those with uncomplicated TS and low OCD severity. No other differences existed amongst subgroups. Our results are therefore consistent with worse clinical severity with advanced comorbidity (Rizzo et al., 2012). Interestingly, comorbidity did not influence age of tic onset, extent of motor or vocal tic presence or levels of impairment. Our results therefore suggest that in adult TS, clinical severity is complicated by and not a consequence of comorbidity.

Investigation of comorbidity on general cognition revealed a significant interaction effect between IED stage and comorbidity subgroup, whereby those with complicated TS made significantly fewer EDS errors than other subgroups. These results are consistent with our findings of the interaction between EDS errors and OCD comorbidity. Furthermore, in Chapter 7, we observed that comorbid OCD was associated with employing extensive alteration to the distribution of CSE as a tic control mechanism, due to a more severe clinical profile. Furthermore, it was

identified that such compensation facilitates cognitive flexibility, especially as compensatory alterations in TS have previously been seen to confer cognitive advantage (Jackson, Parkinson, Jung, et al., 2011; Mueller et al., 2006; Plessen et al., 2009; Plessen et al., 2004; Roessner et al., 2008). Consequently, complicated TS, with the highest OCD symptom scores, may therefore benefit most from the effect of OCD severity on cognitive flexibility, corresponding to significantly fewer EDS errors. Despite this, there was no significant main effect of comorbidity subgroup on IED errors made. Our results therefore suggest that cognitive inflexibility to habitually learned behaviours is a core feature of TS and not a consequence of comorbidity. Cognitive inflexibility being inherent in TS is supported by observations that uncomplicated TS is accountable for the cognitive deficits in related domains of attention and inhibition (Eddy, Rickards, et al., 2012; Eddy et al., 2014; Sherman et al., 1998) and finally, to executive functioning (Channon, Flynn, & Robertson, 1992; Eddy & Cavanna, 2015; Eddy, Rickards, et al., 2012; Goudriaan et al., 2006) where deficits have been observed to occur regardless of comorbidity (Jeter et al., 2015).

Intriguingly, during the SWM task, lone comorbid OCD was related to significantly poorer strategy utilisation than those with complicated TS; no differences existed amongst other subgroups and our results were independent from the effects of antipsychotics. Crucially, comorbidity was not associated with differences in SWM overall performance. Previously, in Chapter 7, we observed better strategy utilisation on the SWM task with comorbid OCD. An explanation for this discrepancy is that classification into subgroups has located the beneficial effect of OCD severity on strategy to those with complicated TS, consistent with our previous results. On the other hand, lone comorbid OCD may be associated with different organisational planning techniques, as seen in those with comorbidities (Laverdure et al., 2013; O'Connor, Audet, Julien, Aardema, Laverdure, & Lavoie, 2015) likely developed to overcome cognitive limitations, implicit to the distracting experience of obsessions (Muller et al., 2003). This explanation is consistent with lone comorbid OCD being associated with a different strategy utilisation that nevertheless achieves similar accuracy to other subgroups.

Investigation of the effects of comorbidity subgroup on attention and inhibition revealed that all participants performed similarly on the CPT and RCF tasks, irrespective of comorbidity. Our results therefore challenge previous findings that

comorbid ADHD is associated with CPT task deficits (Harris et al., 1995; Sallee et al., 1994; Schuerholz et al., 1996; Sherman et al., 1998) and supports findings that comorbid ADHD (Cirino et al., 2000; de Groot et al., 1997; Greimel et al., 2011; Mahone et al., 2002; Rothenberger et al., 2000; Schultz et al., 1998) and comorbid OCD (Aukrust et al., 2003; de Groot et al., 1997; Lee et al., 2009; Milliery et al., 2000; Muller et al., 2003) do not confer additional cognitive disadvantage in attention and inhibition in TS.

Furthermore, despite the majority of our sample experiencing clinical and subclinical impairment in domains of attention and the presence of obsessions and compulsions, TS was not associated with impairment in attention or inhibition. Previously, in Chapter 4 during CPT and RCF tasks, we observed compensatory reduction in motor output to accommodate both tic control and task-specific motor performance, under conditions of increased information processing demands (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). Additionally, such compensatory mechanisms were seen across subgroups. It is plausible that due to the challenging and distracting experiences inherent to TS, associated with urges, tics and comorbidities (Muller et al., 2003), individuals, by adulthood, have acquired compensatory mechanisms. Thus, our results provides evidence that comorbidity does not impair the ability to acquire compensatory mechanisms that function to preserve attention and inhibition in TS.

We found no significant main effect of comorbidity subgroup on interoceptive awareness or resting heart rate. Such findings, implicate altered interoceptive awareness as a core feature of TS as opposed to a consequence of comorbidity. Our results are consistent with our findings in Chapter 5, where we showed that reduced interoceptive awareness is likely due to the inability of adults with TS to be flexible with cognition regarding habitually learned behaviours. Subsequently, reduced interoception is a consequence of difficulty in shifting attention internally to their heartrate and/or difficulty inhibiting tics and urges to utilise attention accurately. Few studies have assessed the effects of comorbidities on interoceptive awareness. However our results are consistent with comorbid ADHD not being associated with further alteration to interoception in TS (Pile et al., 2018). Furthermore, ADHD and OCD occurring in the absence of a tic disorder is found to be associated with intact

interoceptive awareness (Wiersema & Godefroid, 2018; Yoris et al., 2017), further supporting reduced interoception as a core feature of TS.

We found no significant main effect or interaction effects of comorbidity subgroup on motor thresholds, SICI, ICF or SAI. Furthermore, there was no effect of comorbidity subgroup on the changes in CSE following instruction to tic freely or during active tic suppression. In Chapter 7, we established that comorbid ADHD was associated with more extensive enhancement of ICF and that those with comorbid OCD required significantly more stimulation to reach RMT and 1mV thresholds. Unfortunately, the distribution of individuals across comorbidity subgroups is likely accountable for the loss of these effects. Our results are consistent with previous findings that thresholds are similar amongst uncomplicated TS and those with comorbid ADHD (Greenberg et al., 2000) and that comorbid OCD and uncomplicated TS have similar alterations in SICI, ICF and SAI (Gilbert et al., 2005; Orth & Rothwell, 2009). In Chapter 7, whist we identified a significant relationship between that worse ADHD severity and more extensive alteration in ICF, as seen previously in Chapter 6, dopaminergic modulation with antipsychotics in our sample may have reduced the levels of ICF in our subgroups (Cheon et al., 2004). Furthermore, our results did not replicate the observation that comorbid ADHD was associated with extensive alteration in SAI (Orth & Rothwell, 2009). Nevertheless, our results find evidence that reduced SICI and SAI are core features of TS and are not attributable to the effects of comorbid conditions.

Finally, reduced interoceptive awareness, SICI and SAI in all subgroups is consistent with our proposal of the role of perturbed inhibitory mechanisms of the motor and sensorimotor cortex in interoceptive awareness. Furthermore, this link between altered inhibitory mechanisms and interoceptive awareness is seen across subgroups and therefore likely to be a core feature of TS.

Chapter 9. Attention Distraction

9.1. Introduction

The aim was to explore the effects of both voluntary tic suppression and attention distraction on tic frequencies in adult TS. Following CPT task performance, examination of the cumulative effects of attentional load on tic frequency will allow us to infer whether the capacity to inhibit remains constant when attention is variable. Assessment of the summative effects of attention distraction and tic management on task performance and tic frequency will allow us to infer whether distraction can improve tic management and will provide insight into whether task performance is influenced by mechanisms of tic management. Furthermore, the mechanisms of tic management and attention distraction on tic frequencies was evaluated in both uncomplicated and complicated TS. This will allow us to evaluate the efficacy of therapies based on attention distraction.

9.2. Results

Baseline

Tic frequencies

There was a significant main effect of tic management (suppress vs. allow) on tic frequency (log-transformed), F (1.497, 46.420) = 59.136, p = .000, r = .75. Planned contrasts (simple) revealed that in comparison to no tic-related instructions, there were significantly more tics occurring when free to tic, F (1.497, 46.420) = 10.664, p = .003, r = .43, and significantly fewer tics during active tic suppression, F (1.497, 46.420) = 41.153, p = .000, r = .69.

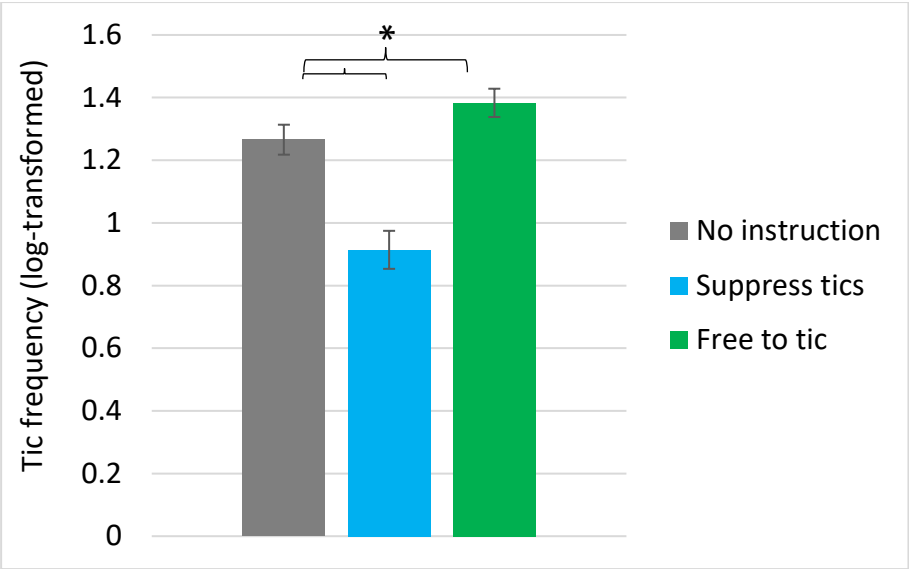


Figure 191. Mean tic frequency (log-transformed) observed under no tic-related instructions, during active tic suppression and free to tic conditions. Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Additionally, tic frequency observed under no tic-related instruction significantly correlated with tic frequency during active tic suppression, r_s = .472, p = .000 and free to tic conditions, r_s = .764, p = .000. Fewer tics at baseline corresponded with fewer tics occurring during tic conditions of tic management. Differences remained significant following Benjamini-Hochberg FDR correction.

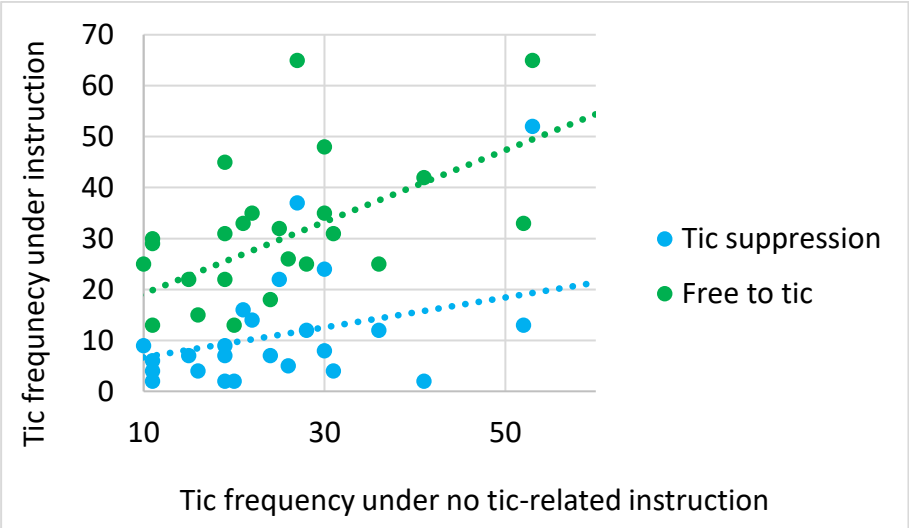


Figure 192. Relationship between tic-frequency observed under no tic-related instructions, during active tic suppression and free to tic conditions at baseline.

Medication

Medication with antipsychotics was not significantly related to tic frequency measures at baseline, F (1, 31) = .789, p = .381, r = .16, during active tic suppression, F (1, 30) = .666, p = .421, r = .15, or when free to tic, F (1, 30) = .382, p = .541, r = .11.

Interoceptive awareness

At baseline, fewer observed tics (log-transformed) correlated with significantly better interoceptive awareness (log-transformed) when free to tic, r = -.439, p = .012, but not when actively suppressing tics, r = -.279, p = .122. Differences remained following Benjamini-Hochberg FDR correction.

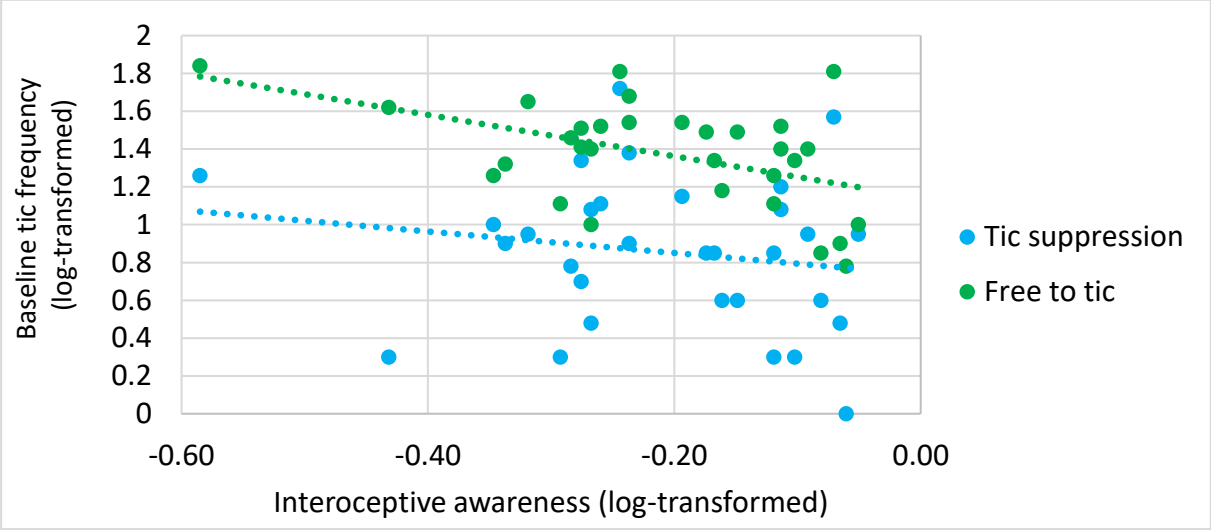


Figure 193. Relationship between interoceptive awareness and tic frequency at baseline (all log-transformed) when actively suppressing tics or when free to tic.

Summary

During assessment of the effects of tic management on tic frequency, at baseline, in the absence of attention distraction, significantly fewer tics occurred during active tic suppression compared to free ticcing.

Furthermore, tic frequency observed at baseline under no tic-related instructions corresponded significantly to frequencies at baseline observed during tic

management instruction. Fewer tics under no tic-related instructions equated to fewer tics during active tic suppression and free to tic conditions.

Furthermore, interoceptive awareness was found to correlate significantly with the number of tics occurring at baseline when free to tic. Specifically, fewer tics observed when free to tic was related to significantly better interoceptive awareness.

Continuous Performance Task (CPT)

Tic frequencies

Target set-size

There was a significant main effect of tic management on tic frequency, F (1, 30) = 35.521, p = .000, r = .74, with significantly more tics occurring when free to tic compared to active tic suppression.

There was a significant main effect of attentional load (target set-size manipulation) on tic frequency, F (3, 90) = 4.548, p = .005, r = .22. Planned contrasts (difference) that make comparisons to the mean tic frequency of all previous conditions revealed that there were significantly fewer tics at the highest attentional load, F (1, 30) = 7.466, p = .010, but no difference between target set-sizes of 2 and 1 target, F (1, 30) = .620, p = .437, r = .14.

There was no significant interaction effect between tic management and attentional load, F (3, 90) = .519, p = .670, r = .08.

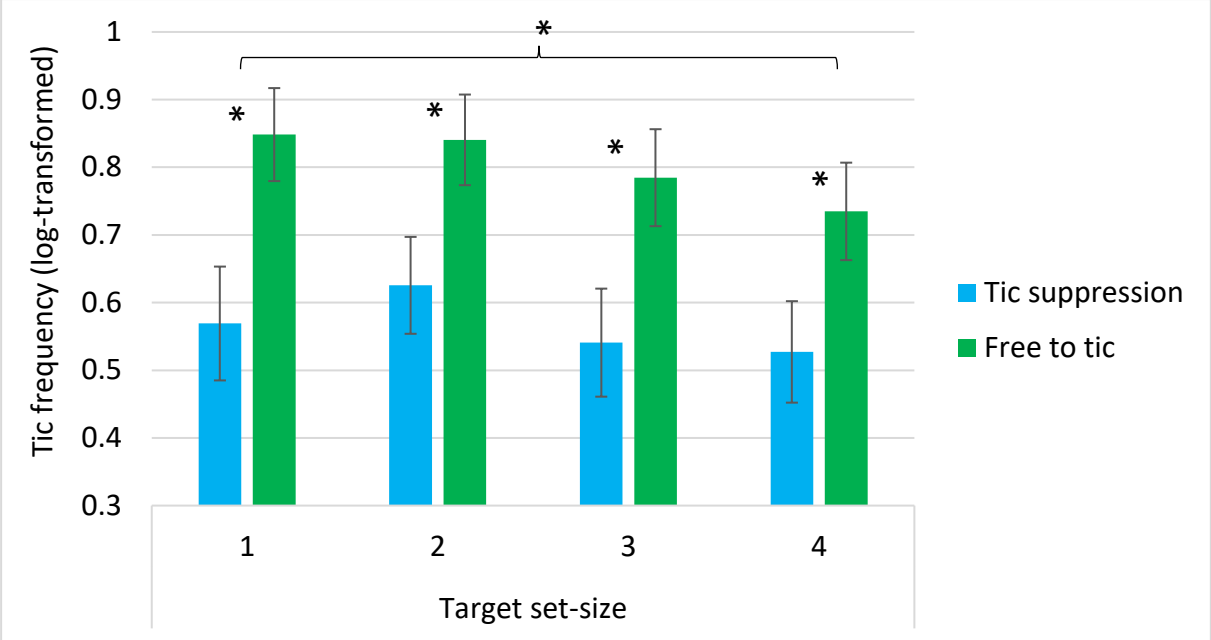


Figure 194. Mean tic frequency (log-transformed) observed during active tic suppression or when free to tic during performance of the CPT task at varying target set-size. Error bars representing SEM. *Effects of tic management condition and attentional load (target set-size) on tic frequencies remained significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to tic frequency measures observed during CPT task performance during active tic suppression, F (1, 29) = .345, p = .561, r = .47, or when free to tic, F (1, 29) = .077, p = .784, r = .47.

Experimental block

There was a significant main effect of tic management on tic frequency, F (1, 30) = 32.736, p = .000, r = .72, with significantly more tics occurring when free to tic compared to active tic suppression.

There was no significant main effect of experimental block on tic frequency, F (3, 90) = 1.728, p = .167, r = .14 and no interaction effect between tic management and experimental block, F (3, 90) = 1.743, p = .164, r = .23.

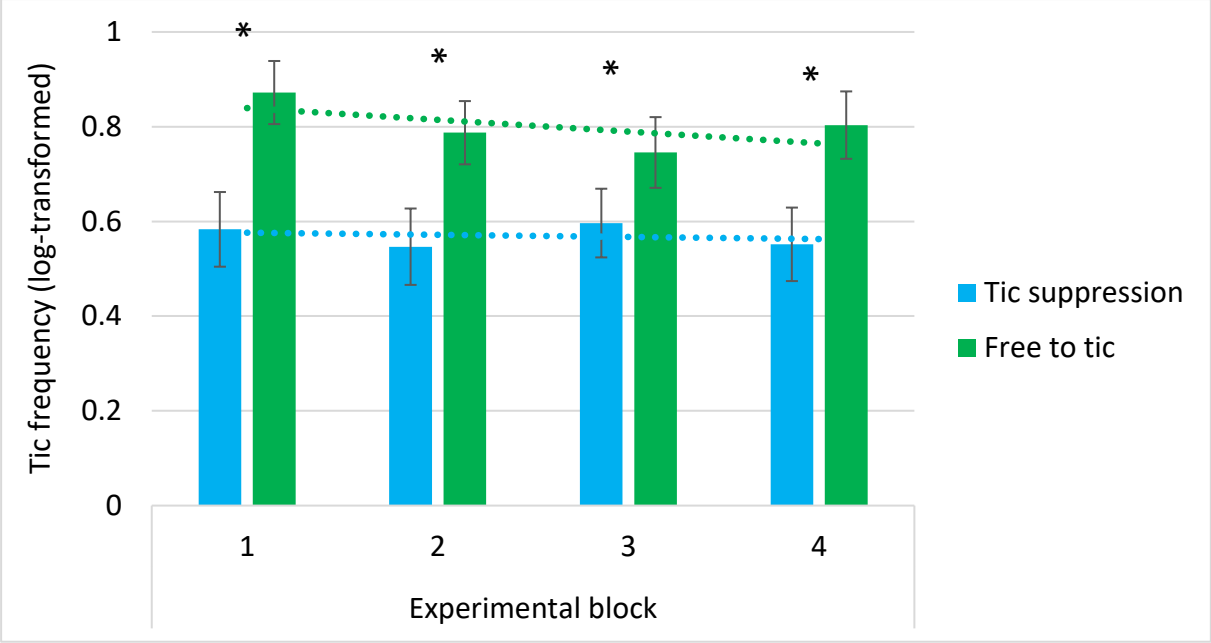


Figure 195. Mean tic frequency (log-transformed) observed under instruction to actively suppress tics (inhibit) or when free to tic (allow) during performance of the CPT task at each experimental block. Error bars representing SEM. *Significant following Benjamini-Hochberg FDR correction.

Tic management

To obtain a measure of how successful active tic management is on reducing tic frequency, tic frequencies observed at baseline during active tic suppression were normalised to the amount of tics observed at baseline under no tic-related instructions. Normalised frequencies were converted to a percentage, with the resulting value representing the degree to which successful tic inhibition can be achieved; an index of the capacity to suppress tics.

Subsequently, the better the capacity to suppress tics at baseline (smaller values) there were significantly fewer tics observed during attention distraction (CPT task) when actively suppressing tics, r_s = .382, p = .034 but not when participants were free to tic, r_s = .339, p = .062. Differences remained following correction with Benjamini-Hochberg correction.

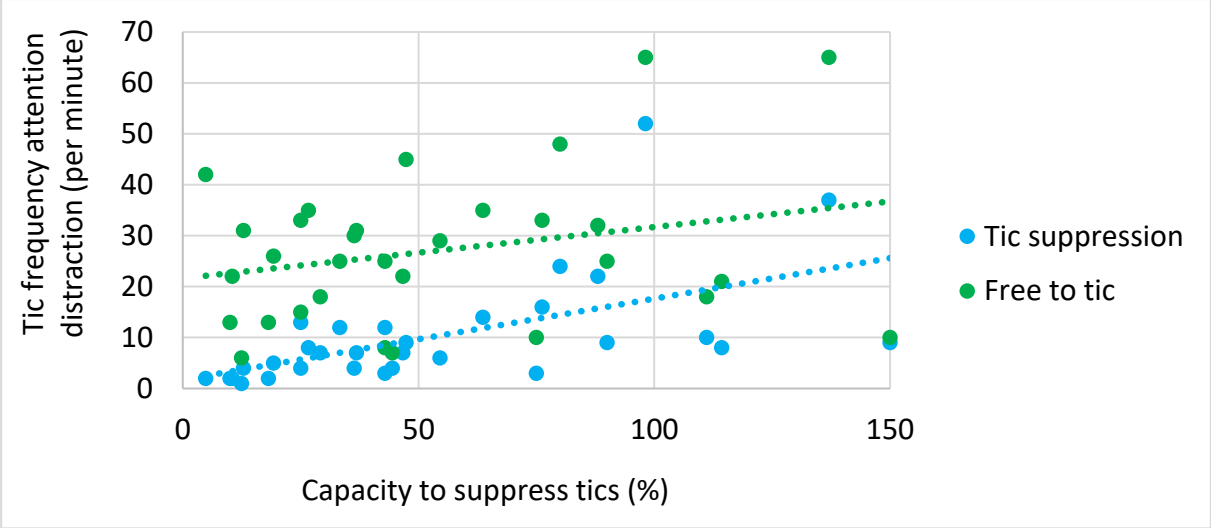


Figure 196. Relationship between the degree to which individuals can successfully inhibit tics at baseline (active tic suppression at baseline, normalised to baseline no tic-instructions) and the raw tic frequencies (tics per minute) observed during attention distraction (CPT task) when actively suppressing tics or when free to tic.

Tic frequencies observed at baseline during no tic-related instructions, may occur during voluntarily and/or unconscious suppression of tics. Therefore, in an attempt to control for the influence of tic suppression mechanisms, baseline tic frequencies during instruction to tic freely were normalised to baseline tics frequencies during active tic suppression. Subsequently, the percentage value represents the degree to which active tic suppression is successful; the larger the value the more significant the reduction to tic frequency following active tic suppression.

Reduced capacity to successfully inhibit tics (smaller values) correlated significantly with higher tic frequencies observed during attention distraction whilst actively suppressing tics, r_s = -.401, p = .025, but not when free to tic, r_s = -.353, p = .052. Differences remained following Benjamini-Hochberg FDR correction.

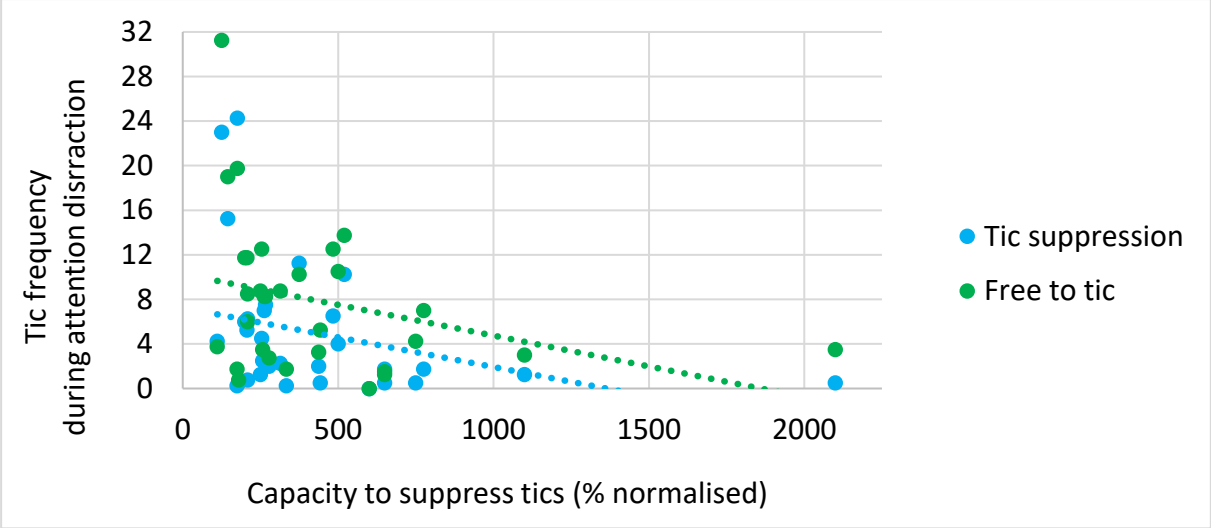


Figure 197. Relationship between the degree to which individuals can successfully inhibit tics at baseline (free ticcing at baseline normalised to baseline active tic suppression) and the raw tic frequencies observed during attention distraction (CPT task) when actively suppressing tics or when free to tic.

Task performance

Hit Reaction Time

Target set-size

There was a significant main effect of target set-size on HRTs, F (3, 93) = 58.504, p = .000, r = .62. Planned contrasts (Helmert) comparing one target to the main effect of all subsequent set-sizes revealed significantly slower HRTs with increasing set-size, F (1, 31) = 137.931, p = .000, r = .90.

There was no significant main effect of tic management (suppress vs. allow) on HRTs, F (1, 31) = 1.360, p = .252, r = .21. There was also no significant interaction effect between tic instructions and target set-size, F (2.233, 69.211) = .339, p = .737, r = .07.

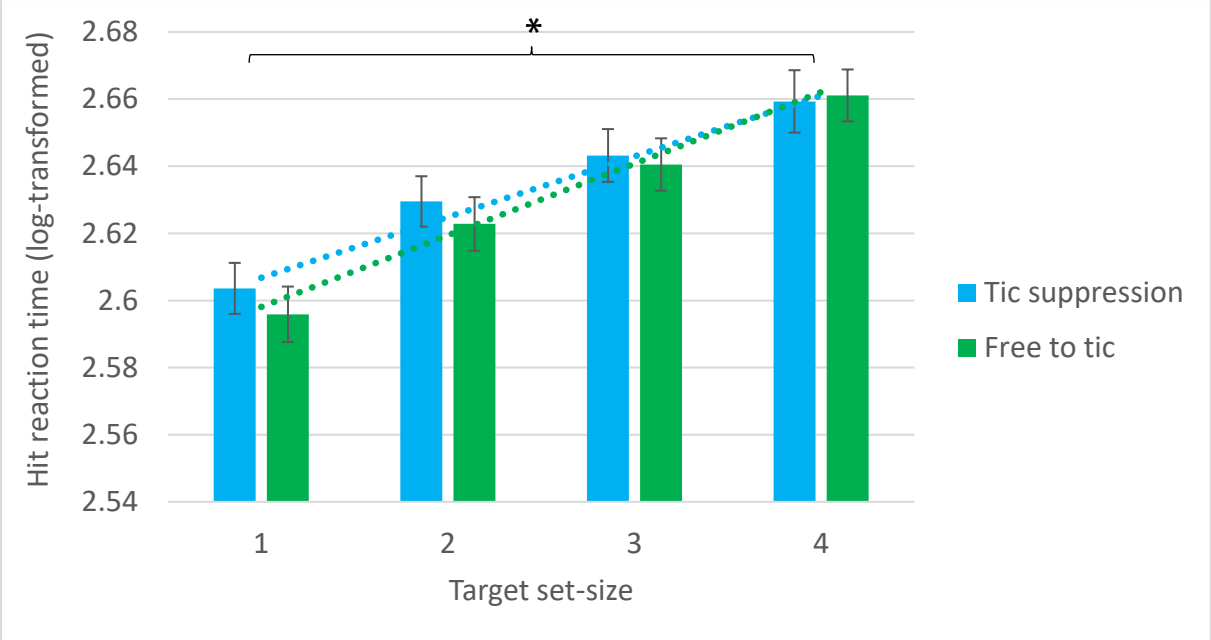


Figure 198. Mean hit reaction times (ms, log-transformed) at varying target set-sizes during performance of the CPT during instruction to actively suppress tics or free to tic. Error bars represent SEM. *Effect of target-set size significant following Benjamini-Hochberg FDR correction.

Experimental block

There was a significant main effect of experimental block on HRTs, F (2.214, 68.634) = 18.325, p = .000, r = .46. Planned contrasts (repeated) revealed that participants had significantly quicker HRTs during the first block of the experiment compared to the second block, F (1, 31) = 42.787, p = .000, r = .76; and significantly quicker RTs for four compared to three blocks, F (1, 31) = 10.613, p = .003, r = .51. There was no difference in HRTs for blocks two and three, F (1, 31) = .667, p = .420, r = .15.

There was no significant main effect of tic management on block HRTs, F (1, 31) = .474, p = .496, r = .12; and no significant interaction effect between tic management and experimental block, F (2.175, 67.414) = 1.270, p = .289, r = .14.

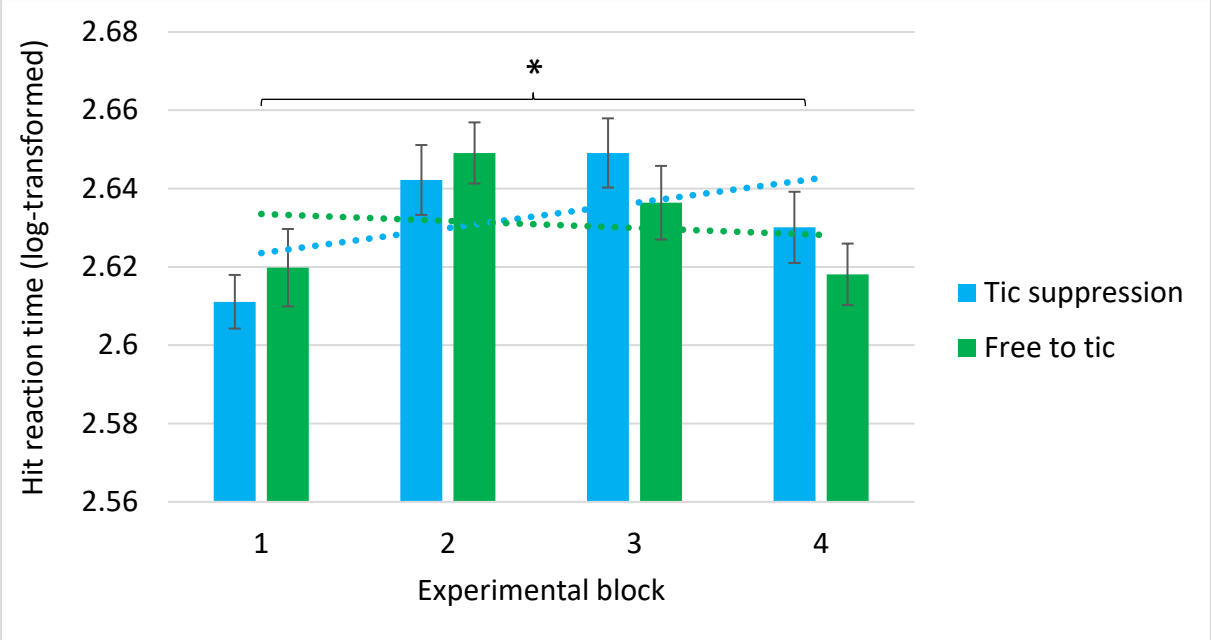


Figure 199. Mean hit reaction times (ms, log-transformed) for each experimental block during performance of the CPT during instruction to actively suppress tics or free to tic. Error bars represent SEM. *Effect of experimental block significant following Benjamini-Hochberg FDR correction.

Number errors

There was a significant main effect of tic management on the number of errors made on the CPT task, F (1, 31) = 6.720, p = .014, r = .42, whereby when actively suppressing tics, participants make significantly fewer errors; remaining significant following Benjamini-Hochberg FDR correction.

There was no significant main effect of error type on the number of errors made on the CPT task, F (1, 31) = 2.279, p = .141, r = .26. However, there was a significant interaction effect between tic management and error type, F (1, 31) = 8.820, p = .006, r = .47, whereby when actively suppressing tics compared to being free to tic, significantly fewer commission errors were made.

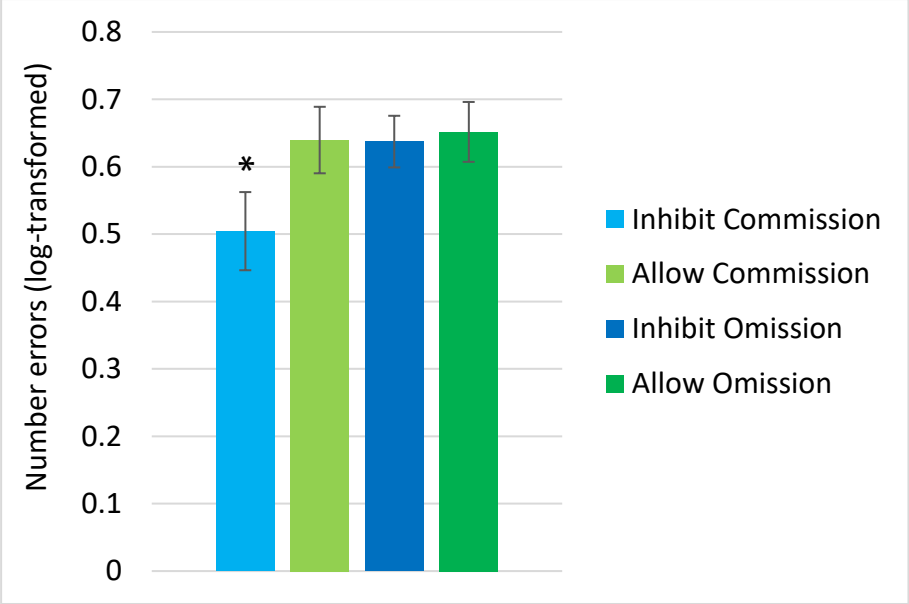


Figure 200. Mean number of commission and omission errors made on the CPT task during instruction to actively suppress tics (inhibit) or free to tic (allow). Error bars represent SEM. *Significant following Benjamini-Hochberg FDR correction.

Medication

Medication with antipsychotics was not significantly related to the number of commission errors made (log-transformed) under instruction to inhibit tics, F (1, 30) = 2.145, p = .153, r = .47.

Detectability *d*

There was no significant main effect of tic management on detectability *d*, F (1, 31) = .487, p = .491, r = .12. There was also no significant main effect of target set-size, F (3, 93) = .896, p = .447, r = .10, and no significant interaction between tic management and target set-size on detectability *d*, F (3, 93) = .997, p = .398, r = .10.

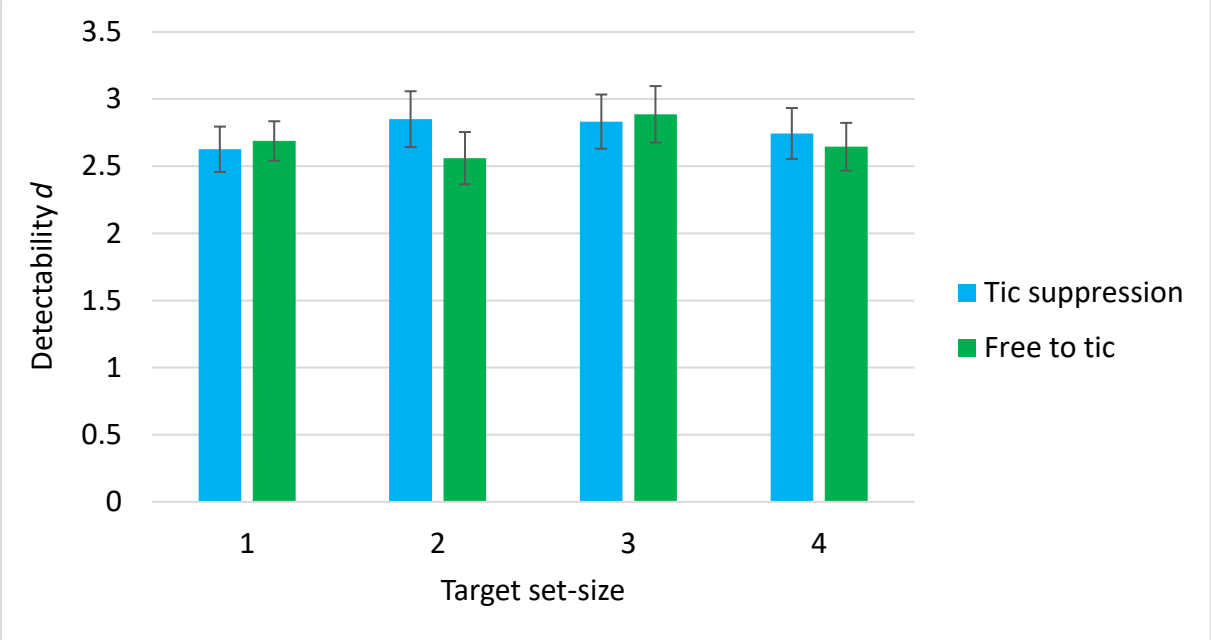


Figure 201. Mean detectability *d* at varying target set-sizes during performance of the CPT task during instruction to actively suppress tics or free to tic. Error bars represent SEM.

Response style *c*

There was no significant main effect of tic management on response style *c*, F (1, 31) = .001, p = .977, r = .01. There was a significant main effect of target set-size on response style *c*, F (3, 93) = 5.813, p = .001, r = .24, with planned contrasts (simple) comparing one target to the mean effect of all subsequent set-sizes revealed a significantly smaller response style with fewer targets, F (1, 31) = 13.193, p = .001, r = .55. These results indicated that participants become more liberal in their response style with increasing target set-size.

There was also no significant interaction between tic management and target set-size on response style *c*, F (3, 93) = .997, p = .398, r = .10.

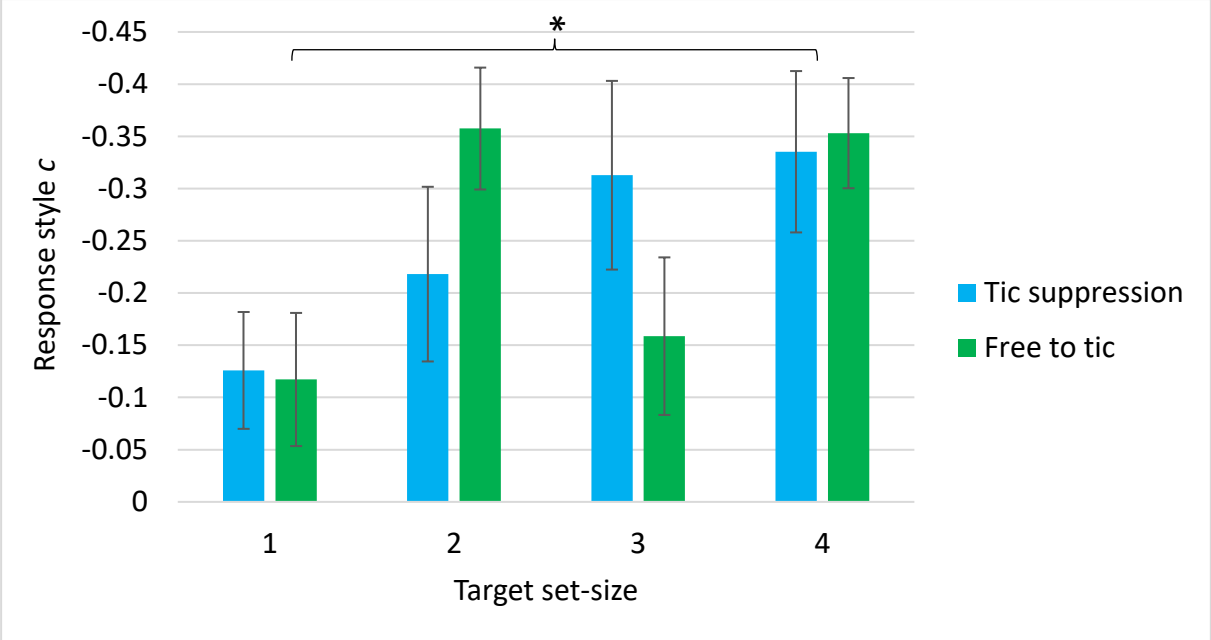


Figure 202. Mean response style *c* at varying target set-sizes during performance of the CPT task under instruction to actively suppress tics or free to tic. Error bars represent SEM. *Effect of target set-size significant following Benjamini-Hochberg FDR correction.

A paired-samples T-test conducted on all set-size data, revealed that there was no significant difference in response style *c* during instruction to actively suppress tics or when free to tic, t (31) = .013, p = .990, r = .00.

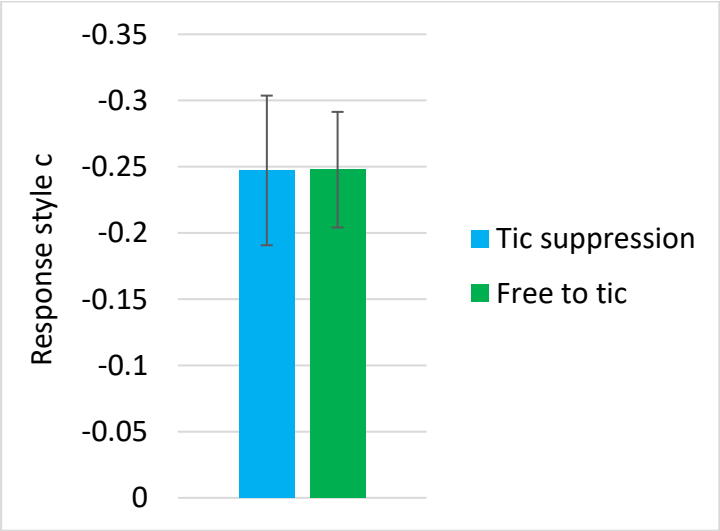


Figure 203. Mean response style *c* during performance of the CPT task under instruction to actively suppress tics (inhibit) or free to tic (allow). Error bars SEM.

Tic management

Tic frequencies observed at baseline when free to tic were normalised to tic frequencies with no tic-related instructions. Normalised frequencies were then converted to a percentage, with the resulting value representing the degree to which successful tic inhibition can be achieved; an index of the capacity to suppress tics.

Subsequently, the better an individual's capacity to suppress tics at baseline (smaller values) correlated significantly with fewer omission errors, r_s = .412, p = .021, and commission errors, r_s = .411, p = .022, made during CPT task performance whilst actively suppressing tics, but not when free to tic (all p > .05). Significance remained following Benjamini-Hochberg FDR correction.

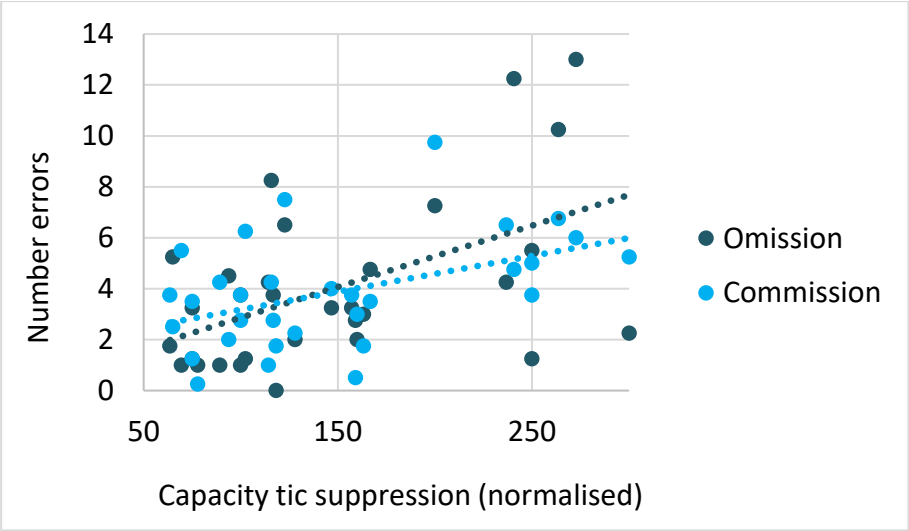


Figure 204. Relationship between the capacity for successful tic suppression at baseline (free ticcing at baseline normalised to baseline active tic suppression) and the number of errors (omission or commission) made during CPT task under active tic suppression.

Furthermore, more frequent tics observed at baseline whilst free to tic (raw data) correlated significantly with more commission errors made during active tic suppression, r_s = .389, p = .028; remaining following Benjamini-Hochberg FDR correction.

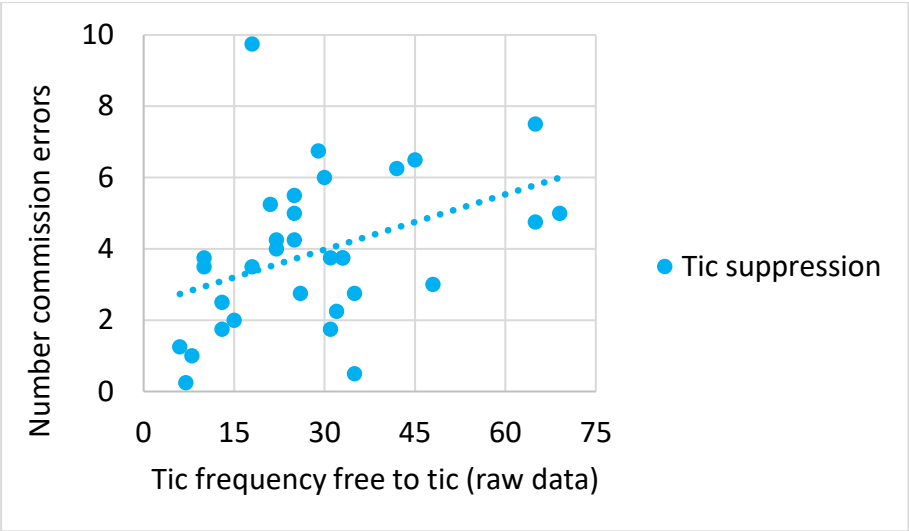


Figure 205. Relationship between tic frequency at baseline whilst free to tic and the number of commission errors made during the CPT whilst actively suppressing tics.

Interoceptive awareness

During CPT task performance interoceptive awareness (log-transformed) was found to correlate significantly with total commission errors (log-transformed) made overall, irrespective of tic management instruction, r = -.429, p = .014 but not with total omission errors, r = -.100, p = .586. Worse interoceptive awareness was associated with making more commission errors. Differences remained following Benjamini-Hochberg FDR correction.

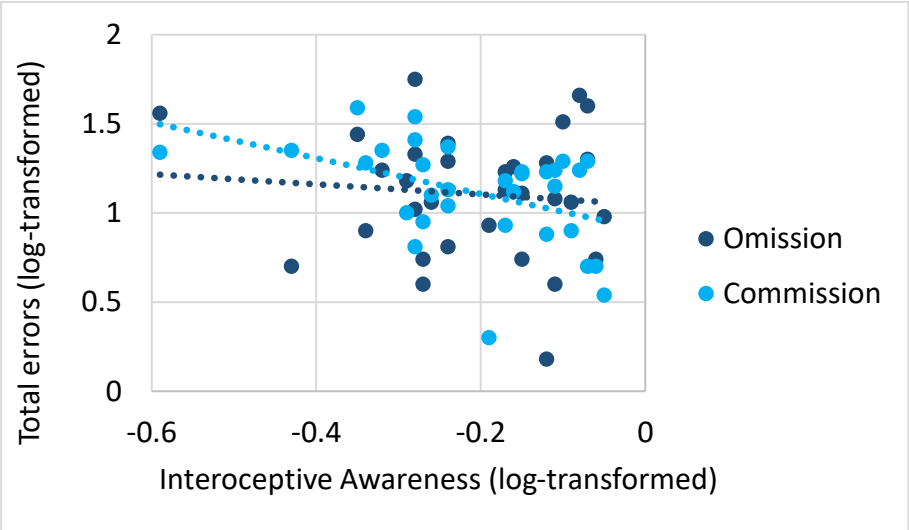


Figure 206. Relationship between interoceptive awareness (log-transformed) and the number of commission and omission errors made on the total CPT task.

Furthermore, under active tic suppression interoceptive awareness (log-transformed) was found to correlate significantly with total task commission errors (log-transformed), r = -.466, p = .007, but not omission errors, r = -.157, p = .391. Better interoceptive awareness was associated with making fewer commission errors. Significance remained following Benjamini-Hochberg FDR correction.

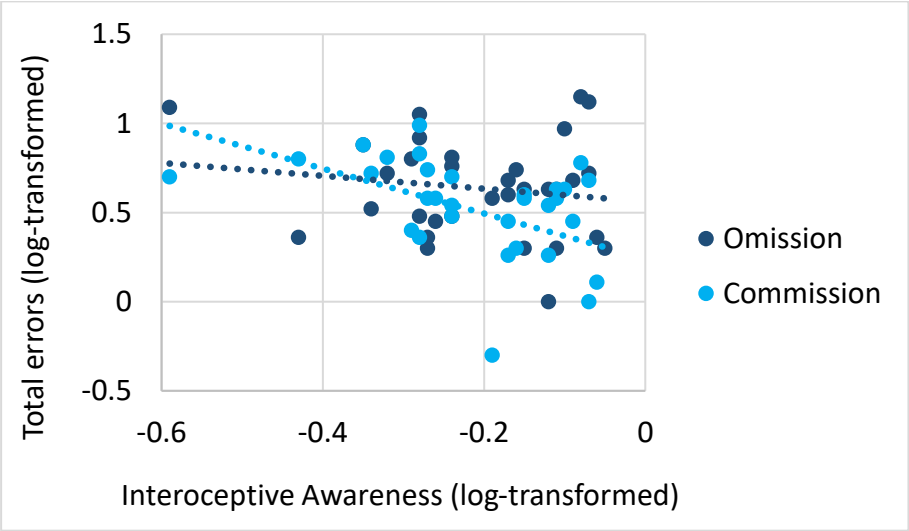


Figure 207. Relationship between interoceptive awareness (log-transformed) and the number of commission and omission errors made on the CPT task under instruction to inhibit tics.

Summary

During CPT-mediated attention distraction, whilst significantly more tics occurred when individuals were free to tic, there was a significant main effect of attentional load on reducing tic frequency. Specifically, the highest load of attention resulted in the fewest tics, with all levels of attention significantly reducing tic frequency. Our results occurred irrespective of tic management condition. In addition, medication with antipsychotics did not account for any differences observed and there was no effect of experimental block or interaction with tic management on tic frequencies. Furthermore, the better the capacity to suppress tics at baseline correlated significantly with fewer tics during attention distraction and active tic suppression but not when free to tic.

CPT task performance undertaken during active tic suppression or when free to tic was found to have no effect on HRTs. HRTs were quicker during the first and last blocks of the CPT, with similar yet slower HRTs during middle blocks; all occurring irrespective of tic management. There was also no effect of tic management on signal detection measures (*d* or *c*). There was however, a significant effect of tic management on the number of errors made during the CPT task, an effect independent from antipsychotic medication. Specifically, during active tic suppression, participants made significantly fewer commission errors. Additionally, we observed that the better an individual's capacity to suppress tics at baseline, the fewer errors made when actively suppressing tics; but not when free to tic. Furthermore, fewer tics at baseline when free to tic correlated with significantly fewer commission errors. Finally, during active tic suppression, better interoceptive awareness was associated with making significantly fewer errors of commission.

Tic management vs. attention distraction

Tic frequencies

There was a significant main effect of tic management on tic frequency, F (1, 30) = 61.647, p = .000, r = .74, with significantly more tics occurring when free to tic compared to active tic suppression.

There was a significant main effect of attentional load on tic frequency, F (2.475, 74.262) = 57.028, p = .000, r = .22. Planned contrasts (difference) that make comparisons to the mean tic frequency of all previous conditions revealed that there were significantly fewer tics at the highest attentional load, F (1, 30) = 39.446, p = .000. Furthermore, there was a significant interaction effect between tic management and attentional load, F (4, 120) = 5.897, p = .000, r = .08. Planned contrasts (Helmert) that compares tic frequency at the lowest attentional load (baseline, no CPT) to the mean tic frequency of all subsequent conditions (levels of attention distraction, during CPT) revealed that there were significantly more tics at baseline (no attention distraction) compared to during attention distraction, F (1, 30) = 24.305, p = .000. Furthermore, in comparison to the tic frequencies observed at target set-size of 1 to the mean tic frequency of all subsequent attentional loads, there was no significant difference in tic frequencies, F (1, 30) = 1.337, p = .257.

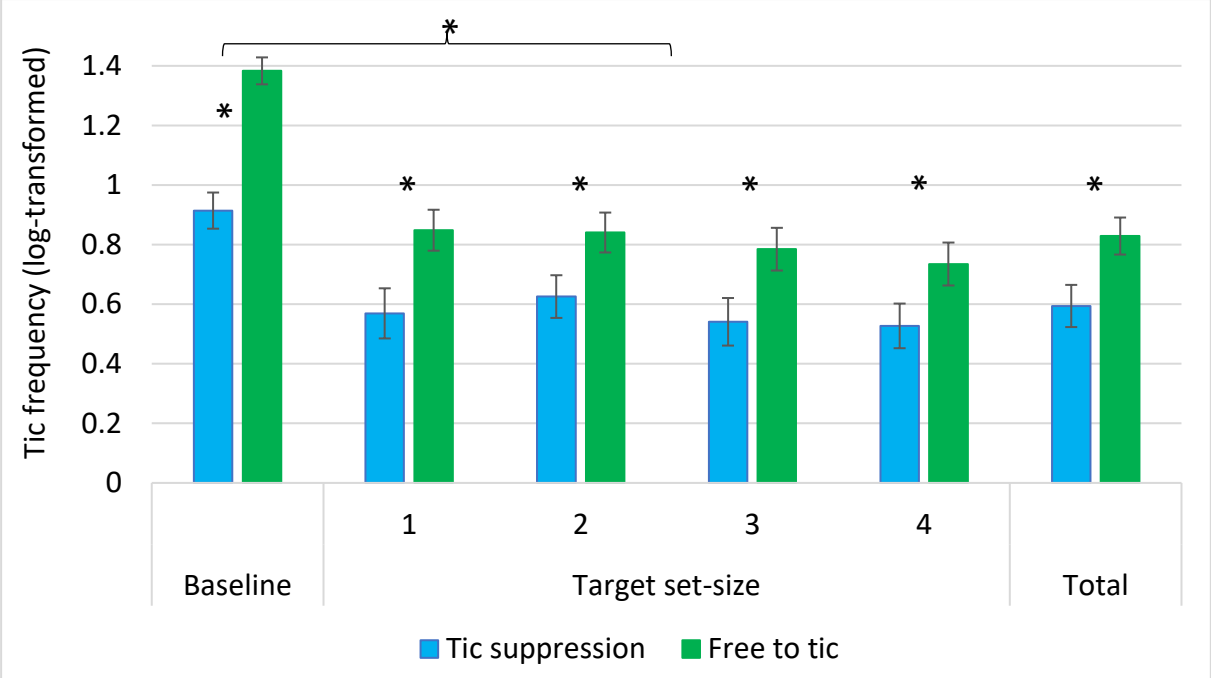


Figure 208. Mean tic frequency (log-transformed) observed during active tic suppression or when free to tic at baseline or during CPT task performance at varying target set-size. Error bars representing SEM. *Effect of tic management condition and attentional load (target set-size) significant following Benjamini-Hochberg FDR correction.

A two-way ANOVA was also conducted to examine the effects of attention distraction and tic suppression on tic frequency. There was a trend towards a significant interaction between the effects of attention distraction and tic suppression on tic frequencies, F (1, 120) = 3.762, p = .055, ω^2 = .002. There was a significant main effect of attention distraction on tic frequency, with attention distraction significantly reducing tic frequency, F (1, 120) = 52.404, p = .000, ω^2 = .06, and a significant main effect of tic suppression on tic frequency, with active tic suppression significantly reducing tic frequency, F (1, 120) = 33.947, p = .000, ω^2 = .04. Results remained significant following Benjamini-Hochberg FDR correction.

Under conditions of active tic suppression, tic frequency was observed to be significantly less during conditions of attention distraction than without, t (30) = 5.666, p =.000, d = .88. Furthermore, tic frequency did not differ between active tic suppression at baseline and during attention distraction when free to tic, t (30) = 1.831, p =.077, d = .25.

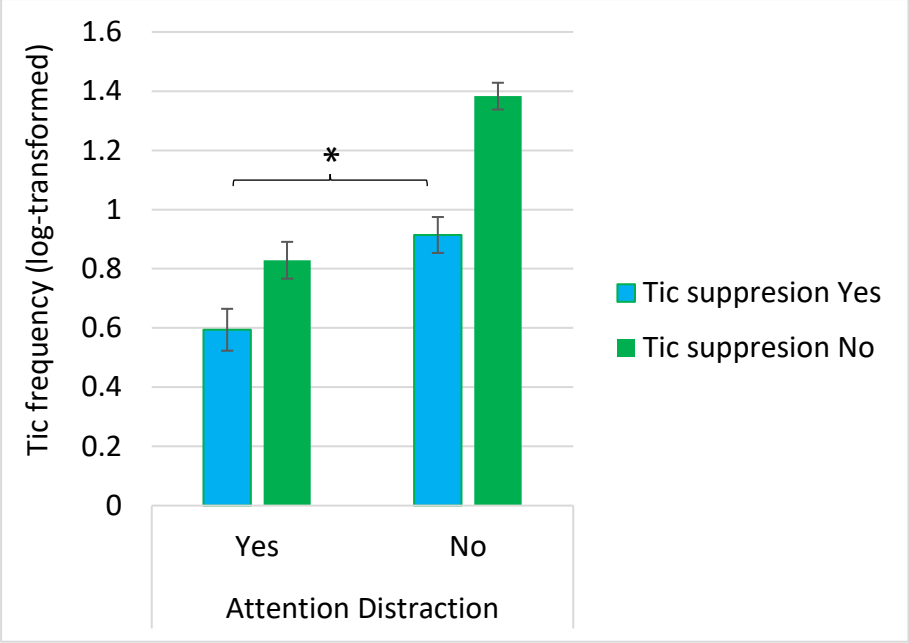


Figure 209. Mean tic frequency (log-transformed) observed during active tic suppression (yes) or when free to tic (no) during attention distraction (yes) or not (no). Error bars SEM. *Significant following Benjamini-Hochberg FDR correction.

Summary

Compared to baseline, engagement of attention in performance of a CPT task resulted in tic frequency reducing significantly, regardless of tic management condition or level of attentional load. Furthermore, tic frequencies during tic suppression was significantly less during the addition of attention distraction than without, indicative of a summative effect of active suppression and attention distraction. Finally, engagement in attention distraction without tic suppression resulted in tic reduction equivalent to active tic suppression at baseline.

Comorbidity

Tic frequencies

Baseline

There was a significant main effect of tic management on tic frequency, F (2, 56) = 47.310, p = .000, r = .86. Planned contrasts (simple) revealed that in comparison to baseline (no tic-related instructions) there were significantly more tics occurring when

free to tic, F (1, 28) = 7.653, p = .010, r = .43, and significantly fewer tics during active tic suppression, F (1, 28) = 34.389, p = .000, r = .69. Differences remained significant following Benjamini-Hochberg FDR correction.

There was, however, no interaction between tic management and comorbidity subgroup, F (6, 56) = .668, p = .676, r = .08 and no main effect of comorbidity subgroup on tic frequencies, F (1, 3) = .288, p = .834, r = .18.

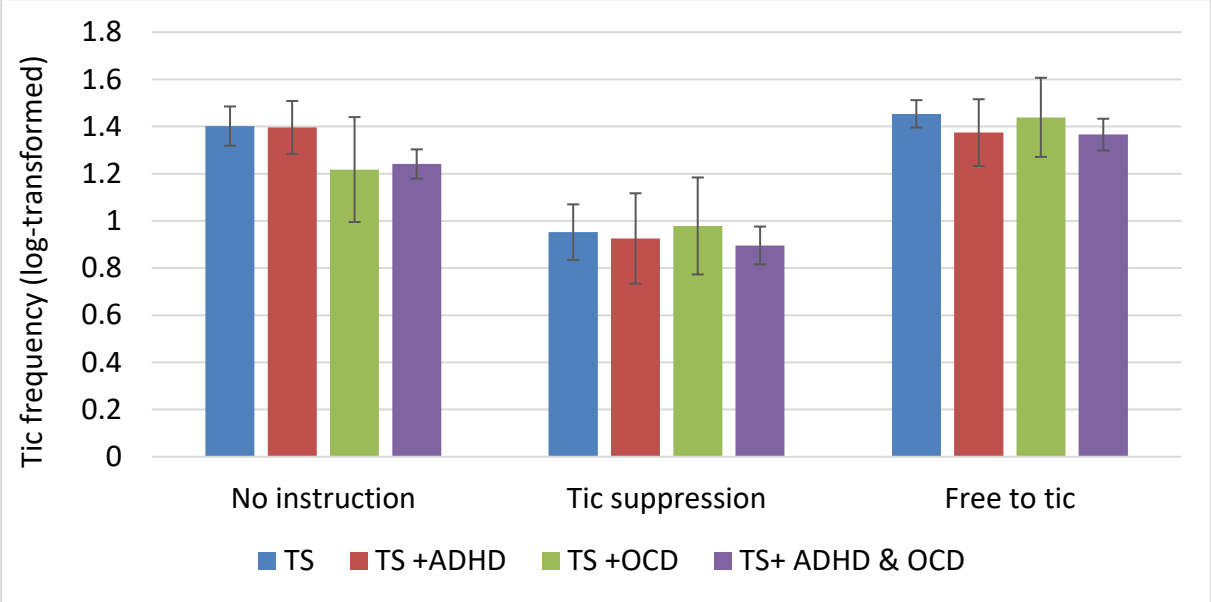


Figure 210. Mean tic frequency (log-transformed) observed at baseline under no tic-related instructions, during active tic suppression or when free to tic for different TS comorbidity subgroups. Error bars representing SEM.

Tic management vs. attention distraction

As identified previously, there was a significant main effect of tic management on tic frequency, F (1, 27) = 73.622, p = .000, r = .86, with significantly more tics occurring when free to tic compared to active tic suppression. There was, however, no interaction between tic management and comorbidity subgroup, F (3, 27) = .181, p = .908, r = .08. Similarly, there was a significant main effect of attentional distraction on tic frequency, F (1, 27) = 70.771, p = .000, r = .85, with significantly fewer tics occurring during attentional distraction. There was no significant interaction between attention distraction condition and comorbidity subgroup, F (3, 27) = .900, p = .454, r = .18.

There was a significant interaction between tic management and attention distraction on tic frequency, F (1, 27) = 17.708, p = .000, r = .63, whereby significantly fewer tics occur under active tic suppression during attention distraction. Finally, there was no significant interaction between tic management, attention distraction condition and comorbidity subgroup, F (3, 27) = .242, p = .866, r = .09.

All differences remained significant following Benjamini-Hochberg FDR correction.

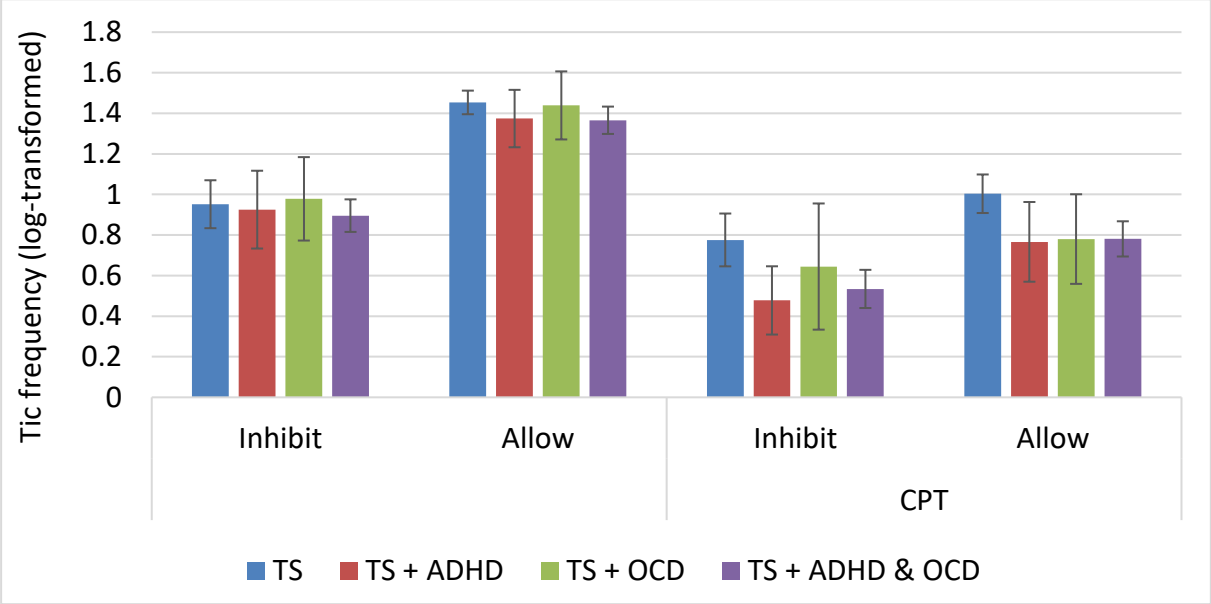


Figure 211. Mean tic frequency (log-transformed) observed under active tic suppression (inhibit) or when free to tic (allow) at baseline or during performance of the CPT task (attention distraction) for different TS comorbidity subgroups. Error bars representing SEM.

ADHD

The composite ADHD score correlated significantly with tic frequency observed during attention distraction when actively suppressing tics, r_s = -.404, p = .024, and when free to tic, r_s = -.484, p = .006; remaining significant following Benjamini-Hochberg FDR correction.

There was no significant correlations (p > .05) between ADHD composite score and tic frequencies under other tic management.

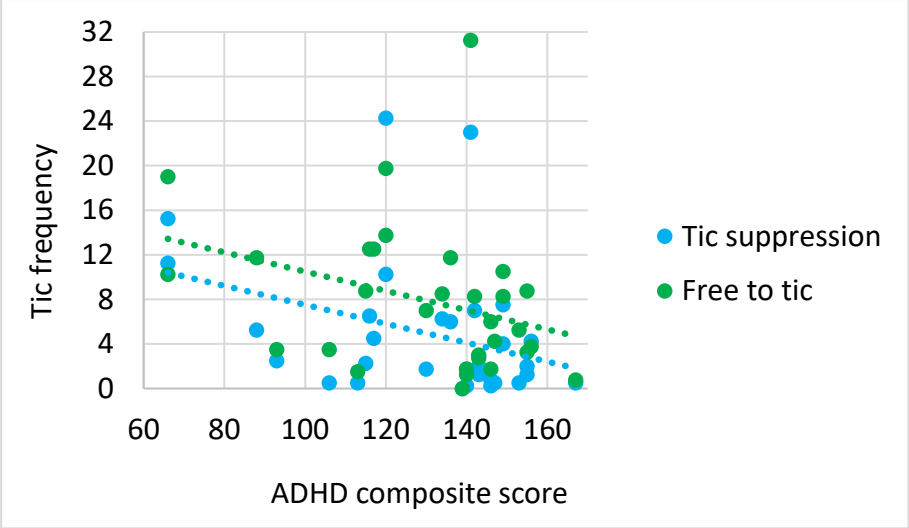


Figure 212. Relationship between ADHD composite score and tic frequency observed during attention distraction (CPT task) when actively suppressing tics (inhibit) and when free to tic (allow).

Summary

At baseline, compared to no tic-related instructions, active tic suppression resulted in significantly fewer tics and free ticcing in significantly more tics. Furthermore, the effects of tic management on tic frequencies were similar across comorbidity subgroups. There were no significant main effects or interaction effects identified for comorbidity on tic frequency observed at baseline or during attention distraction. Subsequently, the beneficial effects of attention distraction on reducing tic frequency was seen to the same extent across comorbidity subgroups. Finally, worse ADHD symptoms corresponded with significantly fewer tics during attention distraction when participants actively suppressed their tics but not when free to tic.

9.3. Discussion

In TS, compared to other movement disorders, there is a unique ability of individuals to actively suppress their tics (Jahanshahi & Rothwell, 2017; Koller & Biary, 1989; van der Salm, de Haan, Cath, van Rootselaar, & Tijssen, 2013). Following reports that tics are fully or partially voluntary responses to premonitory urges (Cavanna & Nani, 2013; Cohen & Leckman, 1992; Leckman et al., 1993) and that individuals with TS are susceptible to suggestibility (Stern, 2018), debate remains regarding the

degree to which tics are voluntary or involuntary behaviours (Cavanna & Nani, 2013; Flanagan, Jakobson, & Munhall, 1999; Ganos, Asmuss, Bongert, Brandt, Münchau, et al., 2015; Karp, Porter, Toro, & Hallett, 1996; Lang, 1991; Obeso, Rothwell, & Marsden, 1981; van der Salm, Tijssen, Koelman, & van Rootselaar, 2012). Tics are likely a voluntary response to an involuntary urge (Bliss, 1980; Ganos, Rothwell, & Haggard, 2018), arising secondary to involuntary activation of the voluntary motor pathway (Ganos & Martino, 2015). However, voluntary action and voluntary control of an involuntary action are likely to be distinct mechanisms (Ganos, Rothwell, et al., 2018).

Typically, with development, we acquire the ability to discern voluntary from involuntary signals (Piaget, 1952), however, perturbed neurodevelopment in TS could disrupt the ability to discriminate between signals of volition and those related to tics and urges (Ganos, Rothwell, et al., 2018). Specifically, altered neurodevelopment likely results in neurophysiological imbalance, and consequently a loss of tonic GABAergic inhibition (Jackson et al., 2015). Thus, over-activity occurs within sensory and motor cortices, generating motor system noise, complicating the detection of voluntary motor signals (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Plessen et al., 2009).

Interestingly, during suppression of tics, it has been observed that as urge intensity increases, there is a corresponding reduction in the relationship between tic and urge severity (Brandt, Beck, Sajin, Baaske, et al., 2016). A mechanism of tic suppression may therefore be to uncouple tic and urge phenomena (Brabson et al., 2016; Brandt, Beck, Sajin, Baaske, et al., 2016; Specht et al., 2013). In doing so, there may be a reduction in motor system noise as the combined signal, relating to the association between these two phenomena, is reduced (Cox et al., 2018). Furthermore, instruction to use urges as a signal to initiate tic control, resulted in more effective voluntary tic suppression (Piacentini et al., 2010), with earlier awareness that urges signal when to implement tic suppression, resulting in more effective control (Ganos, Asmuss, Bongert, Brandt, Munchau, et al., 2015). By instructing individuals to interpret their urges as a signal to initiate tic suppression, this places a degree of control regarding the valence of premonitory urge experience. Compared to evoking anxiety and stress, implementing a voluntary action in response to urges may help dissociate urge-related noise from signals related to volition (Ganos, Rothwell, et al.,

2018). Subsequently, effective tic control may involve mechanisms that regulate neurophysiological imbalance, reduces motor system noise and facilitates the ability to distinguish involuntary and voluntary signals.

Tic control can be achieved via several different mechanisms (Ganos, Rothwell, et al., 2018). Firstly, tic control can be achieved by therapeutic intervention. Interventions include behavioural therapies, such as CBIT and HRT (Bate et al., 2011; Deckersbach et al., 2006; Dutta & Cavanna, 2013; Frank & Cavanna, 2013; Frundt, Woods, & Ganos, 2017; Piacentini et al., 2010; Piacentini & Chang, 2006), pharmacological interventions including antipsychotics, anticonvulsants or botox injections (Bloch et al., 2011; Debes, 2009; Janik & Szejko, 2018; McNaught & Mink, 2011; Rizzo et al., 2013; Roessner et al., 2011; Roth, 2018; Singer et al., 2010; J. S. Stern, 2018; Waldon et al., 2013) and, in extreme cases, surgical intervention with deep brain stimulation (Cavanna, Eddy, et al., 2011; Fraint & Pal, 2015; Hariz & Robertson, 2010; Martinez-Ramirez et al., 2018). Whilst pharmacological intervention can be effective, long-term treatment is unfavourable due to negative side effects and a minority of TS patients are treatment refractory (Macerollo et al., 2016; Robertson, 2000; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, et al., 2017; Singer, 2010). Similarly, the mechanisms of behavioural therapies is yet to be fully elucidated, with benefits likely associated with psychoeducation and stress reduction (Piacentini et al., 2010; Wilhelm et al., 2012). There is also a lack of well-trained therapists (Ganos, Martino, & Pringsheim, 2017). Furthermore, behavioural therapies are less efficacious in adults, where comorbidities and symptoms of psychopathologies (e.g. anxiety) reduce suitability of treatments (Piacentini et al., 2010; Sukhodolsky et al., 2017). Unfortunately, for a subset of people, TS is a chronic lifelong disorder not easily managed with therapeutic interventions (Cohen et al., 2013; Stern, 2018).

Secondly, tic control is observed to occur naturally with age, following key stages of brain maturation (Church, Fair, et al., 2009; Hassan & Cavanna, 2012; Leckman et al., 1998; Pepes et al., 2016; Tamm, Menon, & Reiss, 2002; Vink et al., 2014). Subsequently, maturation and compensatory change is proposed to reduce motor system noise via tonic GABAergic inhibition to over-excitatory primary and supplementary motor regions (Jackson et al., 2015). Furthermore, adaptive changes in response to CSTC dysfunction, both structural and functional, coincides with the

acquisition of more optimal cognitive control, typically associated with enhanced pre-frontal and fronto-parietal network activity (Jackson, Parkinson, Jung, et al., 2011; Johannes, Wieringa, Mantey, et al., 2001; Marsh et al., 2007; Morand-Beaulieu et al., 2015; Serrien et al., 2005; Thibault et al., 2009; Thomalla et al., 2014). Conversely, lack of adaptive changes and poor tic control is related to hypoactivity of executive control circuits (Burguiere et al., 2013; Kataoka et al., 2010; Swerdlow & Sutherland, 2005; Xu et al., 2015). These compensatory mechanisms acquired with brain maturation are automatic and typically consolidated by adulthood (Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Verbruggen & Logan, 2008). Thus, by 30 years of age the majority of tics are reported to be significantly reduced (Bloch et al., 2006; Hassan & Cavanna, 2012; Pappert et al., 2003). However, in a subset of individuals, effective tic control is not acquired overtime, resulting in TS persisting into adulthood (Bloch et al., 2011; Bloch et al., 2006; Cath et al., 2011; Goetz et al., 1992; Hirschtritt et al., 2015; Robertson, Eapen, Singer, Martino, Scharf, Paschou, Roessner, et al., 2017; Sambrani et al., 2016).

Thirdly, tic control can be achieved by voluntary tic suppression (Jahanshahi et al., 2015; Verbruggen & Logan, 2008). During tic suppression, activation has been seen to occur within the ACC, caudate, putamen and frontal and sensorimotor cortices, alongside deactivation of the basal ganglia and thalamus (Ganos, Kahl, Brandt, Schunke, Baumer, et al., 2014; Hong et al., 2013; Peterson et al., 1998; Pourfar et al., 2011; Serrien et al., 2005; Stern et al., 2000). The ability to employ tic suppression is primarily associated with prefrontal control that corresponds to increased activity to cortico-striatal and fronto-striatal regions (Kawohl et al., 2009; Peterson et al., 1998; Raz et al., 2009), mediated by increased local connectivity of the inferior frontal gyrus (Deckersbach et al., 2014; Ganos, Kahl, Brandt, Schunke, Baumer, et al., 2014; Ganos, Kahl, Brandt, Schunke, Bäumer, et al., 2014; Peterson et al., 1998). Interestingly, these structures play a key role alongside the basal ganglia in volitional action and mediation of executive functions relating to inhibitory control (Jackson et al., 2015; Jahanshahi & Rothwell, 2017; Kalsi et al., 2015). It is difficult to distinguish between voluntary and automatic types of tic control in TS, as the ability to employ cognitive control may be dependent on adaptive structural brain changes (Jung et al., 2015; van Gaal, Ridderinkhof, Scholte, & Lamme, 2010; Verbruggen, Best, Bowditch, Stevens, & McLaren, 2014). Intriguingly, the acquisition

of inhibitory control overtime does not always equate to a significant change in TS severity (Abramovitch et al., 2017; Yaniv et al., 2018). During tic suppression, there is mounting urge severity that is only alleviated upon tic performance and is associated with post-suppression rebound in tic severity (Brandt, Beck, Sajin, Baaske, et al., 2016; Grados & Mathews, 2009; Muller-Vahl, Riemann, & Bokemeyer, 2014; Verdellen et al., 2007; Woods & Himle, 2004). Subsequently, active tic suppression is an unpleasant method of tic control. Furthermore, the role of comorbidity on the ability to engage in successful tic suppression is yet to be elucidated (Ganos, Rothwell, et al., 2018).

Finally, tic control can be achieved passively by attentional distraction, occurring as a result of focusing attention away from urges and tics (Misirlisoy, Brandt, Ganos, Tubing, et al., 2015; Schaich, 2018). Previously, the effects of attention distraction on tic frequency was explored using a rhythmic finger movement paradigm (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015) with attention distraction significantly reducing tic frequency, and the greatest reduction occurring when attention was focused onto voluntary action compared to external task features (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). As voluntary action has been shown to regulate the distribution of CSE (Orth, 2009; Orth et al., 2005; Orth, Münchau, et al., 2008), diverting attention externally or to actions of volition appears critical to effective tic management (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). Furthermore, attention distraction can reduce resources available to focus on urges, reducing the likelihood of these signals being perceived as a trigger to tic and minimising the occurrence of anxiety and stress, in turn reducing tic frequency (Caurin et al., 2014; Conelea & Woods, 2008; Ganos, Rothwell, et al., 2018; Hoekstra, Lundervold, et al., 2013; O'Connor et al., 2014). Moreover, alongside regulating CSE, diverting attention to voluntary action may help reinforce the distinctions between voluntary and involuntary motor pathways, perhaps by recruiting attentional resources to one system over the other (Ganos, 2016; Misirlisoy, Brandt, Ganos, Tübing, et al., 2015).

Tic behaviours have anxiolytic effects in temporarily alleviating urge discomfort (Hawksley et al., 2015; Nagai et al., 2009). Unfortunately, in TS, due to aberrant dopamine, maladaptive habit formation occurs overtime, whereby in adulthood, tics have become both inducers and reducers of stress (Godar & Bortolato, 2017). If tics are in part retained as a stress-coping mechanism, therapies that help to unlearn or

detract from this negative association would be beneficial. Therefore, interventions based upon attention distraction hold therapeutic promise with recent preliminary evidence (*n*=3) that attention training technique (ATT) therapy may be beneficial at reducing tic severity and frequency (Schaich, 2018). Such therapies may be particularly favourable where individuals have not acquired effective tic control mechanisms and/or are prone to negative experiences upon internalising attention, including those with comorbidities or aberrant interoceptive awareness (Ganos, 2016; Misirlisoy, Brandt, Ganos, Tübing, et al., 2015; Robertson, 2015a). Ideally, attention distraction interventions would be most effective during childhood to reduce the initial consolidation of negative reinforcement occurring between tic performance, urge relief and subsequent habit formation (Cravedi et al., 2017; Sukhodolsky et al., 2017). Further characterisation of the mechanisms of attention distraction on reducing tic severity is needed, with investigation into how distraction both relates and compares to active tic management required. In addition, evaluation of the efficacy of attention distraction in adults with uncomplicated and complicated TS is warranted.

In our sample of adults with TS, unsurprisingly we found that active tic suppression significantly reduces tics, whilst free ticcing significantly increases tic frequency. Furthermore, lower tic frequency at baseline under no tic-related instructions corresponded to fewer tics during tic management instruction. Such results likely reflects the relationship between automatic tic control, acquired via structural brain alterations, and active tic suppression whereby adaptive brain changes underpins the ability to employ successful tic control (Jahanshahi et al., 2015; Verbruggen & Logan, 2008). Conversely, more tics under no tic-related instruction and tic management may reflect ineffective ability to suppress tics, due to under-developed adaptive brain changes, that corresponds to enhanced motor system CSE; with active effort to remove automatic inhibitory control, further enhancing CSE and generating more tics (Ganos, Rocchi, et al., 2018).

Interestingly, the tic frequencies observed when free to tic corresponded to interoceptive awareness, with fewer tics associated with better interoception. Previously, in Chapter 6, we identified reduced inhibitory mechanisms of the sensory and motor system (SICI and SAI) as neural correlates of reduced interoceptive awareness. Consequently, better interoceptive awareness would correspond with

better utilisation of inhibitory mechanisms. Intact mechanisms of inhibition, that likely act to reduce over-activity within sensory and motor cortices (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Plessen et al., 2009), would therefore equate to reduced tic generation. Consequently, on instruction to tic freely, with active attempts to remove inhibitory control, fewer tics would occur. Thus, our results reinforce the functional relationship between neurophysiological mechanisms of inhibition and interoceptive awareness.

To further our understanding of tic control mechanisms achieved via attention distraction and active tic suppression, we assessed, objectively, the effect of differing attentional loads on tic frequencies, under active tic suppression and free-to-tic conditions. Evaluation of CPT performance and tic frequencies revealed that our results replicated previous findings, that attention distraction significantly reduces tics (Misirlisoy, Brandt, Ganos, Tübing, et al., 2015). We found that the fewest tics occurred at the highest load of attention; highlighting the cumulative effects of attentional load on distraction-based tic control. Furthermore, we found the better the capacity to suppress tics as baseline, the fewer the tics occurring during attention distraction and active tic suppression, but not when free to tic. Firstly, these results highlight the summative nature of tic control, with combined tic control mechanisms being most efficacious. Secondly, our results illustrate that automatic tic control, arising from adaptive brain change, not only underpins mechanisms of active tic suppression, but also corresponds to the efficacy of distraction-based tic control.

As discussed previously, adaptive changes in response to CSTC disruption, coincides with the acquisition of cognitive control, mediated by enhanced frontal control (Deckersbach et al., 2014; Ganos, Kahl, Brandt, Schunke, Baumer, et al., 2014; Jackson, Parkinson, Jung, et al., 2011; Johannes, Wieringa, Mantey, et al., 2001; Kawohl et al., 2009; Marsh et al., 2007; Morand-Beaulieu et al., 2015; Peterson et al., 1998; Raz et al., 2009; Serrien et al., 2005; Thibault et al., 2009; Thomalla et al., 2014). During CPT task performance, we found that better capacity to suppress tics at baseline corresponded to making significantly fewer commission errors during active tic suppression, but not when free to tic. Furthermore, fewer tics at baseline, when free to tic, corresponded to significantly fewer commission errors. Therefore, our results illustrate the functional relationship between the inhibitory mechanisms of tic control, both active and passive, and cognitive control.

Interestingly, omission errors were not found to be associated with the capacity to inhibit tics, suggesting that the gain of cognitive control, associated with mechanisms of tic control, is specific to executive functions relating to inhibition (Jackson et al., 2015; Jahanshahi & Rothwell, 2017; Kalsi et al., 2015). Our results provide evidence that attention and inhibition are separate, yet inter-related constructs, as attention distraction facilitates inhibitory mechanisms of tic control in a cumulative nature. Furthermore, better frontal control, synonymous with attention, corresponds to more efficient inhibitory control.

During active tic suppression, better interoceptive awareness was associated with making significantly fewer errors of commission. These observations reiterate the association between mechanisms of active and passive tic control, inhibitory functioning of sensory and motor cortices (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Orth, 2009; Orth & Rothwell, 2009; Plessen et al., 2009) and interoceptive awareness. Furthermore, we have identified that better interoceptive awareness corresponds with better cognitive control, specifically to inhibitory functioning. Our results identify a functional relationship between cognitive inhibitory control and interoceptive awareness.

In our study, we found that attention distraction occurring during free ticcing reduced tics to the same extent as active tic suppression occurring at baseline. Additionally, attention distraction and active tic suppression in tandem, due to the summative effects of inhibitory mechanisms, results in the most efficient tic control. Furthermore, the beneficial effects of attention distraction alone and in combination with active tic suppression occurs across all comorbidity subgroups. In conclusion, we found that attention distraction significantly reduces tic frequency, irrespective of tic management and is therefore an effective method of tic control, suitable for adults with uncomplicated and complicated TS (Ganos, Rothwell, et al., 2018; Misirlisoy, Brandt, Ganos, Tubing, et al., 2015).

Chapter 10. Conclusion

In Chapter 3, we found that in adult TS general intelligence is normal. Impairment was found specifically in cognitive flexibility to habitually learned behaviours. All other aspects of general cognition were found to be intact in adult TS. Thus, our results support the existence of specific, as opposed to global cognitive impairment in adult TS (Morand-Beaulieu, Leclerc, et al., 2017) and is consistent with maladaptive habit formation in TS (Delorme et al., 2016; Kim et al., 2018).

In Chapter 4, a Response Conflict Flanker variant and a novel Continuous Performance Task were developed to investigate inhibition and attention in parallel. Despite being challenging with minimal working memory demands, there were no deficits found in adults with TS. However, adults with TS displayed significantly slower reaction times. Compromised speed appears to be an adaptive response to increased information processing demands, occurring due to clinical phenomena (urges, tics, comorbid symptoms), in order to achieve task demands (Eichele et al., 2010; Morand-Beaulieu, Grot, et al., 2017; Shephard et al., 2016). By evaluating attention and inhibition in parallel, we found evidence to suggest that these are two separate but highly interlinked entities. For example, increasing attentional load decreased response inhibition, yet corresponded to a gain of attentional vigilance on the CPT task.

In Chapter 5, our results found evidence that interoceptive awareness is significantly reduced in adults with TS, replicating previous findings (Ganos, Garrido, Navalpotro-Gomez, et al., 2015). We propose that reduced interoception is caused by the difficulty adults with TS have with cognitive flexibility for habitually learned behaviours. Thus, adults with TS have reduced interoceptive accuracy due to difficulty with shifting attention to interoceptive events and or/inhibiting tics and urges, to utilise their attention accurately.

In Chapter 6, we found evidence of neurophysiological imbalance in the corticospinal motor system in adults with TS, with significantly reduced intercortical and intracortical inhibitory mechanisms of the motor and sensory cortices. Furthermore, we found that, at rest, adult TS is associated with alteration to the distribution of CSE and that modulation of this, is a likely tic control mechanism. Furthermore, we

identified reduced inhibition mechanisms of the sensory and motor systems as neural correlates of altered interoceptive awareness.

In Chapter 7, our results show that in adult TS, alongside marked urge and tic severity, there are prevalent and persistent psychopathologies and comorbidities. Interestingly, we found that regulating the distribution of CSE is a possible tic control mechanism for those with a more severe clinical profile and that this process may facilitate cognitive flexibility. Such results are consistent with adaptive brain changes in TS as a prerequisite for enhanced cognitive control (Jackson, Parkinson, Jung, et al., 2011; Johannes, Wieringa, Mantey, et al., 2001; Marsh et al., 2007; Morand-Beaulieu et al., 2015; Serrien et al., 2005; Thibault et al., 2009; Thomalla et al., 2014).

In Chapter 8, we found that the more complex the comorbidity, the more severe the clinical profile in adult TS (Rizzo et al., 2012). However, comorbidity was not found to affect measures of impairment, suggesting that in adult TS, worse clinical severity is complicated by, but not a consequence of, comorbidity. Whilst individuals with lone comorbid OCD are less efficient in utilising a strategy on the SWM task, comorbidity subgroups performed similarly on all measures of general cognition. Our results therefore suggest that cognitive inflexibility to habitually learned behaviours is a core feature of TS. Similarly, we found comparable performance, including adaptive reduction in motor responses, during CPT and RCF tasks in all comorbidity subgroups. Thus, our results provide evidence that comorbidity presence does not impair acquisition of adaptive skills that function to preserve attention and inhibition in TS. Furthermore, we found that alterations in the distribution of CSE, at rest and during tic management, and significantly reduced interoceptive awareness, SICI and SAI are core features of TS and not attributable to comorbidities. Furthermore, the link between altered physiological inhibitory mechanisms and interoceptive awareness was seen across subgroups, reinforcing that these are features inherent to TS.

In Chapter 9, we found that passive tic control, likely arising from adaptive brain changes, not only underpins mechanisms of active tic suppression and the ability to employ successful tic control, but also corresponds to the efficacy of distraction-based tic control (Jahanshahi et al., 2015; Verbruggen & Logan, 2008). Furthermore, the inhibitory mechanisms of tic control, both active and passive, corresponds to

cognitive control, specifically inhibitory functioning (Jackson et al., 2015; Jahanshahi & Rothwell, 2017; Kalsi et al., 2015). It was also found that better interoceptive awareness corresponds to better utilisation of inhibitory physiological mechanisms that likely functions to reduce over-activity within sensory and motor cortices, thereby reducing tic generation and enhancing cognitive control (Jackson et al., 2015; Jackson, Parkinson, Jung, et al., 2011; Plessen et al., 2009). Evaluation of CPT performance and tic frequencies revealed that there is a cumulative effect of attentional load on distraction-based tic control, with fewer tics the larger the attentional load. Furthermore, we revealed the summative nature of tic control, with combined mechanisms, distraction and active tic suppression, being most efficacious. Importantly, attention distraction occurring during free ticcing reduced tics to the same extent as active tic suppression occurring at baseline, illustrating the benefit of distraction-based tic control mechanisms. Critically, we found that attention distraction significantly reduces tic frequency, irrespective of tic management and is an effective method of tic control, for adults with uncomplicated and complicated TS (Ganos, Rothwell, et al., 2018; Misirlisoy, Brandt, Ganos, Tubing, et al., 2015).

A limitation of this research was the failure of our Response Conflict Flanker design, and subsequently, the inability to properly explore basal-ganglia dependent action selection and ACC-dependent conflict detection (Beste, Saft, Andrich, Gold, & Falkenstein, 2008; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Eriksen & Eriksen, 1974; Mink, 1996). Future research with previously validated task versions should be undertaken (Egner, 2008). Furthermore, the role of reduced interoceptive awareness in adult TS warrants further exploration; replication of our results, including relationships between inhibitory physiological mechanisms and tic control, using alternative methods of investigating interoceptive awareness (Mehling et al., 2009; Mehling et al., 2012) is warranted, to further validate our findings. Finally, future research focusing on the role of dopamine in adult TS would be beneficial. Originally, a TMS paradigm by Galea *et al* (Galea, Ruge, Buijink, Bestmann, & Rothwell, 2013) was to be used to assess low-level motor control and higher-order action selection, both dopamine-dependent processes (Ganos, 2016; Mazzoni, Hristova, & Krakauer, 2007; Pekny, Izawa, & Shadmehr, 2015). Use of this paradigm in adult TS would provide insight into the mechanisms of function and how disruption to dopaminergic signalling, a key feature of TS pathology (Maia & Conceicao, 2018;

McNaught & Mink, 2011; Mink, 2006), may influence the motor system and cognition; furthermore the efficacy of antipsychotic medication in adult TS can be explored.

To summarise, adult TS is associated with marked urge and tic severity with highly prevalent and persistent psychopathologies and comorbidities. Furthermore, in adult TS, there is evidence for, a specific deficit in cognitive flexibility for habitually learned behaviours and adaptive motor slowing that functions to preserve attentional and inhibitory cognitions. TS was found to be associated with alteration in the distribution of CSE and that modulation of this, is a likely mechanism of active tic control. Passive tic control, likely arising from adaptive brain change, was found to underpin mechanisms of active tic suppression, the ability to employ successful tic control, the efficacy of distraction-based tic control as well as inhibitory cognitive control (Jahanshahi et al., 2015; Verbruggen & Logan, 2008). Altered interoceptive awareness likely arises due to cognitive inflexibility and was related to significantly reduced inhibitory mechanisms of the motor system, both identified as core features of TS. Thus, we have identified neurophysiological correlates of perturbed sensory-based attention. Finally, we found that attention distraction significantly reduces tic frequency and is an effective method of tic control, for uncomplicated and complicated adult TS (Ganos, Rothwell, et al., 2018; Misirlisoy, Brandt, Ganos, Tubing, et al., 2015). In conclusion, our results provide a theoretical basis for the development of new therapies in TS based on attention distraction.

Table 13. Summary of main thesis findings.

Thesis section	Assessment	Key Result(s)	Relationship(s) identified					Main Finding(s)
			Cognition	Interoceptive Awareness	Clinical Symptoms / comorbidity	Neurophysiology	Attention Distraction / Tic control	
Chapter 3: General Cognition	CANTAB Intra-Extra Dimensional Set-shift (IED)	TS make significantly more errors than HVs at the EDS stage.	No relationship with other measures of cognition	No relationship between EDS errors and I/A	No relationships identified	No relationships identified	No relationships identified	Impaired cognitive flexibility to habitually learned behaviours Specific compared to global cognitive impairment associated with maladaptive habit formation
Chapter 4: Attention and Inhibition	Continuous Performance Task (CPT) Response Conflict Flanker (RCF)	Adults with TS significantly slower RTs on CPT and RCF task with no detriment to accuracy Increasing attentional load decreased response inhibition, yet corresponded to a gain of attentional vigilance on the CPT task	No relationship with other measures of cognition	Better I/A associated with more conservative responding, prioritising accuracy over speed on CPT task I/A correlated significantly with response style *C*	TS slower even after controlling for the effects of antipsychotic medication	No relationships identified	Fewer commission errors made when suppressing tics vs. free to tic Better capacity to suppress tics associated with fewer omission and commission errors during tic suppression Higher baseline tic frequency related to more commission errors during active tic suppression	In adults with TS, there is evidence of adaptive slowing in motor responses, in response to increasing information processing demands with no impact to task performance accuracy Attention and inhibition separate but highly interlinked entities
Chapter 5: Interoceptive Awareness (IA)	Heart-beat mental tracking method	I/A (accuracy of estimating heartbeats to actual measurement) significantly reduced in TS	Better I/A associated with more conservative responding, prioritising accuracy over speed on CPT task		No relationship with PUTS scores No relationship between urge or tic severity and I/A	Trend relationship between SICI 2ms and I/A and significant relationship between SICI 3ms and I/A in TS Significant relationship		Adults with TS have reduced interoceptive accuracy. Reduced I/A could be due to adults with TS having difficulty with cognitive flexibility for habitually learned behaviours. Thus, adults with TS have difficulty shifting attention to interoceptive events and

			I/A correlated significantly with response style *C* No relationship between EDS errors and I/A			between SAI $N20^{+6ms}$ and I/A in TS		or/inhibiting tics and urges, to utilise their attention accurately.
Chapter 6: Neurophysiology	SICI, ICF and SAI	Reduced inter-cortical (SICI) and intra-cortical (SAI) inhibition of the motor and sensory cortices in adults with TS Alteration to distribution of CSE in adults with TS at rest	No relationships identified	Correlation between interoceptive awareness and SICI (3ms) and SAI ($N20^{+6ms}$) in adults with TS Trend relationship between SICI 2ms and I/A and significant relationship between SICI 3ms and I/A in TS Significant relationship between SAI $N20^{+6ms}$ and I/A in TS	No relationships identified	Reduced inter-cortical (SICI) and intra-cortical (SAI) inhibition of the motor and sensory cortices in adults with TS Alteration to distribution of CSE in adults with TS at rest	MEPs significantly smaller during tic inhibition and larger (trend) when instructed to free tic	Neurophysiological imbalance in cortico-spinal motor system in adults with TS with significantly reduced intercortical and intracortical inhibitory mechanisms of the motor and sensory cortices Reduced inhibition mechanisms of the sensory and motor systems are neural correlates of altered interoceptive awareness At rest, adult TS is associated with alteration to the distribution of CSE and that modulation of this, is a likely tic control mechanism
Chapter 7: Clinical Profile	PUTS YGTSS RUSH-M MINI ADHD (BAARS-IV; ASRS) OCD (OCI, Y-BOCS, Padua-L)	In adults with TS there is marked premonitory urge impairment (≥ 24 PUTS), severe tic severity impairment (>30 YGTSS) and prevalent psychopathologies and comorbidities	Higher PUTS related to fewer EDS errors Higher PUTS related to faster RTs on RVP. Higher YGTSS related to more false alarms on RVP ADHD composite related to more perseverative errors on CPT	No relationship between urge or tic severity and I/A No relationship between comorbidities and I/A	Comorbid OCD associated with higher PUTS scores	No relationship between urge or tic severity and neurophysiology measures No relationship identified between comorbidities and SICI or SAI ADHD composite related to more ICF Comorbid OCD required higher	YGTSS and MRVS total scores correlated significantly with the size of normalised MEPs recorded under instruction to tic freely No relationship identified between comorbidities and mechanisms of tic control	In adults with TS, alongside marked urge and tic severity there are prevalent and persistent psychopathologies and comorbidities Regulation of the distribution of CSE may be a possible tic control mechanism for those with more severe clinical profile; a process which may facilitate cognitive flexibility

			Comorbid OCD associated with fewer EDS errors OCD composite related to better SWM strategy			levels of stimulation to evoke MEPs at rest and of 1mV amplitude		
Chapter 8: Comorbidities	CANTAB battery RCF & CPT I/A Motor thresholding, SICI, ICF and SAI	Whilst individuals with lone comorbid OCD are less efficient utilising a strategy on SWM task, comorbidity subgroups performed similarly on all measures of general cognition	No effect of comorbidity on performance	No differences, reduced IA core feature of TS Correlation between reduced SICI/SAI and I/A same across all comorbidities	No differences	No differences, reduced SICI and SAI core features of TS	No differences, alterations to CSE during tic management core feature of TS	More complex the comorbidity the more severe the clinical profile No impact of comorbidity or clinical severity identified. Thus, cognitive inflexibility to habitually learned behaviours is a core feature of TS and not attributable to comorbidities results therefore suggest that. Presence of comorbidity does not impair acquisition of adaptive skills (motor slowing) that function to preserve functioning of attention and inhibition Similarly, adaptive reduction in motor responses, during CPT and RCF tasks occurred in all comorbidity subgroups. Thus, comorbidities do not impair acquisition of adaptive skills that function to preserve attention and inhibition in TS. Altered distribution of CSE, at rest and during tic management, and significantly reduced interoceptive awareness, SICI and SAI are core features of TS and not attributable to comorbidities. Furthermore, the link between altered physiological inhibitory mechanisms and interoceptive awareness was seen across

								subgroups, reinforcing that these are features inherent to TS.
Chapter 9: Attention Distraction	CPT Tic frequency	Fewer tics during active tic suppression vs. free to tic Attention distraction reduces tic frequency regardless of tic management condition or level of attentional load Cumulative effect of attentional load on reducing tic frequency Summative effect of active tic suppression and attention distraction on tic frequencies Attention distraction without tic suppression efficacious in reducing tic levels to frequencies observed during active tic suppression	Fewer commission errors made when suppressing tics vs. free to tic Better capacity to suppress tics associated with fewer omission and commission errors during tic suppression Higher baseline tic frequency related to more commission errors during active tic suppression	Fewer tics at baseline correlated with better I/A when free to tic Better I/A associated with making fewer commission errors irrespective of tic management instruction	No effect of comorbidity on tic frequencies Beneficial effects of attention distraction on reducing tic frequency seen to the same extent across comorbidity subgroups Worse ADHD symptoms correspond to fewer tics during attention distraction and tic suppression	MEPs significantly smaller during tic inhibition and larger (trend) when instructed to free tic	The better the capacity to suppress tics at baseline correlated with fewer tics during attention distraction and active tic suppression .	Attention distraction significantly reduces tic frequency, irrespective of tic management and is an effective method of tic control, for adults with uncomplicated and complicated TS Inhibitory mechanisms of tic control, both active and passive, corresponds to cognitive control, specifically inhibitory functioning Better I/A corresponds to better utilisation of cognitive control There is a cumulative effect of attentional load on distraction-based tic control and a summative effect of tic control, and attention distraction on tic frequencies. Attention distraction during free to tic conditions reduce tic frequency to same extent as active tic suppression, illustrating the benefit of distraction-based tic control mechanisms. Our results provide a theoretical basis for the development of new therapies in TS based on attention distraction

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Appendix

1. The Wechsler Test of Adult Reading WTAR

Discontinue Rule

Discontinue after 12 consecutive scores of 0.

Instructions

Begin administration of the WTAR by saying:

I will show you some words that I will ask you to pronounce:

Place the WTAR Word Card in front of the examinee. As you point to the card, say:

Beginning with the first word on the list, pronounce each word aloud. Start with this word (point to Item 1***) and go down this column, one right after the other, without skipping any. When you finish this column, go to the next column*** (point to the second column). ***Pronounce each word even if you are unsure. Do you understand?***

If the examinee does not understand the instructions, you may repeat the instructions, paraphrasing if necessary.

When you are sure that the examinee understands the task, say.

Ready? Begin.

Recording and Scoring.

Acceptable pronunciations, including alternate pronunciations for the WTAR words are provided on the record form (over page). The examinee is required to give only one pronunciation of a word.

Award 1 point for each correct response and 0 points for each incorrect response Sum the points to obtain the WTAR raw score. **The maximum raw score is 50**.

Attached to this document is the “Standard score equivalent”. Look-up the corresponding Standard Score based on WTAR raw score and age of participant.

WTAR Word List - UK pronunciation guide

Say, **I will show you some words that I will ask you to pronounce.** Place the WTAR Word Card in front of the examinee. As you point to the card, say, **Beginning with the first word on the list, pronounce each word aloud. Start with this word** (point to item 1), **and go down this column, one after the other, without skipping any. When you finish this column, go to the next column** (point to the second column). **Pronounce each word even if you are unsure. Do you understand?** When you are sure that the examinee understands the task, say, **Ready? Begin.**

	Item	Pronunciation	Score (0, 1)		Item	Pronunciation	Score (0, 1)
1.	again	ah-GEHN ah-GAIN *or* uh-GEHN or uh-GAIN		26.	conscientious	con-shee-EN-shss	
2.	address	ah-DRESS *or* uh-DRESS		27.	homily	HOM-ih-lay *or* HOM-ih-lee	
3.	cough	kawf *or* kof		28.	malady	MAL-uh-day *or* MAL-uh-dee	
4.	preview	PREE-vyue		29.	subtle	SUH-tl	
5.	although	awl-THO		30.	fecund	FE-cund *or* FEE-cund	
6.	most	mohst		31.	palatable	PAL-ah-tuh-bul *or* PAL-uh-tuh-bul	
7.	excitement	eck-SITE-munt *or* ik-SITE-munt		32.	menagerie	meh-NA-juh-ree	
8.	know	noh *or* no		33.	obfuscate	OB-fuh-skate	
9.	plumb	plum		34.	liaison	lee-AY-zon *or* lee-AY-zn	
10	decorate	DEK-oh-rate *or* DEK-uh-rate		35.	exigency	eks-IH-jen-say *or* eks-IH-jen-see	
11.	fierce	fee-us *or* feerss		36.	xenophobia	zen-oh-FO-bee-uh	
12.	knead	need		37.	ogre	OH-gur	
13.	aisle	iyle		38.	scurrilous	SKUR-ih-lus *or* SKUR-uh-lus	
14.	vengeance	VEN-jnss		39.	ethereal	ih-THEE-ree-ul *or* ih-THEER-ee-ul	
15.	prestigious	pre-STIJ-us *or* pre-STEEJ-us		40.	paradigm	PAH-rah-dime	
16.	wreathe	reeTH *or* REEEth		41.	perspicuity	per-spuh-KYEW-uh-tee	
17.	gnat	nat		42.	plethora	PLETH-oh-rah *or* PLETH-eh-rah	
18.	amphitheatre	AM-fih-thee-uh-ter		43.	lugubrious	loo-GOOB-ree-uss *or* loo-GOO-bree-uss	
19.	lieu	loo *or* l(y)oo		44.	treatise	TREE-tiz *or* TREET-iz	
20.	grotesque	gro-TESK		45.	dilettante	DILL-ih-tan-tay *or* DILL-uh-tahnt	
21.	iridescent	ihr-ih-DESS-unt *or* ihr-uh-DESS-unt		46.	vertiginous	ver-TIDJ-in-iss	
22.	ballet	BA-lay *or* ba-LAY *or* bal-ay		47.	ubiquitous	you-BIC-wuh-tiss *or* you-BIC-wuh-tus	
23.	equestrian	eh-KWESS-tree-un *or* ih- KWESS-tree-un		48.	hyperbole	hy-PER-bul-lay *or* hy-PUR-bul-lay	
24.	porpoise	PAW-pss *or* POR-poyz (Scots)		49.	insouciant	in-SOO-see-yunt	
25.	aesthetic	ess-THET-ik *or* ees-THET-ik		50.	hegemony	heh-GEM-o-nee *or* heh-JEM-o-nee *or* HEH-geh-mon-ee	
						WTAR Raw Score	
						WTAR Standard Score	

Table A.2. Standard Score Equivalents of WTAR Raw Scores

WTAR Raw Score	16–24	25–44	45–64	65–79	80–89	Reference Group
0	50	50	50	50	50	50
1	50	50	50	50	50	50
2	50	50	50	50	50	50
3	50	50	50	50	50	50
4	50	50	50	50	50	50
5	50	50	50	50	50	50
6	51	50	50	50	50	50
7	53	50	50	50	50	50
8	55	50	50	50	50	50
9	57	51	50	50	50	50
10	59	53	50	50	52	51
11	60	55	51	52	54	53
12	62	57	53	54	56	55
13	64	59	55	56	58	57
14	66	60	57	58	60	59
15	67	62	59	60	62	61
16	69	64	60	62	63	63
17	71	66	62	63	65	64
18	73	67	64	65	67	66
19	74	69	66	67	69	68
20	76	71	67	69	71	70
21	78	73	69	71	73	72
22	80	74	71	73	75	74
23	81	76	73	75	77	76
24	83	78	74	77	78	78
25	85	80	76	78	80	79
26	87	81	78	80	82	81
27	89	83	80	82	84	83
28	90	85	81	84	86	85
29	92	87	83	86	88	87
30	94	89	85	88	90	89
31	96	90	87	90	92	91
32	97	92	89	92	93	93
33	99	94	90	93	95	94
34	101	96	92	95	97	96
35	103	97	94	97	99	98
36	104	99	96	99	101	100
37	106	101	97	101	103	102
38	108	103	99	103	105	104
39	110	104	101	105	107	106
40	111	106	103	107	108	108
41	113	108	104	108	110	109
42	115	110	106	110	112	111
43	117	111	108	112	114	113
44	119	113	110	114	116	115
45	120	115	111	116	118	117
46	122	117	113	118	120	119
47	124	119	115	120	122	121
48	126	120	117	122	123	123
49	127	122	119	123	125	124
50	129	124	120	125	127	126

2. TMS screening tool

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
3. Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
4. Do you have any hearing problems or ringing in your ears?
5. Do you have cochlear implants?
6. Are you pregnant or is there any chance that you might be?
7. Do you have metal in the brain, skull or elsewhere in your body (e.g. splinters, fragments, clips etc.)? If so, specify the type of metal.
8. Do you have an implanted neurostimulator (e.g. DBS, epidural/subdural, VNS)?
9. Do you have a cardiac pacemaker or intracardiac lines?
10. Do you have a medication infusion device?
11. Are you taking any medications? (please list)
12. Did you ever undergo TMS in the past? If so, were there any problems?
13. Did you ever undergo MRI in the past? If so, were there any problems?

3. The Yale Global Tic Severity Scale (YGTSS)

NAME: TODAYS DATE: / /
RATER:

MOTOR TIC SYMPTOM CHECKLIST

Description of Motor Tic Symptoms. Motor tics usually begin in childhood and are characterized by sudden jerks or movements, such as forceful eye blinking or a rapid head jerk to one side or the other. The same tics seem to recur in bouts during the day and are worse during periods of fatigue and/or stress. Many tics occur without warning and may not even be noticed by the person doing them. Others are preceded by a subtle urge that is difficult to describe (some liken it to the urge to scratch an itch). In many cases it is possible to voluntarily hold back the tics for brief periods of time. Although any part of the body may be affected, the face, head, neck, and shoulders are the most common areas involved. Over periods of weeks to months, motor tics wax and wane and old tics may be replaced by totally new ones.

Simple motor tics can be described as a sudden, brief, "meaningless" movement that recurs in bouts (such as excessive eye blinking or squinting). Complex motor tics are sudden, stereotyped (i.e., always done in the same manner) semi-purposeful (i.e., the movement may resemble a meaningful act, but is usually involuntary and not related to what is occurring at the time) movements that involve more than one muscle group. There may often be a constellation of movements such as facial grimacing together with body movements. Some complex tics may be misunderstood by other people (i.e., as if you were shrugging to say "I don't know"). Complex tics can be difficult to distinguish from compulsions; however, it is unusual to see complex tics in the absence of simple ones. Often there is a tendency to explain away the tics with elaborate explanations (e.g., "I have hay fever that has persisted" even though it is not the right time of year). Tics are usually at their worst in childhood and may virtually disappear by early adulthood, so if you are completing this form for yourself, it may be helpful to talk to your parents, an older sibling, or a relative, as you answer the following questions.

- **Age of first motor tics?** _____ years old
- **Describe first motor tic:** _____
- **Was tic onset sudden or gradual?** _____
- **Age of worst motor tics?** _____ years old

Motor Tic Symptom Checklist

In the boxes on the left below, please check with a mark (x) the tics the patient

1) *has* **EVER** *experienced*
2) *is* **CURRENTLY** *experiencing (during the past week)*

State **AGE OF ONSET** *(in years) if patient has had that behavior.*

Also, in the tic descriptions below, please **circle** *or* **underline** *the specific tics that the patient has experienced (circle or underline the words that apply).*

Ever	Current	Age of onset	The patient has experienced, or others have noticed, involuntary and apparently purposeless bouts of:	Ever
			-eye movements.	
			eye blinking, squinting, a quick turning of the eyes, rolling of the eyes to one side, or opening eyes wide very briefly.	
			eye gestures such as looking surprised or quizzical, or looking to one side for a brief period of time, as if s/he heard a noise.	
			-nose, mouth, tongue movements, or facial grimacing.	
			nose twitching, biting the tongue, chewing on the lip or licking the lip, lip pouting, teeth baring, or teeth grinding.	
			broadening the nostrils as if smelling something, smiling, or other gestures involving the mouth, holding funny expressions, or sticking out the tongue.	
			-head jerks/movements.	
			touching the shoulder with the chin or lifting the chin up.	
			throwing the head back, as if to get hair out of the eyes.	
			-shoulder jerks/movements.	
			jerking a shoulder.	
			shrugging the shoulder as if to say "I don't know."	
			-arm or hand movements.	
			quickly flexing the arms or extending them, nail biting, picking with fingers, or popping knuckles.	
			passing hand through the hair in a combing like fashion, or touching objects or others, pinching, or counting with fingers for no purpose, or writing tics, such as writing over and over the same letter or word, or pulling back on the pencil while writing.	
			-leg, foot or toe movements.	
			kicking, stepping, knee-bending, flexing or extension of the ankles; shaking, stomping, or tapping the foot.	
			taking a step forward and two steps backward, squatting, or deep knee-bending.	

Ever	Current	Age of onset	The patient has experienced, or others have noticed, involuntary and apparently purposeless bouts of:	Ver
			-abdominal/trunk/pelvis movements.	
			tensing the abdomen, tensing the buttocks.	
			-other simple motor tics.	
			Please write example(s): _____ _____	
			-other complex motor tics.	
			touching	
			tapping	
			picking	
			evening-up	
			reckless behaviors	
			stimulus-dependent tics (a tic which follows, for example, hearing a particular word or phrase, seeing a specific object, smelling a particular odor). Please write example(s): _____	
			rude/obscene gestures; obscene finger/hand gestures.	
			unusual postures.	
			bending or gyrating, such as bending over.	
			rotating or spinning on one foot.	
			copying the action of another (echopraxia)	
			sudden tic-like impulsive behaviors. Please describe: _____	
			tic-like behaviors that could injure/mutilate others. Please describe: _____	
			self-injurious tic-like behavior(s). Please describe: _____	
			-other involuntary and apparently purposeless motor tics (that do not fit in any previous categories).	
			Please describe any other patterns or sequences of motor tic behaviors: _____ _____ _____ _____ _____	

Phonic (Vocal) Tics

Description of Phonic (or Vocal) Tic Symptoms Phonic tics usually begin in childhood, typically after motor tics have already started, but they can be the first tic symptoms. They are characterized by a sudden utterance of sounds such as throat clearing or sniffing. The same tics seem to recur in bouts during the day and are worse during periods of fatigue and/or stress. Many tics occur without warning and may not even be noticed by the person doing them. Others are preceded by a subtle urge that is difficult to describe (some liken it to the urge to scratch an itch). In many cases it is possible to voluntarily hold back the tics for brief periods of time. Over periods of weeks to months, phonic tics wax and wane and old tics may be replaced by totally new ones. Simple phonic tics are utterances of fast, meaningless sounds whereas complex phonic tics are involuntary, repetitive, purposeless utterances of words, phrases or statements that are out of context, such as uttering obscenities (i.e., coprolalia), or repeating over and over again what other people have said (i.e., echolalia). Complex tics can be difficult to distinguish from compulsions; however, it is unusual to see complex tics in the absence of simple ones. Often there is a tendency to explain away the tics with elaborate explanations (e.g., "I have hay fever that has persisted" even though it is not the right time of year). Tics are usually at their worst in childhood and may virtually disappear by early adulthood, so if you are completing this form for yourself, it may be helpful to talk to your parents, an older brother or sister, or older relative, as you answer the following questions.

- Age of first vocal tics? _____ years old.
- Describe first vocal tic: _____
- Was tic onset sudden or gradual? _____
- Age of worst vocal tics? _____ years old.

Phonic Tic Symptom Checklist

In the boxes on the left below, please check with a mark (x) the tics the patient

*1) has **EVER** experienced*
*2) is **CURRENTLY** experiencing (during the past week)*

*State **AGE OF ONSET** (in years) if patient has had that behavior.*

Also, in the tic descriptions below, please circle or underline the specific tics that the patient has experienced (circle or underline the words that apply).

Ever	Current	Age of onset [In Years]	The patient has experienced, or others have noticed, bouts of involuntary and apparently purposeless utterance of:	Ver
			-coughing.	
			-throat clearing.	
			-sniffing.	
			-whistling.	
			-animal or bird noises.	
			-Other simple phonic tics. Please list:	
			-syllables. Please list:	
			-words. Please list:	
			-rude or obscene words or phrases. Please list:	
			-repeating what someone else said, either sounds, single words or sentences. Perhaps repeating what's said on TV (echolalia).	
			-repeating something the patient said over and over again (palilalia).	
			-other tic-like speech problems, such as sudden changes in volume or pitch. Please describe:	
			Describe any other patterns or sequences of phonic tic behaviors:	

SEVERITY RATINGS

NUMBER	Motor	Phonic	
None	❑	❑	0
Single tic	❑	❑	1
Multiple discrete tics (2-5)	❑	❑	2
Multiple discrete tics (>5)	❑	❑	3
Multiple discrete tics plus as least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics	❑	❑	4
Multiple discrete tics plus several (>2) orchestrated paroxysms of multiple simultaneous or sequential tics that where it is difficult to distinguish discrete tics	❑	❑	5

FREQUENCY	Motor	Phonic	
NONE No evidence of specific tic behaviors	❑	❑	0
RARELY Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.	❑	❑	1
OCCASIONALLY Specific tic behaviors are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.	❑	❑	2
FREQUENTLY Specific tic behaviors are present on a daily basis. tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.	❑	❑	3
ALMOST ALWAYS Specific tic behaviors are present virtually every waking hour of every day, and periods of sustained tic behaviors occur regularly. Bouts of tics are common and are not limited to a single setting.	❑	❑	4
ALWAYS Specific tic behaviors are present virtually all the time. Tic free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.	❑	❑	5

INTENSITY	Motor	Phonic	
ABSENT	❑	❑	0
MINIMAL INTENSITY Tics not visible or audible (based solely on patient's private experience) or tics are less forceful than comparable voluntary actions and are typically not noticed because of their intensity.	❑	❑	1
MILD INTENSITY Tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.	❑	❑	2
MODERATE INTENSITY Tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character.	❑	❑	3
MARKED INTENSITY Tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character. Such tics frequently call attention to the individual because of their forceful and exaggerated character.	❑	❑	4
SEVERE INTENSITY Tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.	❑	❑	5

COMPLEXITY

	Motor	Phonic	
NONE If present, all tics are clearly "simple" (sudden, brief, purposeless) in character.	❑	❑	0
BORDERLINE Some tics are not clearly "simple" in character.	❑	❑	1
MILD Some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviors, such as grooming, syllables, or brief meaningful utterances such as "ah huh," "hi" that could be readily camouflaged.	❑	❑	2
MODERATE Some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behavior or speech (picking, tapping, saying "you bet" or "honey", brief echolalia).	❑	❑	3
MARKED Some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre or obscene character (a lengthy facial contortion, touching genitals, echolalia, speech atypicalities, longer bouts of saying "what do you mean" repeatedly, or saying "fu" or "sh").	❑	❑	4
SEVERE Some tics involve lengthy bouts of orchestrated behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre or obscene character (lengthy displays or utterances often involving copropraxia, self-abusive behavior, or coprolalia).	❑	❑	5

INTERFERENCE

	Motor	Phonic	
NONE	❑	❑	0
MINIMAL When tics are present, they do not interrupt the flow of behavior or speech.	❑	❑	1
MILD When tics are present, they occasionally interrupt the flow of behavior or speech.	❑	❑	2
MODERATE When tics are present, they frequently interrupt the flow of behavior or speech.	❑	❑	3
MARKED When tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt intended action or communication.	❑	❑	4
SEVERE When tics are present, they frequently disrupt intended action or communication.	❑	❑	5

IMPAIRMENT

NONE	❑	0
MINIMAL Tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics vis a vis the future, periodic, slight increase in family tensions because of tics, friends or acquaintances may occasionally notice or comment about tics in an upsetting way).	❑	10
MILD Tics associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning.	❑	20
MODERATE Tics associated with some clear problems in self-esteem family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school or job performance because of tics).	❑	30
MARKED Tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.	❑	40
SEVERE Tics associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (severe depression with suicidal ideation, disruption of the family (separation/divorce, residential placement), disruption of social tics - severely restricted life because of social stigma and social avoidance, removal from school or loss of job).	❑	50

Appendix

The Yale Global Tic Severity Scale

A. *Instructions*

This clinical rating scale is designed to rate the overall severity of tic symptoms across a range of dimensions (number, frequency, intensity, complexity, and interference). Use of the YGTSSS requires the rater to have clinical experience with Tourette's syndrome patients. The final rating is based on all available information and reflects the clinician's overall impression for each of the items to be rated.

The style of the interview is semistructured. The interviewer should first complete the Tic Inventory (a list of motor and phonic tics present during the past week, as reported by the parent/patient, and observed during the evaluation). It is then best to proceed with questions based on each of the individual items, using the content of the anchor points as a guide.

B. *Tic Inventory*

1. *Description of Motor Tics:* (Check motor tics present during past week)

a. *Simple Motor Tics:* (Rapid, Darting, "Meaningless"):

_____ Eye blinking
_____ Eye movements
_____ Nose movements
_____ Mouth movements
_____ Facial grimace
_____ Head jerks/movements
_____ Shoulder shrugs
_____ Arm movements
_____ Hand movements
_____ Abdominal tensing
_____ Leg or foot or toe movements
_____ Other _____

b. *Complex Motor Tics:* (Slower, "Purposeful"):

_____ Eye gestures or movements
_____ Mouth movements
_____ Facial movements or expressions
_____ Head gestures or movements
_____ Shoulder gestures
_____ Arm or hand gestures
_____ Writing tics
_____ Dystonic postures
_____ Bending or gyrating
_____ Rotating
_____ Leg or foot or toe movements
_____ Tic-related compulsive behaviors (touching, tapping, grooming, evening-up)
_____ Copropraxia
_____ Self abusive behavior (describe)_____

_____ Paroxysms of tics (displays), duration _____seconds
_____ Disinhibited behavior (describe)* _____

_____ Other _____

_____ Describe any orchestrated patterns or sequences of motor tic behaviors _____

*Do not include this item in rating the ordinal scales.

2. *Description of Phonic Tic Symptoms:* (Check phonic tics present over the past week)

_____ a. *Simple Phonic Symptoms:* (Fast, "Meaningless" Sounds):
Sounds, noises: (circle: coughing, throat clearing, sniffing, grunting, whistling, animal or bird noises)
Other (list) _____

b. *Complex Phonic Symptoms:* (Language: Words, Phrases, Statements):

_____ Syllables: (list) _____
_____ Words: (list) _____
_____ Coprolalia: (list) _____
_____ Echolalia _____
_____ Palalalia _____
_____ Blocking _____
_____ Speech atypicalities: (describe) _____

_____ Disinhibited speech: (describe)* _____

_____ Describe any orchestrated patterns or sequences of phonic tic behaviors _____

C. *Ordinal Scales* (Rate motor and phonic tics separately unless otherwise indicated).

a. *Number:* Motor Score: [ ] Phonic Score: [ ]

Score	*Description (Anchor Point)*
0	None
1	Single tic
2	Multiple discrete tics (2–5)
3	Multiple discrete tics (>5)
4	Multiple discrete tics plus at least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics.
5	Multiple discrete tics plus several (>2) orchestrated patterns of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics.

b. *Frequency:* Motor Score: [ ] Phonic Score: [ ]

Score	*Description (Anchor Point)*
0	*None*. No evidence of specific tic behaviors.
1	*Rarely*. Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.
2	*Occassionally*. Specific tic behaviors are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.
3	*Frequently*. Specific tic behaviors are present on a daily basis. Tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.
4	*Almost Always*. Specific tic behaviors are present virtually every waking hour of every day, and periods of sustained tic behaviors occur regularly. Bouts of tics are common and are not limited to a single setting.
5	*Always*. Specific tic behaviors are present virtually all the time. Tic-free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.

c. *Intensity* Motor Score: [ ] Phonic Score: [ ]

Score	*Description (Anchor Point)*
0	*Absent*
1	*Minimal intensity*, tics not visible or audible (based solely on patient's private experience) or tics are less forceful than comparable voluntary actions and are typically not noticed because of their intensity.
2	*Mild intensity*, tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.
3	*Moderate intensity*, tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character.
4	*Marked intensity*, tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character. Such tics frequently call attention to the individual because of their forceful and exaggerated character.
5	*Severe intensity*, tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.

d. *Complexity:* Motor Score: [ ] Phonic Score: [ ]

Score	*Description (Anchor Point)*
0	*None*, if present, all tics are clearly "simple" (sudden, brief, purposeless) in character.
1	*Borderline*, some tics are not clearly "simple" in character.
2	*Mild*, some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviors, such as grooming, syllables or brief meaningful utterances such as "ah huh," "hi," that could be readily camouflaged.
3	*Moderate*, some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behavior or speech (picking, tapping, saying "you bet" or "honey," brief echolalia).
4	*Marked*, some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre, or obscene character (a lengthy facial contortion, touching genitals, echolalia, speech atypicalities, longer bouts of saying "what do you mean" repeatedly, or saying "fu" or "sh").
5	*Severe*, some tics involve lengthy bouts of orchestrated behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre, or obscene character (lengthy displays or utterances often involving copropraxia, self-abusive behavior, or coprolalia).

e. *Interference:* Motor Score: [ ] Phonic Score: [ ]

Score	*Description (Anchor Point)*
0	*None*
1	*Minimal*, when tics are present, they do not interrupt the flow of behavior or speech.
2	*Mild*, when tics are present, they occasionally interrupt the flow of behavior or speech.
3	*Moderate*, when tics are present, they frequently interrupt the flow of behavior or speech.
4	*Marked*, when tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt intended action or communication.
5	*Severe*, when tics are present, they frequently disrupt intended action or communication.

f. *Impairment* Overall Impairment: [ ] (Rate Overall Impairment for Motor and Phonic Tics):

Score	*Description (Anchor Point)*
0	*None*
10	*Minimal*, tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics vis à vis the future; periodic, slight increase in family tensions because of tics; friends or acquaintances may occasionally notice or comment about tics in an upsetting way).
20	*Mild*, tics associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning.
30	*Moderate*, tics associated with some clear problems in self-esteem, family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or epidodic social avoidance, periodic interference in school or job performance because of tics).
40	*Marked*, tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.
50	*Severe*, tics associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (sever depression with suicidal ideation, disruption of the family [separation/divorce, residential placement], disruption of social ties—severely restricted life because of social stigma and social avoidance, removal from school or loss of job).

D. *Score Sheet.*

Name _____ Date _____
DOB _____ Sex _____
Sources of Information _____

Raters _____

Motor Tics:	
Number	[ ]
Frequency	[ ]
Intensity	[ ]
Complexity	[ ]
Interference	[ ]
Total Motor Tic Score	[ ]
Phonic Tics:	
Number	[ ]
Frequency	[ ]
Intensity	[ ]
Complexity	[ ]
Interference	[ ]
Total Phonic Tic Score	[ ]
Overall Impairment Rating	[ ]
Global Severity Score (Motor + Phonic + Impairment)	[ ]

References

Achenbach, T. M. & Edelbrock, C. S. (1983), *Manual for the Child*

4. The Modified Rush Video-Based Rating Scale (MRVS)

Number of body areas (eyes, nose, mouth, neck, shoulders, arms, hands, trunk, pelvis, legs, feet)

0 = no body areas
1 = 1 or 2 body areas
2 = 3 or 4 body areas
3 = 5 or 6 body areas
4 = 7 or more body areas

Motor tic frequency (tics/mic)

0 = no tics
1 = 1-20 tics/min
2 = 21-40 tics/min
3 = 41-60 tics/min
4 = greater than 60 tics/min

Phonic tic frequency

0 = no tics
1 = 1-5 tics/min
2 = 6-10 tics/min
3 = 11-15 tics/min
4 = greater than 15 tics/min

Severity of motor tics

0 = absent tics
1 = minimal: could be normal
2 = mild: limited to a single muscle group
3 = moderate: limited to a single body part
4 = severe: involve more than one body part or complex

Severity of phonic tics

0 = absent tics
1 = minimal: could be normal
2 = mild: single words or sounds, separated by at least one breath or 4 secs
3 = moderate: words of sounds repeated 2 or 3 times in series of single obscenities separated by at least 1 break or 4 seconds
4 = severe: words or sounds repeated four or more times in series or obscenities repeated at least 2-3 times in series

5. The Premonitory Urge for Tics Scale (PUTS)

By Douglas Woods, Ph.D.

Journal of Developmental and Behavioral Pediatrics, volume 26, number 6, December 2005 pp397-403

Name _____ Age _____ Date _____

How I feel	***Not at all***	***A little***	***Pretty much***	***Very much***
Right before I do a tic I feel like my insides are itchy				
Right before I do a tic I feel pressure inside my brain or body				
Right before I do a tic I feel “wound up” or tense inside				
Right before I do a tic I feel like something is not “just right”				
Right before I do a tic I feel like something isn’t complete				
Right before I do a tic I feel like there is energy in my body that needs to get out				
I have these feelings almost all the time before I do a tic				
These feelings happen for every tic I have				
After I do the tic, the itchiness, energy, pressure, tense feelings or feelings that something isn’t “just right” or complete go away, at least for a while				
I am able to stop my tics even if only for a short period of time				
Total scores (except item number ten) *On a scale of 1-4, from least to most*				

6. The Adult ADHD Self-Report Scale Symptom Checklist (ASRS)

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist Instructions

The questions on the back page are designed to stimulate dialogue between you and your patients and to help confirm if they may be suffering from the symptoms of attention-deficit/hyperactivity disorder (ADHD).

Description: The Symptom Checklist is an instrument consisting of the eighteen DSM-IV-TR criteria. Six of the eighteen questions were found to be the most predictive of symptoms consistent with ADHD. These six questions are the basis for the ASRS v1.1 Screener and are also Part A of the Symptom Checklist. Part B of the Symptom Checklist contains the remaining twelve questions.

Instructions:

Symptoms

1. Ask the patient to complete both Part A and Part B of the Symptom Checklist by marking an X in the box that most closely represents the frequency of occurrence of each of the symptoms.

2. Score Part A. If four or more marks appear in the darkly shaded boxes within Part A then the patient has symptoms highly consistent with ADHD in adults and further investigation is warranted.

3. The frequency scores on Part B provide additional cues and can serve as further probes into the patient's symptoms. Pay particular attention to marks appearing in the dark shaded boxes. The frequency-based response is more sensitive with certain questions. No total score or diagnostic likelihood is utilized for the twelve questions. It has been found that the six questions in Part A are the most predictive of the disorder and are best for use as a screening instrument.

Impairments

1. Review the entire Symptom Checklist with your patients and evaluate the level of impairment associated with the symptom.

2. Consider work/school, social and family settings.

3. Symptom frequency is often associated with symptom severity, therefore the Symptom Checklist may also aid in the assessment of impairments. If your patients have frequent symptoms, you may want to ask them to describe how these problems have affected the ability to work, take care of things at home, or get along with other people such as their spouse/significant other.

History

1. Assess the presence of these symptoms or similar symptoms in childhood. Adults who have ADHD need not have been formally diagnosed in childhood. In evaluating a patient's history, look for evidence of early-appearing and long-standing problems with attention or self-control. Some significant symptoms should have been present in childhood, but full symptomology is not necessary.

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date	

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.	Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?					
3. How often do you have problems remembering appointments or obligations?					
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					
					Part A
7. How often do you make careless mistakes when you have to work on a boring or difficult project?					
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
10. How often do you misplace or have difficulty finding things at home or at work?					
11. How often are you distracted by activity or noise around you?					
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
13. How often do you feel restless or fidgety?					
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?					
15. How often do you find yourself talking too much when you are in social situations?					
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
17. How often do you have difficulty waiting your turn in situations when turn taking is required?					
18. How often do you interrupt others when they are busy?					
					Part B

7. The Barkley Adult ADHD Rating Scale-IV (BAARS-IV)

BAARS-IV: Self-Report: Current Symptoms

ID _____

Date _____

Instructions:

For the first 27 items, please place an X in the column next to each item below that best describes your behavior **DURING THE PAST 6 MONTHS**. Then answer the remaining three questions.

Section 1 (Inattention)	***Never or Rarely***	***Sometimes***	***Often***	***Very Often***
1. Fail to give close attention to details or make careless mistakes in my work or other activities				
2. Difficulty sustaining my attention in tasks or fun activities				
3. Don't listen when spoken to directly				
4. Don't follow through on instructions and fail to finish work or chores				
5. Have difficulty organizing tasks and activities				
6. Avoid, dislike, or am reluctant to engage in tasks that require sustained mental effort				
7. Lose things necessary for tasks or activities				
8. Easily distracted by extraneous stimuli or irrelevant thoughts				
9. Forgetful in daily activities				
Section 2 (Hyperactivity)				
10. Fidget with hands or feet or squirm in seat				
11. Leave my seat in classrooms or in other situations in which remaining seated is expected				

12. Shift around excessively or feel restless or hemmed in				
13. Have difficulty engaging in leisure activities quietly) feel uncomfortable, or am loud or noisy)				
14. I am "on the go" or act as if "driven by a motor" (or I feel like I have to be busy as always doing something)				
Section 3 (Impulsivity)				
15. Talk excessively (in social situations)				
16. Blurt out answers before questions have been completed, complete others' sentences, or jump the gun				
17. Have difficulty awaiting my turn				
18. Interrupt or intrude on others (butt into conversations or activities without permission or take over what others are doing)				
Section 4 (Sluggish Cognitive Tempo)				
19. Prone to delaying when I should be concentrating on something or working				
20. Have trouble staying alert or awake in boring situations				
21. Easily confused				
22. Easily bored				
23. Spacey or "in a fog"				
24. Lethargic, more tired than others				
25. Underactive or have less energy than others				
26. Slow moving				
27. I don't seem to process information as quickly or as accurately as others				
28. Did you experience any of these 27 symptoms at least 'Often' or more frequently? **YES NO**				
29. If so, how old were you when those symptoms began? I was years old				

30. If so, in which of these settings did those symptoms impair your function? Please place an X next to all of the areas that apply to you.
School _____
Home_____
Work_____
Social Relationships_____

Instructions:

For the first 18 items, please put an X in the column that best describes your behavior when you were a child **BETWEEN 5 AND 12 YEARS OF AGE**. Then answer the remaining two questions.

Section 1 (Inattention)	***Never or Rarely***	***Sometimes***	***Often***	***Very Often***
1. Failed to give close attention to details or made careless mistakes in my work or other activities				
2. Had difficulty sustaining my attention in tasks or fun activities				
3. Didn't listen when spoken to directly				
4. Didn't follow through on instructions and failed to finish work or chores				
5. Had difficulty organizing tasks and activities				
6. Avoided, disliked, or was reluctant to engage in tasks that required sustained mental effort				
7. Lost things necessary for tasks or activities				
8. Was easily distracted by extraneous stimuli or irrelevant thoughts				
9. Was forgetful in daily activities				
Section 2 (Hyperactivity)				

10. Fidgeted with hands or feet or squirmed in seat				
11. Left my seat in classrooms or in other situations in which remaining seated was expected				
12. Shifted around excessively or felt restless or hemmed in				
13. Had difficulty engaging in leisure activities quietly (felt uncomfortable, or was loud or noisy)				
14. Was "on the go" or acted as if "driven by a motor				
15. Talked excessively (in social situations)				
16. Blurted out answers before questions had been completed, completed others' sentences, or jumped the gun				
17. Had difficulty awaiting my turn				
18. Interrupted or intruded on others (butted into conversations or activities without permission or took over what others were doing)				
19. Did you experience *any* of these 18 symtpms at least 'Often' or more frequently? **YES NO**				
20. If so, in which of these settings did those symptoms impair your functioning? Place an X next to all the areas that apply to you. School _____ Home _____ Social Relationships _____				

8. The Padua Inventory Long Version (Padua-L)

Participant ID:_____ **Date:**_____

INSTRUCTIONS: The following statements refer to thoughts and behaviours which may occur to everyone in everyday life. For each statement, choose the reply (place an X in the column) which best seems to fit you and the degree of disturbance which such thoughts or behaviours may create.

	Not at all	A little	Quite a lot	A lot	Very much
1) I feel my hands are dirty when I touch money.					
2) I think even slight contact with bodily secretions (perspiration, saliva. urine etc.) may contaminate my clothes or somehow harm me.					
3) I find it difficult to touch an object when I know it has been touched by strangers or by certain people.					
4) I find it difficult to touch garbage or dirty things.					
5) I avoid using public toilets because I am afraid of disease and contamination.					
6) I avoid using public telephones because I am afraid of contagion and disease.					
7) I wash my hands more often and longer than necessary.					
8) I sometimes have to wash or clean myself simply because I think I may be dirty or 'contaminated'.					
9) If I touch something I think is 'contaminated' I immediately have to wash or clean myself.					
10) If an animal touches me, I feel dirty and immediately have to wash myself or change my clothing.					
11) When doubts and worries come to my mind, I cannot rest until I have talked them over with a reassuring person.					

	Not at all	A little	Quite a lot	A lot	Very much
12) When I talk I tend to repeat the same things and the same sentences several times.					
13) I tend to ask people to repeat the same things to me several times consecutively, even though I did understand what they said the first time.					
14) I feel obliged to follow a particular order in dressing, undressing and washing myself.					
15) Before going to sleep I have to do certain things in a certain order.					
16) Before going to bed I have to hang up or fold my clothes in a special way.					
17) I feel I have to repeat certain numbers for no reason.					
18) I have to do things several times before I think they are properly done.					
19) I tend to keep on checking things more often than necessary.					
20) I check and recheck gas and water taps and light switches after turning them off.					
21) I return home to check doors, windows, drawers etc., to make sure they are properly shut.					
22) I keep on checking forms, documents, checks etc. in detail, to make sure I have filled them in correctly.					
23) I keep on going back to see that matches. cigarettes etc. are properly extinguished.					

	Not at all	A little	Quite a lot	A lot	Very much
24) When I handle money I count and recount it several times.					
25) I check letters carefully many times before posting them.					
26) I find it difficult to take decisions, even about unimportant matters.					
27) Sometimes I am not sure I have done things which in fact I know I have done.					
28) I have the impression that I will never be able to explain things clearly, especially when talking about important matters that involve me.					
29) After doing something carefully, I still have the impression I have either done it badly or not finished it.					
30) I am sometimes late because I keep on doing certain things more often than necessary.					
31) I invent doubts and problems about most of the things I do.					
32) When I start thinking of certain things, I become obsessed with them.					
33) Unpleasant thoughts come into my mind against my will and I cannot get rid of them.					
34) Obscene or dirty words come into my mind and I cannot get rid of them.					
35) My brain constantly goes its own way and I find it difficult to attend to what is happening round me.					
36) I imagine catastrophic consequences as a result of absent-mindedness or minor errors which I make.					

	Not at all	A little	Quite a lot	A lot	Very much
37) I think or worry at length about having hurt someone without knowing it.					
38) When I hear about a disaster, I think it is somehow my fault.					
39) I sometimes worry at length for no reason that I have hurt myself or have some disease.					
40) I sometimes start counting objects for no reason.					
41) I feel I have to remember completely unimportant numbers.					
42) When I read I have the impression I have missed something important and must go back and reread the passage at least two or three times.					
43) I worry about remembering completely unimportant things and make an effort not to forget them.					
44) When a thought or doubt comes into my mind, I have to examine it from all points of view and cannot stop until I have done so.					
45) In certain situations, I am afraid of losing *my* self-control and doing embarrassing things.					
46) When I look down from a bridge or a very high window, I feel an impulse to throw myself into space.					
47) When I see a train approaching I sometimes think I could throw myself under its wheels.					
48) At certain moments I am tempted to tear off my clothes in public.					

	Not at all	A little	Quite a lot	A lot	Very much
49) While driving I sometimes feel an impulse to drive the car into someone or something.					
50) Seeing weapons excites me and makes me think violent thoughts.					
51) I get upset and worried at the sight of knives, daggers and other pointed objects.					
52) I sometimes feel something inside me which makes me do things which are really senseless and which I do not want to do.					
53) I sometimes feel the need to break or damage things for no reason.					
54) I sometimes have an impulse to steal other people's belongings, even if they are of no use to me.					
55) I am sometimes almost irresistibly tempted to steal something from the supermarket.					
56) I sometimes have an impulse to hurt defenceless children or animals.					
57) I feel I have to make special gestures or walk in a certain way.					
58) In certain situations, I feel an impulse to eat too much. Even if I am then ill.					
59) When I hear about a suicide or a crime, I am upset for a long time and find it difficult to stop thinking about it.					
60) I invent useless worries about germs and diseases					

9. The Obsessive Compulsive Inventory (OCI)

Participant ID:_____ **Date:**_____

INSTRUCTIONS: The following statements refer to thoughts and behaviours which many people have in their everyday life. In the column labelled DISTRESS, for each statement, place and X in the column which best describes HOW MUCH that experience has DISTRESSED or BOTHERED YOU DURING THE PAST MONTH.

	DISTRESS				
	Not at all	**A little**	**Moderately**	**A lot**	**Extremely**
1) Unpleasant thoughts come into my mind against my will and I cannot get rid of them					
2) I think contact with bodily secretions (perspiration, saliva blood, urine, etc) may contaminate my clothes or somehow harm me					
3) I ask people to repeat things to me several times, even though I understood them the first time.					
4) I wash and clean obsessively.					
5) I have to review mentally past events, conversations and actions to make sure that I didn't do something wrong.					
6) I have saved up so many things that they get in the way					
7) I check things more often than necessary					
8) I avoid using public toilets because I am afraid of disease or contamination					
9) I repeatedly check doors, windows, drawers etc.					

	DISTRESS				
	Not at all	**A little**	**Moderately**	**A lot**	**Extremely**
10) I repeatedly check gas and water taps and light switches after turning them off.					
11) I collect things I don't need.					
12) I have thoughts of having hurt someone without knowing it.					
13) I have thoughts that I might want to harm myself or others.					
14) I get upset if objects are not arranged properly.					
15) I feel obliged to follow a particular order in dressing, undressing and washing myself.					
16) I feel compelled to count while I am doing things.					
17) I am afraid of impulsively doing embarrassing or harmful things.					
18) I need to pray to cancel bad thoughts or feelings.					
19) I keep on checking forms or other things I have written.					
20) I get upset at the sight of knives, scissors and other sharp objects in case I lose control with them.					
21) I am excessively concerned about cleanliness.					

	DISTRESS				
	Not at all	A little	Moderately	A lot	Extremely
22) I find it difficult to touch an object when I know it has been touched by strangers or certain people.					
23) I need things to be arranged in a particular order.					
24) I get behind in my work because I repeat things over and over again.					
25) I feel I have to repeat certain numbers.					
26) After doing something carefully, I still have the impression I have not finished it.					
27) I find it difficult to touch garbage or dirty things.					
28) I find it difficult to control my own thoughts.					
29) I have to do things over and over again until it feels right.					
30) I am upset by unpleasant thoughts that come into my mind against my will.					
31) Before going to sleep I have to do certain things in a certain way.					
32) I go back to places to make sure that I have not harmed anyone.					
33) I frequently get nasty thoughts and have difficulty in getting rid of them.					

	DISTRESS				
	Not at all	A little	Moderately	A lot	Extremely
34) I avoid throwing things away because I am afraid I might need them later.					
35) I get upset if others change the way I have arranged my things.					
36) I feel that I must repeat certain words or phrases in my mind in order to wipe out bad thoughts, feelings or actions.					
37) After I have done things, I have persistent doubts about whether I really did them.					
38) I sometimes have to wash or clean myself simply because I feel contaminated.					
39) I feel that there are good and bad numbers.					
40) I repeatedly check anything which might cause a fire.					
41) Even when I do something very carefully I feel that it is not quite right.					
42) I wash my hands more often or longer than necessary.					

10. The Yale Brown Obsessive Compulsive Scale (Y-BOCS)

PATIENT NAME _____ **DATE** _____ 22.

YALE-BROWN OBSESSIVE COMPULSIVE SCALE (Y-BOCS)*

Questions 1 to 5 are about your obsessive thoughts

Obsessions are unwanted ideas, images or impulses that intrude on thinking against your wishes and efforts to resist them. They usually involve themes of harm, risk and danger. Common obsessions are excessive fears of contamination; recurring doubts about danger, extreme concern with order, symmetry, or exactness; fear of losing important things.

Please answer each question by circling the appropriate number.

1. TIME OCCUPIED BY OBSESSIVE THOUGHTS SCORE _____
   How much of your time is occupied by obsessive thoughts?
   - 0 = None
   - 1 = Less than 1 hr/day or occasional occurrence
   - 2 = 1 to 3 hrs/day or frequent
   - 3 = Greater than 3 and up to 8 hrs/day or very frequent occurrence
   - 4 = Greater than 8 hrs/day or nearly constant occurrence

2. INTERFERENCE DUE TO OBSESSIVE THOUGHTS SCORE _____
   How much do your obsessive thoughts interfere with your work, school, social, or other important role functioning? Is there anything that you don't do because of them?
   - 0 = None
   - 1 = Slight interference with social or other activities, but overall performance not impaired
   - 2 = Definite interference with social or occupational performance, but still manageable
   - 3 = Causes substantial impairment in social or occupational performance
   - 4 = Incapacitating

3. DISTRESS ASSOCIATED WITH OBSESSIVE THOUGHTS SCORE _____
   How much distress do your obsessive thoughts cause you?
   - 0 = None
   - 1 = Not too disturbing
   - 2 = Disturbing, but still manageable
   - 3 = Very disturbing
   - 4 = Near constant and disabling distress

4. RESISTANCE AGAINST OBSESSIONS SCORE _____
   How much of an effort do you make to resist the obsessive thoughts? How often do you try to disregard or turn your attention away from these thoughts as they enter your mind?
   - 0 = Try to resist all the time
   - 1 = Try to resist most of the time
   - 2 = Make some effort to resist
   - 3 = Yield to all obsessions without attempting to control them, but with some reluctance
   - 4 = Completely and willingly yield to all obsessions

23.

5. DEGREE OF CONTROL OVER OBSESSIVE THOUGHTS SCORE _____
   How much control do you have over your obsessive thoughts? How successful are you in stopping or diverting your obsessive thinking? Can you dismiss them?
   - 0 = Complete control
   - 1 = Usually able to stop or divert obsessions with some effort and concentration
   - 2 = Sometimes able to stop or divert obsessions
   - 3 = Rarely successful in stopping or dismissing obsessions, can only divert attention with difficulty
   - 4 = Obsessions are completely involuntary, rarely able to even momentarily alter obsessive thinking.

The next several questions are about your compulsive behaviors.
Compulsions are urges that people have to do something to lessen feelings of anxiety or other discomfort. Often they do repetitive, purposeful, intentional behaviors called rituals. The behavior itself may seem appropriate but it becomes a ritual when done to excess. Washing, checking, repeating, straightening, hoarding and many other behaviors can be rituals. Some rituals are mental. For example, thinking or saying things over and over under your breath.

6. TIME SPENT PERFORMING COMPULSIVE BEHAVIORS SCORE _____
   How much time do you spend performing compulsive behaviors? How much longer than most people does it take to complete routine activities because of your rituals? How frequently do you do rituals?
   - 0 = None
   - 1 = Less than 1 hr/day or occasional performance of compulsive behaviors
   - 2 = From 1 to 3 hrs/day, or frequent performance of compulsive behaviors
   - 3 = More than 3 and up to 8 hrs/day, or very frequent performance of compulsive behaviors
   - 4 = More than 8 hrs/day, or near constant performance of compulsive behaviors (too numerous to count)

7. INTERFERENCE DUE TO COMPULSIVE BEHAVIORS SCORE _____
   How much do your compulsive behaviors interfere with your work, school, social, or other important role functioning? Is there anything that you don't do because of the compulsions?
   - 0 = None
   - 1 = Slight interference with social or other activities, but overall performance not impaired
   - 2 = Definite interference with social or occupational performance, but still manageable
   - 3 = Causes substantial impairment in social or occupational performance
   - 4 = Incapacitating

8. DISTRESS ASSOCIATED WITH COMPULSIVE BEHAVIOR SCORE _____

How would you feel if prevented from performing your compulsion(s)? How anxious would you become?

0 = None
1 = Only slightly anxious if compulsions prevented
2 = Anxiety would mount but remain manageable if compulsions prevented
3 = Prominent and very disturbing increase in anxiety if compulsions interrupted
4 = Incapacitating anxiety from any intervention aimed at modifying activity

9. RESISTANCE AGAINST COMPULSIONS SCORE _____

How much of an effort do you make to resist the compulsions?

0 = Always try to resist
1 = Try to resist most of the time
2 = Make some effort to resist
3 = Yield to almost all compulsions without attempting to control them, but with some reluctance
4 = Completely and willingly yield to all compulsions

10. DEGREE OF CONTROL OVER COMPULSIVE BEHAVIOR SCORE _____

How strong is the drive to perform the compulsive behavior? How much control do you have over the compulsions?

0 = Complete control
1 = Pressure to perform the behavior but usually able to exercise voluntary control over it
2 = Strong pressure to perform behavior, can control it only with difficulty
3 = Very strong drive to perform behavior, must be carried to completion, can only delay with difficulty
4 = Drive to perform behavior experienced as completely involuntary and over-powering, rarely able to even momentarily delay activity.

_____

TOTAL SCORE _____

Y-BOCS Symptom Checklist

Instructions: Generate *a Target Symptoms List from* the attached Y-BOCS Symptom Checklist by asking the patient about specific obsessions and compulsions. Chock all that apply. Distinguish between current and past symptoms. Mark principal symptoms with a "p". These will form the basis of the Target Symptoms *List*. Items marked may "*" or may not be an OCD phenomena.

Current Past

AGGRESSIVE OBSESSIONS
- ___ ___ Fear might harm self
- ___ ___ Fear might harm others
- ___ ___ Violent or horrific images
- ___ ___ Fear of blurting out obscenities or insults
- ___ ___ Fear of doing something else embarrassing*
- ___ ___ Fear will act on unwanted impulses (e.g., to stab friend)
- ___ ___ Fear will steal things
- ___ ___ Fear will harm others because not careful enough (e.g. hit/run motor vehicle accident)
- ___ ___ Fear will be responsible for something else terrible happening (e.g., fire, burglary

Other:

CONTAMINATION OBSESSIONS
- ___ ___ Concerns or disgust w\ with bodily waste or secretions (e.g., urine, feces, saliva Concern with dirt or germs
- ___ ___ Excessive concern with environmental contaminants (e.g. asbestos, radiation toxic waste)
- ___ ___ Excessive concern with household items (e.g., cleansers solvents)
- ___ ___ Excessive concern with animals (e.g., insects)
- ___ ___ Bothered by sticky substances or residues
- ___ ___ Concerned will get ill because of contaminant
- ___ ___ Concerned will get others ill by spreading contaminant (Aggressive)
- ___ ___ No concern with consequences of contamination other than how it might feel

SEXUAL OBSESSIONS
- ___ ___ Forbidden or perverse sexual thoughts. images. or impulses
- ___ ___ Content involves children or incest
- ___ ___ Content involves homosexuality*
- ___ ___ Sexual behavior towards others (Aggressive)*
- ___ ___ Other:

HOARDING/SAVING OBSESSIONS
(distinguish from hobbies and concern with objects of monetary or sentimental value)

___ ___ _____

RELIGIOUS OBSESSIONS (Scrupulosity)
- ___ ___ Concerned with sacrilege and blasphemy
- ___ ___ Excess concern with right/wrong, morality
- ___ ___ Other:

OBSESSION WITH NEED FOR SYMMETRY OR EXACTNESS
- ___ ___ Accompanied by magical thinking (e.g., concerned that another will have accident dent unless less things are in the right place)
- ___ ___ Not accompanied by magical thinking

MISCELLANEOUS OBSESSIONS
- ___ ___ Need to know or remember
- ___ ___ Fear of saying certain things
- ___ ___ Fear of not saying just the right thing
- ___ ___ Fear of losing things
- ___ ___ Intrusive (nonviolent) images
- ___ ___ Intrusive nonsense sounds, words, or music
- ___ ___ Bothered by certain sounds/noises*
- ___ ___ Lucky/unlucky numbers
- ___ ___ Colors with special significance
- ___ ___ 3 superstitious fears
- ___ ___ Other:

Current Past

SOMATIC OBSESSIONS
- ___ ___ Concern with illness or disease*
- ___ ___ Excessive concern with body part or aspect of Appearance (eg., dysmorphophobia)*
- ___ ___ Other

CLEANING/WASHING COMPULSIONS
- ___ ___ Excessive or ritualized handwashing
- ___ ___ Excessive or ritualized showering, bathing, toothbrushing grooming, or toilet routine Involves cleaning of household items or other inanimate objects
- ___ ___ Other measures to prevent or remove contact with contaminants
- ___ ___ Other

CHECKING COMPULSIONS
- ___ ___ Checking locks, stove, appliances etc.
- ___ ___ Checking that did not/will not harm others
- ___ ___ Checking that did not/will not harm self
- ___ ___ Checking that nothing terrible did/will happen
- ___ ___ Checking that did not make mistake
- ___ ___ Checking tied to somatic obsessions
- ___ ___ Other:

REPEATING RITUALS
- ___ ___ Rereading or rewriting
- ___ ___ Need to repeat routine activities jog, in\out door, up/down from chair)
- ___ ___ Other _____

COUNTING COMPULSIONS

___ ___ _____

ORDERING/ARRANGING COMPULSIONS

___ ___ _____

HOARDING/COLLECTING COMPULSIONS
(distinguish from hobbies and concern with objects of monetary or sentimental value (e.g., carefully reads junk mail, piles up old newspapers, sorts through garbage, collects useless objects.)

___ _____

MISCELLANEOUS COMPULSIONS
- ___ ___ Mental rituals (other than checking/counting)
- ___ ___ Excessive listmaking
- ___ ___ Need to tell, ask, or confess
- ___ ___ Need to touch, tap, or rub*
- ___ ___ Rituals involving blinking or staring*
- ___ ___ Measures (not checking) to prevent: harm to self - harm to others terrible consequences
- ___ ___ Ritualized eating behaviors*
- ___ ___ Superstitious behaviors
- ___ ___ Trichotillomania *
- ___ ___ Other self-damaging or self-mutilating behaviors*
- ___ ___ Other

Adapted from Goodman, W.K., Price, L.H., Rasmussen, S.A. et al.: "The Yale-Brown Obsessive Compulsive Scale." Arch Gen Psychiatry 46:1006-1011,1989

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

USA: **D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan**
University of South Florida - Tampa

FRANCE: **Y. Lecrubier, E. Weiller, T. Hergueta, P. Amorim, L. I. Bonora, J. P. Lépine**
Hôpital de la Salpétrière - Paris

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)

Patient Name:		*Patient Number:*	
Date of Birth:		*Time Interview Began:*	
Interviewer's Name:		*Time Interview Ended:*	
Date of Interview:		*Total Time:*	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10	
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	❐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	❐
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	❐
	Optional			296.30-296.36 Recurrent	F33.x	❐
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1	❐
C	SUICIDALITY	Current (Past Month)	☐			❐
		Risk: ☐ Low ☐ Medium ☐ High				
D	MANIC EPISODE	Current	☐	296.00-296.06	F30.x-F31.9	❐
		Past	☐			
	HYPOMANIC EPISODE	Current	☐	296.80-296.89	F31.8-F31.9/F34.0	❐
		Past	☐			
E	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	❐
		Lifetime	☐			
F	AGORAPHOBIA	Current	☐	300.22	F40.00	❐
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1	❐
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	❐
I	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	❐
J	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	❐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	❐
K	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	❐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	❐
L	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	❐
		Current	☐	297.3/293.81/293.82/ 293.89/298.8/298.9		
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/	❐
		Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5 F31.8/F31.9/F39	❐
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	❐
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	❐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	❐

O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	☐
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2	☐

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es).

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **module**s identified by letters, each corresponding to a diagnostic category.
•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

David V Sheehan, M.D., M.B.A.
University of South Florida College of Medicine
3515 East Fletcher Avenue
Tampa, FL USA 33613-4788
tel : +1 813 974 4544; fax : +1 813 974 4575
e-mail : dsheehan@hsc.usf.edu

Yves Lecrubier, M.D. / Thierry Hergueta, M.S.
INSERM U302
Hôpital de la Salpétrière
47, boulevard de l'Hôpital
F. 75651 PARIS, FRANCE
tel : +33 (0) 1 42 16 16 59; fax : +33 (0) 1 45 85 28 00
e-mail : hergueta@ext.jussieu.fr

A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	➡ IS **A1** OR **A2** CODED **YES**?	NO	YES
A3	**Over the past two weeks, when you felt depressed or uninterested:**		
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF YES TO EITHER, CODE **YES**.	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES**?

NO **YES ***

MAJOR DEPRESSIVE EPISODE, CURRENT

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4, OTHERWISE MOVE TO MODULE B:

A4	a	During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?	NO	YES
	b	In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?		

NO **YES**

MAJOR DEPRESSIVE EPISODE, RECURRENT

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

B. DYSTHYMIA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	➡ NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	NO	➡ YES
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	➡ ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	NO	YES

B4	Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	**NO**	**YES**

DYSTHYMIA
CURRENT

D. (HYPO) MANIC EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF NO, CODE NO TO **D1b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
D2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **D2b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling persistently irritable?	NO	YES
		IS **D1a** OR **D2a** CODED **YES**? ➡	NO	YES

D3 IF **D1b** OR **D2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **D1b** AND **D2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

		Current Episode		Past Episode	
D3 (SUMMARY):	ARE 3 OR MORE **D3** ANSWERS CODED **YES** (OR 4 OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) AND **D1b** IS NO (IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE **D3** SYMPTOMS. VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.	NO	YES	➡ NO	YES
D4	Did these symptoms last at least a week **and** cause significant problems at home, at work, socially, or at school, **or** were you hospitalized for these problems?	NO ↓	YES ↓	NO ↓	YES ↓
	THE EPISODE EXPLORED WAS A:	❒ *HYPOMANIC EPISODE*	❒ *MANIC EPISODE*	❒ *HYPOMANIC EPISODE*	❒ *MANIC EPISODE*

IS **D4** CODED **NO**?

NO	YES
HYPOMANIC EPISODE	

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

CURRENT ❒
PAST ❒

IS **D4** CODED **YES**?

NO	YES
	MANIC EPISODE

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

CURRENT ❒
PAST ❒

E. PANIC DISORDER

(➡ MEANS : CIRCLE **NO** IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?	NO	YES
E4		**During the worst spell that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH **E3**, AND **4** OR MORE **E4** ANSWERS, CODED **YES**?	NO	YES *PANIC DISORDER LIFETIME*
		IF YES TO E5, SKIP TO E7.		
E6		IF **E5** = **NO**, ARE ANY E4 ANSWERS CODED **YES**?	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*
		THEN SKIP TO **F1**.		
E7		In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO	YES *PANIC DISORDER CURRENT*

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO	YES
	IF **F1** = **NO**, CIRCLE **NO** IN **F2**.		
F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO	YES *AGORAPHOBIA CURRENT*

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO YES
G2	Is this social fear excessive or unreasonable?	➡ NO YES
G3	Do you fear these social situations so much that you avoid them or suffer through them?	➡ NO YES
G4	Do these social fears disrupt your normal work or social functioning or cause you significant distress?	NO YES

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

EXAMPLES OF SUCH SOCIAL SITUATIONSTYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.

NO YES

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

H. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn't want to, or fearing you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **H4**
H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO **H4**
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES obsessions
H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES compulsions
	IS **H3** OR **H4** CODED YES?	➡ NO YES
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
H6	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	NO YES ***O.C.D.*** ***CURRENT***

J. ALCOHOL ABUSE AND DEPENDENCE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

		➡ NO	YES
J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?		

J2 **In the past 12 months**:

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF YES TO EITHER, CODE YES.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE 3 OR MORE J2 ANSWERS CODED YES?

NO **YES***

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

ALCOHOL DEPENDENCE
CURRENT

J3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE 1 OR MORE J3 ANSWERS CODED YES?

NO **N/A** **YES**

ALCOHOL ABUSE
CURRENT

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡ NO	YES
K1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?		

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED. ☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED) ☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE: _____

K2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? IF YES TO EITHER, CODE YES.	NO	YES
c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? NO YES

ARE 3 OR MORE **K2** ANSWERS CODED **YES**?

NO **YES ***

SPECIFY DRUG(S): _____

SUBSTANCE DEPENDENCE
CURRENT

* IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? NO YES

ARE 1 OR MORE **K3** ANSWERS CODED **YES**?

NO **N/A** **YES**

SPECIFY DRUG(S): _____

SUBSTANCE ABUSE
CURRENT

L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

Now I am going to ask you about unusual experiences that some people have. BIZARRE

L1 a Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NO YES YES
NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.

b **IF YES OR YES BIZARRE:** do you currently believe these things? NO YES YES →L6

L2 a Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking? NO YES YES

b **IF YES OR YES BIZARRE:** do you currently believe these things? NO YES YES →L6

L3 a Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? NO YES YES
CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.

b **IF YES OR YES BIZARRE:** do you currently believe these things? NO YES YES →L6

L4 a Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you? NO YES YES

b **IF YES OR YES BIZARRE:** do you currently believe these things? NO YES YES →L6

L5 a Have your relatives or friends ever considered any of your beliefs strange or unusual? NO YES YES
INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.

b **IF YES OR YES BIZARRE:** do they currently consider your beliefs strange? NO YES YES

L6 a Have you ever heard things other people couldn't hear, such as voices? NO YES
HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:

IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other? NO YES

b **IF YES OR YES BIZARRE TO L6a:** have you heard these things in the past month? NO YES YES →L8b
HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:
Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 a ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO YES
➡L13

IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **L1a** TO **L7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

LIFETIME

L12 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

CURRENT

L13 ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L6b, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS FROM L1b TO L10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

L14 IS L13 CODED **YES**

OR

ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L6a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS FROM L1a TO L7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

O. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO ➡	YES
	b	Are these worries present most days?	NO ➡	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES ➡
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO ➡	YES
O3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE 3 OR MORE O3 ANSWERS CODED **YES**?

NO	YES
	GENERALIZED ANXIETY DISORDER **CURRENT**