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Review article

Neuropsychological aspects of Tourette syndrome: A review

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Abstract

Tourette syndrome (TS) is assumed to result from frontostriatal dysfunction, which would be expected to result in impairments in neuropsychological functions. This possibility has been explored in a number of studies that have assessed the performance of patients with TS within major cognitive domains and on tests involving executive functioning. We aim to summarize the main findings of these studies while evaluating the influence of task limitations and potentially critical confounding factors such as the presence of comorbidity. Although there is clearly a need for improved study design, we tentatively suggest that there is considerable evidence for cognitive impairment in a subgroup of patients, and that some difficulties seem to be intrinsic to TS. These impairments may reflect dysfunction of the anterior cingulate network within the frontostriatal pathway.

Keywords: Tourette syndrome; Neuropsychology; Executive functions; Cognition

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder that is most commonly diagnosed in childhood or early adolescence [1]. The core symptoms of TS include multiple motor tics and one or more phonic tics, which last for more than a year. The tics may be simple or complex in nature and vary in number, frequency, and severity over time. Comorbid disorders include anxiety, depression, learning difficulties, and sleep disorders, although attention deficit/hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) are most common [2].

Tics may reflect changes in striatal functioning [3], and studies of patients with TS have indicated structural changes within the basal ganglia such as decreased volume of the left side of the caudate, putamen, and globus pallidus [4], and decreased striatal metabolism [5]. Striatal changes may result in dysfunction within frontostriatal circuits, which are formed through connections between the striatum and different regions of the frontal cortex [6]. Dysfunction within circuits involving cortical motor regions is likely to lead to tics. However, three of these parallel circuits involve frontal areas that are likely to subserve cognitive functions—the lateral orbitofrontal cortex, the dorsolateral prefrontal cortex, and the anterior cingulate cortex—and dysfunction within these circuits may lead to cognitive impairments [7]. Support for frontal dysfunction in TS has been provided by studies indicating changes in the activity and metabolism of this region [5,8,9].

Frontostriatal dysfunction has been associated with significant deficits in cognitive functions in other disorders of the basal ganglia such as Parkinson's disease [10–12] and Huntington's disease [13,14]. A considerable number of studies have similarly shown patients with TS to have related cognitive impairments. However, the exact nature of the

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deficits attributable to TS, rather than to comorbid disorders, has yet to be elucidated.

This review will summarize findings in core domains (visual perceptual, motor, attention, memory, and learning) and will then discuss patients' performance on tasks involving higher cognitive or executive functions (working memory, fluency, planning, shifting, and inhibition). The discussion will focus on the possible implications of patients' deficits on dysfunction within three specific frontostriatal pathways involving the dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices. The dorsolateral prefrontal cortex is implicated in cognitive flexibility [15], memory [16], and attentional processes [17]; orbitofrontal dysfunction is more selectively associated with deficits in reinforcement and reversal learning tasks [18]; and the anterior cingulate cortex is important for conflict monitoring and resolution [19] and is active during tasks involving response inhibition [20].

Recent factor analytic studies [21] have shown that there may be more than one TS phenotype. Among these, the "pure TS" phenotype (patients with "uncomplicated" TS, i.e., without comorbid psychiatric conditions) has been consistently replicated [2,22,23] and accounts for about 10% of patients diagnosed with TS in both community [24] and clinical [25] settings. Due to the high rates of comorbidity in TS, many studies have included patients with symptoms of ADHD or OCD. Patients with ADHD alone may exhibit deficits in response inhibition [26], working memory [27], and cognitive flexibility [28], while OCD has been associated with poor reversal learning [29] in addition to inhibitory dysfunction [30]. Special attention has been paid to the issue of comorbidity, although we will consider the potential influence of other sample and task limitations. Despite these difficulties, some preliminary conclusions about the nature and basis of cognitive impairment in TS can be drawn.

Perceptual, motor, and visuomotor performance

The most relevant studies providing support for difficulties in fine-motor, perceptual, and visuomotor skills are shown in Table 1. A number of studies have reported that children with TS exhibit deficits in visuomotor integration skills based on performance on the Beery Visual Motor Integration Test (Beery VMI) [31], although one study reported no impairment [32]. Furthermore, some of these studies have indicated that patients' deficits are unlikely to be due to comorbid ADHD [33,34]. The results of studies that have assessed performance on design-copying tasks, such as the Rey Osterreith Complex Figure Test (ROCFT), are more varied. Harris et al. [35] found evidence for a deficit in children with TS and comorbid ADHD, but not in those with TS only. In contrast, another study [34] showed that TS patients without ADHD exhibited impairment similar to the impairment exhibited by those with comorbid ADHD, and that these difficulties were unrelated to poor attention or motor inhibition. Other studies, however, failed to reveal significant deficits in groups of TS patients, including "uncomplicated" cases [32,33,36].

Poor performance on visuomotor integration tasks could reflect deficits in either the component skills that contribute to task performance or the combination of these abilities; thus, research has addressed performance within perceptual and motor domains. In a study of monozygotic twins, Randolph et al. [36] found that greater tic severity was associated with poorer performance on a face perception task. However, the children with TS in this study did not exhibit deficits on a block-design task, and comorbid ADHD may have influenced some patients' performance. Children with TS also performed poorly on a motor free visual perception test in one study [37], and there are also indications of perceptual deficits on performance IQ tests in children [38] and adults [39] with TS. Other studies have reported intact performance on perceptual integration [35] and line orientation [31] tasks.

There is stronger evidence of disrupted motor performance in TS. While research has revealed little evidence of changes in motor speed performance during finger-tapping tasks [40–42], many studies have highlighted impairments in motor skills on the Purdue Pegboard [33,36,43], but few have controlled for comorbid ADHD [33,34]. Subjects with TS have also been shown to perform poorly on the Grooved Pegboard [40,42], although one study [31] found only a trend for poorer performance in the TS group. These motor impairments are perhaps likely to reflect basal ganglia dysfunction, and some similar deficits have been reported in Parkinson's disease [44]. Schultz et al. [34] suggested that deficits in TS on these tasks could lie in the synthesis of perceptual and motor inputs, whereas Margolis et al. [43] suggested that poor performance may reflect poor motor integration across the hemispheres, and that changes in interhemispheric connectivity in TS may also explain the increased corpus callosum sizes exhibited by their patient sample. Support for this claim may be provided by other studies that have reported abnormalities of the corpus callosum in TS [45].

In summary, the evidence for deficits in perceptual processes in "uncomplicated" TS is certainly limited, and while difficulties in motor skills may contribute to impairments reported on visuomotor integration tasks, further research is needed to establish whether such difficulties are independent of comorbid ADHD.

Attention

A number of studies have provided evidence for the presence of attentional deficits in TS, and the most relevant findings are listed in Table 2. The presence of comorbid ADHD plays a central role in the investigation of possible attentional impairment in TS. Channon et al. [46] found

Table 1
Studies providing evidence of possible perceptual, motor, and visuomotor deficits in TS

Study	Test(s)	Sample	Comorbidity controlled for?
Randolph et al. [36]	Face perception Purdue Pegboard	8 TS (including 8 TS+ADHD)	No
Shapiro et al. [38]	Performance IQ	50 TS (22 children and 28 adults)	No
Sutherland et al. [39]	Performance IQ	32 TS	No
Harris et al. [35]	ROCFT	10 TS and 32 TS+ADHD	No
Schultz et al. [34]	Purdue Pegboard Beery VMI ROCFT	50 TS (including 34 TS+ADHD and 6 TS+OCD)	Analyzed
Brookshire et al. [31]	Beery VMI	31 TS	No
Bloch et al. [33]	Beery VMI	32 TS (including 9 TS+OCD)	Ex+ADHD
Margolis et al. [43]	Purdue Pegboard	38 TS (including 14 TS+OCD, 2 TS+ADHD, and 2 TS+ADHD+OCD	No
Bornstein [41]	Grooved Pegboard	36 TS	No
Bornstein et al. [42]	Grooved Pegboard	28 TS	Ex+ADHD

TS+ADHD, subjects with TS and comorbid ADHD; TS+OCD, subjects with TS and comorbid OCD; Ex+ADHD, excluded subjects with TS and comorbid ADHD.

that a group of adults with TS performed poorly on attentional tasks including the Trail Making Test (TMT), a serial addition task, and a vigilance test, in comparison to control subjects with an equivalent IQ. However, they failed to screen for comorbid ADHD. Another study [47] reported significant deficits on both the TMT and the Speech Sounds Perception Test (SSPT) compared to normative data, but almost half of the children and adolescents tested exhibited ADHD in addition to TS. Silverstein et al. [48] found no evidence that TS patients without ADHD were worse on the TMT in comparison to controls, but showed that this comorbid disorder had a detrimental effect on performance. Other studies have failed to find evidence of attentional deficits in TS [42,49] even in patients with comorbid ADHD [50]. However, Chang et al. [32] found evidence of poor performance on a test of spatial attention in TS even after controlling for ADHD. Other findings indicate that tasks involving sustained attention may be more sensitive to impairment in TS, and they have revealed deficits on continuous performance tasks [35,51]. While Sherman et al. [52] reported that deficits were uncommon in TS alone and more evident in patients with comorbid ADHD, another study provided evidence that impairment on the Test of Variables of Attention task may be present in patients without comorbid ADHD [53]. Overall, however, it is difficult to conclude that "uncomplicated" TS is reliably associated with attentional difficulties when most findings may have been influenced by comorbidity.

Additional drawbacks may lie in the use of measures such as the TMT. Shucard et al. [51] suggested that the face and construct validities of measures such as the SSPT and the TMT are questionable, and it is difficult to specify the cause of impaired performance due to the possible influence of factors such as motor speed and cognitive flexibility [54]. In any case, attentional deficits in TS may be subtle or difficult to detect. In a study using event-related potential, Johannes et al. [55] showed that although children and adults with TS showed normal behavioral performance on a dual-performance task, they demonstrated evidence of increased attention to irrelevant stimuli. The same authors noted that interference from irrelevant stimuli could arise due to inhibitory, rather than attentional, deficits. The influence of these subtle attentional problems on performance in tasks assessing inhibitory ability, set shifting, memory, or learning clearly merits further investigation.

Table 2
Studies providing evidence of possible attentional deficits in TS

Study	Test(s)	Sample	Comorbidity controlled for?
Channon et al. [46]	TMT Serial addition Vigilance test	19 TS	No
Bornstein and Yang [47]	TMT SSPT	96 TS	No
Chang et al. [32]	Spatial attention: finger windows	15 TS	Analyzed
Harris et al. [35]	Continuous performance task	10 TS and 32 TS+ADHD	No
Shucard et al. [51]	Continuous performance task	22 TS	No
Sherman et al. [52]	Continuous performance task	74 TS (uncomplicated), 14 TS+ADHD, and 21 ADHD	Yes
Silverstein et al. [48]	TMT span of apprehension task	17 TS (including 6 TS+ADHD) and 17 ADHD	Analyzed

Memory, learning, and decision making

Key studies highlighting the presence of memory deficits have been summarized in Table 3. Evidence for deficits on measures of visual memory performance in TS was provided by Watkins et al. [56], who reported spatial recognition memory deficits in a group of 20 TS patients, among whom only 3 TS patients exhibited comorbid ADHD. Another study found evidence of poor performance on a design-recall task in 32 adolescents with TS [39], and Bornstein [41] reported that adults with TS exhibited evidence of impairment on the logical memory subtest of the Weschler Memory Scale—Revised (WMS-R), although differences were not significant after correction. Studies have provided equivocal evidence for deficits in verbal memory recall. Channon et al. [57] found little evidence of poor story recall in children with "uncomplicated" TS, and apparent impairments on a word list learning test were considered insignificant. However, another study by Channon et al. [58] did report evidence of memory impairments in an "uncomplicated" sample of adults with TS who demonstrated poor strategic encoding or retrieval when tested immediately or after a delay.

Perhaps the most comprehensive study of memory in TS was carried out by Stebbins et al. [59] in adults without ADHD. Deficits in strategic and procedural memory were apparent based on TS patients' performance on a rotary pursuit task. Immediate and semantic memory, however, appeared to be intact. These authors concluded that the main performance deficit in TS may be reflected on measures of effortful or strategic cognitive function, which could explain the variation in performance across studies. Some impairments on memory measures, such as increased intrusions during recall on a word list learning task [60], are perhaps more likely to reflect deficits in inhibitory, rather than memory, processes.

Memory processes may contribute to performance on learning tasks, although few studies have addressed potential changes in learning or decision-making processes in TS. One study, however [61], yielded interesting findings. Patients performed poorly on a weather prediction task that involved stimulus response associations, and they exhibited impairments in declarative learning. A wide age range was assessed, and comorbidities did not appear to influence patients' apparent deficit. However, the rate of patients' learning was found to correlate inversely with tics, indicating a possible role for symptom severity. Other studies have looked at object alternation learning in TS, which is considered to involve switching, so a summary of these findings is provided in Shifting and cognitive flexibility. Finally, Crawford et al. [62] found normal performance on a gambling task in 20 adolescents with "uncomplicated" TS.

In conclusion, patients with "uncomplicated" TS may exhibit some subtle changes in strategic memory, but more general deficits are likely to be attributable to comorbid conditions such as ADHD.

Executive function

Tests of executive function assess higher cognitive abilities such as working memory and response inhibition. Studies providing evidence of possible executive deficits in TS are shown in Table 4. Many executive tasks are thought to involve the dorsolateral prefrontal and anterior cingulate cortices, while the orbitofrontal cortex is most likely to contribute to performance on tasks involving reward-related learning [63]. Patients with other disorders involving frontostriatal dysfunction, such as Parkinson's disease and Huntington's disease, may exhibit deficits on tasks involving planning, shifting, and working memory [10–14]. Reports of increased dysexecutive behavior in everyday life in TS [62] encourage further investigation.

Working memory

Studies of patients with "uncomplicated" TS have yielded little evidence of deficits in verbal working memory on the n-back task in children [62] and adults [64]. Similarly, performance on time estimation and digit span tests in a large group of adults with TS was found to be intact [65]. However, Chang et al. [32] showed that children with TS performed poorly on auditory consonant trigrams in comparison to controls and patients with OCD after controlling for ADHD. Although working memory deficits are not always present in samples of TS with high rates of comorbidity [66], comorbid ADHD may make an important contribution to working memory impairment in TS [67]. Although Goudriaan et al. [65] found no deficits in visual working memory on the Benton visual recognition test in an

Table 3
Studies providing evidence of possible memory deficits in TS

Study	Test(s)	Sample	Comorbidity controlled for?
Watkins et al. [56]	Spatial recognition (Cambridge Neuropsychological Test Automated Battery)	20 TS (including 3 TS+ADHD)	Ex+OCD
Sutherland et al. [39]	Design recall	32 TS	No
Bornstein [41]	Logical memory subtest (WMS-R)	36 TS	No
Channon et al. [58]	Story recall	21 TS (uncomplicated)	Yes
Stebbins et al. [59]	Strategic and procedural memory (rotary pursuit)	13 TS	Ex+ADHD

Ex+OCD, excluded subjects with TS and comorbid OCD.

Table 4
Studies providing evidence of possible executive deficits in TS

Domain	Study	Test(s)	Sample	Comorbidity controlled for?
Working memory	Chang et al. [32]	Auditory consonant trigrams	15 TS	No
	Stebbins et al. [59]	Word recall: trials items (not span)	13 TS	Ex+ADHD
	Channon et al. [46]	Visuospatial: Corsi blocks	19 TS	No
Fluency	Bornstein [40]	Verbal	100 TS	No
	Sutherland et al. [39]	Verbal	32 TS	No
	Schuerholz et al. [53]	Letter/word	65 TS	Analyzed
Shifting	Watkins et al. [56]	Set switching	20 TS (including 3 TS+ADHD)	Ex+OCD
Inhibition	Baron-Cohen et al. [81]	Motor: hand game Hand game Verbal: yes/no game	15 TS	No
	Muller et al. [79]	Motor: GNG	14 TS (including TS+OCD)	Ex+ADHD
	Verte et al. [68]	Motor: change/stop task (circle drawing)	24 TS (including 6 TS+ADHD, 8 TS+OCD, and 8 TS+ADHD+OCD)	No
	Goudriaan et al. [65]	Motor: change/stop task	6 TS (including 2 TS+ADHD and 10 TS+OCD)	No
	Crawford et al. [62]	Motor: flanker test Verbal: Hayling test	20 TS (uncomplicated)	Yes
	Channon et al. [58]	Verbal: Hayling test	21 TS (uncomplicated)	Yes
	Channon et al. [64]	Verbal: Hayling test	20 TS (uncomplicated)	Yes

adult TS group with a low prevalence of OCD and ADHD, Verte et al. [68] reported that TS was a good predictor of visual working memory on this task and the Corsi blocks test in children with TS, although not above comorbid ADHD. Comorbidity may also have played a role in a study by Channon et al. [46], who found a significant deficit in performance on the Corsi blocks test in a group of adults with TS who were not screened for comorbidity. Some evidence of impairment on tasks of spatial memory has been reported in TS patients without comorbid ADHD [59], although patients' spans were not significantly poorer than controls'. It would appear that any impairment exhibited by patients with TS is likely to be subtle and most apparent on visual or spatial working memory tasks, although it is difficult to conclude that any such deficit is independent of comorbidity.

Verbal fluency

Some studies that have assessed verbal fluency in TS have revealed possible impairment in children and adolescents [39,40] and in adults [41], although the presence of comorbidities may have influenced patient performance. However, although studies have revealed that comorbid ADHD may be associated with impairments [60,68,69], TS may still be a good predictor of poor verbal fluency performance [68]. In addition, Schuerholz [69] showed that girls with TS and no ADHD exhibited impaired performance on a letter fluency task in comparison to controls, and other studies provided evidence of deficits in "uncomplicated" patients [53]. Other studies reported no evidence of deficits [57,59]. Despite evidence of fluency deficits that appear unrelated to comorbid conditions, the evidence for a broad and consistent deficit in fluency in TS is further weakened by results from two studies that included measures of semantic fluency and reported no difficulties [56,65]. It may be that any reported verbal fluency deficit in TS is associated with inhibitory dysfunction, which could lead to a reduction in the cognitive resources available for word generation.

Planning and multitasking

Numerous studies have assessed performance on planning tasks such as the Tower of London test [56] or the Tower of Hanoi test [70] and reported no deficit. Both children [68] and adults [65] have been shown to perform within normal limits. Similarly, the possibility of difficulties with multitasking in "uncomplicated" cases of TS also appears unlikely [58,71]. However, comorbid ADHD has been shown to be a factor in TS patients that may impair planning [67] or multitasking [57] performance.

Shifting and cognitive flexibility

Switching or shifting deficits appear uncommon in TS on tasks involving object alternation [32,64], and "uncomplicated" patients have demonstrated intact performance on a letter-and-digit-naming task [64]. Deficits may also be unapparent in samples of patients with TS in which comorbid ADHD is common [50], although this factor may contribute to impairment [67]. One exception to this pattern was reported by Watkins et al. [56], who found evidence for poor extradimensional shifting on a set-shifting task in a group of patients with a low prevalence of comorbid ADHD.

Many studies that used the Wisconsin Card Sorting Test (WCST) have reported intact performance in samples of children and adolescents with TS, including those samples containing patients with comorbidities such as ADHD and OCD [39,40,47,57,70,72] and adults with "uncomplicated" TS [58,71]. Harris et al. [35] noted that while children with TS alone did perform poorly on the WCST, these

impairments were too mild to reach significance, and Bornstein [73] found that the presence of OCD symptoms may be more likely to lead to impairment. Deficits on the WCST have been linked to dorsolateral prefrontal damage [74], so reports of intact performance on this measure may indicate that dorsolateral prefrontal dysfunction is unlikely in TS. However, although it may appear unlikely that TS is associated with deficits in cognitive flexibility according to performance on the WCST, some authors [75] have pointed out difficulties with this measure, such that it may not be sensitive enough to indicate the presence of subtle deficits. In summary, however, there is no substantial evidence that patients with "uncomplicated" TS exhibit poor cognitive flexibility.

Inhibition

Inhibition is a central issue in TS because of the nature of patients' involuntary movements and utterances. The assessment of inhibitory function in TS is complicated by the fact that "inhibition" is not a unitary construct, and there may be separable facets of this cognitive function with different underlying neural substrates.

Many studies have used tasks that require inhibition of a motor response. Most tasks addressing performance on the Go–No Go (GNG) task have revealed no deficits in "uncomplicated" TS patients [76,77] or in patients with comorbidities [78]. Contrasting findings were reported by Muller et al. [79], who did find evidence of poor performance on the GNG in a group of 14 patients. TS patients made more commission errors on the task, and the authors suggested that this provided evidence of deficits in response inhibition, as patients performed well on attentional measures. However, some of these patients had comorbid OCD, which may make an important contribution to deficits on this task, as another study found that patients with OCD exhibit deficits in comparison to controls and patients with "uncomplicated" TS [56].

Although Serrien et al. [80] failed to find a performance deficit on the GNG, TS patients were found to exhibit increased activity in a frontomesial network when compared to controls. This network was also active during tic suppression. Serrien et al. suggested that these findings indicate decreased inhibitory control in TS, which leads to compensatory increases in brain activity. Although only a small group (n=9) of patients was tested (among whom two presented with comorbidities), these findings may be particularly important because the suggested compensatory tic mechanisms have the potential to confound study findings [76].

Other evidence of inhibitory impairment has been reported in children with TS playing Luria's hand game [81] and during circle drawing and a change task, in association with comorbid OCD or ADHD [68]. Goudriaan et al. [65] tested 46 patients (among whom only 2 patients had comorbid ADHD) and also found evidence of slower stop signal reaction times in the TS sample in comparison to controls, although this group of patients did not exhibit a deficit on the circle-drawing task. Another study reported impaired performance on incompatible trials of a flanker test in "uncomplicated" TS [62]. A later study, however, failed to replicate these findings in a group of adults with "uncomplicated" TS [64].

Performance on some inhibitory tasks, such as the Stroop test, requires the inhibition of verbal response. Children [32,50,70] and adults [46,65] with TS tend to perform well on this task even when comorbidities are present. However, Baron-Cohen et al. [81] reported deficits on a yes/no inhibition task in children with TS, and reports of a deficit on the Hayling test are particularly persuasive. Channon et al. [58,64] showed that both adults and children [62] with "uncomplicated" TS tend to exhibit deficits on this test, although comorbid ADHD may further impair performance [57]. Impairment on the Hayling test may implicate the involvement of the frontostriatal circuit involving the anterior cingulate cortex [82]. However, the patient's choice of strategy is likely to influence performance on this task, and Crawford et al. [62] suggested that impairments may reflect deficits in verbal or conceptual processes.

Inhibitory dysfunction in TS was also reported by Mahone et al. [60], who found evidence of intrusions during list learning in patients with TS and ADHD, and by Ozonoff et al. [83], who found evidence for reduced inhibition on a negative priming task in youths with TS and comorbidities. In this study, patients without comorbidities performed similarly to controls. Such findings suggested that it is important to control for symptoms associated with ADHD when investigating inhibitory impairment in TS. While the symptoms of ADHD may be more likely to be associated with motor inhibitory difficulty, it may be postulated that any influence of obsessive–compulsive symptoms may affect cognitive inhibitory processes, as poor inhibition of cognition may contribute to rumination, obsessional thoughts, or intrusive thoughts.

In conclusion, deficits on the Hayling test in patients with "uncomplicated" TS appear consistent enough to suggest that TS is associated with alterations in inhibitory functioning independent of comorbid ADHD, although these impairments may only be apparent on particular measures.

Study limitations

Problems with measures

If patients do exhibit deficits in fundamental cognitive functions such as learning or memory, it is clear that these difficulties could affect performance in a range of tasks. Patients may perform more poorly on complex tasks because they involve several executive components, and if patients have even subtle deficits in multiple components, these could contribute to impaired performance. For example, it is

possible that TS patients' poor performance on shifting or memory tasks may at least partly occur in association with a degree of inhibitory dysfunction. The exact skills being assessed should therefore be carefully defined and task requirements should be carefully considered in order to encourage the specification of the exact nature of any impairment detected.

Further difficulties may derive from an evaluation of task performance through the use of normative data rather than the inclusion of a matched control group, an approach adopted by some earlier studies [37,39]. Schultz et al. [34] cautioned that these norms may be obtained without careful control of factors such as the representation of different levels of IQ and socioeconomic status, and that the values generated tend to reflect participants' performance on a single test; thus, they may pose an unfair comparison for patient groups that undertake a battery of tasks and are likely to be influenced by factors such as fatigue.

Confounding factors affecting patients

The presence of confounding factors may help to explain the inconsistent performance of patients on different tasks within the same domain. There is also considerable variation in patient performance within a single group of test subjects [46], and it is usually the case that only a subgroup of patients scores well below control scores. The severity of tics characteristically waxes and wanes in patients with TS, which may be reflected in fluctuating cognitive performance and may help to explain some of the inconsistent findings across neuropsychological studies. Moreover, in subjects with severe symptoms, conscious tic suppression or other underlying factors may influence cognitive functioning. However, perhaps counterintuitively, reports of compensatory changes in neurological functioning that may derive from tic suppression [80] suggest that some changes could actually enhance performance on certain tasks. In fact, Bornstein et al. [42] reported that the presence of neuropsychological abnormalities in TS may be inversely related to symptom severity. Other studies have shown greater impairment in negative priming [83] and performance on the Hayling test [64] in association with greater symptom severity. Shucard et al. [51] found that the severity of complex vocal tics was predictive of reaction time on a continuous performance test (attention), and age of onset [41] or simply the presence of complex tics may be of potential importance for fine-motor ability [40]. As TS symptoms tend to decrease with age, disease chronicity should be investigated as a possible contributing factor to neuropsychological performance. There have been few longitudinal studies, and such an approach could prove informative [84].

The general influence of age on neuropsychological performance in TS is hard to determine, as while many studies have tested children or adolescents, relatively few studies have included adult samples, and studies do not tend to directly compare the performance of children and the performance of adults on the same tasks. Channon et al. [64] suggested that, in general, it may be easier to detect deficits in "uncomplicated" TS in children, rather than in adults. This may be for a number of reasons. Firstly, greater symptom severity in younger patients [85] may reflect greater frontostriatal dysfunction that leads to more significant cognitive impairment. Secondly, the effect of ADHD may be more marked in samples of children with TS, as it is likely that many patients with this comorbid disorder will show improvement with age [86]. Thirdly, it has been suggested that compensatory mechanisms (neural and otherwise) may develop with age and reduce performance decrements on certain tasks such as those involving response inhibition [76].

Although most researchers control for age and IQ, other potentially important factors, such as medication use, may not be evaluated. Some studies have excluded subjects currently taking medications [68], while others have performed within comparisons. In principle, medication could either enhance or impair performance. Bornstein [41] reported that medication use may be associated with poorer performance on a measure of verbal intelligence, although this finding was not deemed significant overall, and Channon et al. [57] found that patients performed better on a habit-learning task if they were taking neuroleptics. Other studies, however, have found no effect of medication on neuropsychological performance [37,47].

There is greater evidence of the impact of the presence of comorbidity on performance, and children with TS and ADHD or OCD often exhibit greater neuropsychological deficits [67]. Children with ADHD alone exhibit deficits on the Stroop, GNG, and conflicting response tasks [87], and OCD may be associated with poor recognition memory and inhibitory deficits on the GNG [56]. Studies have shown that, in patients with TS, comorbid ADHD may exacerbate deficits on tasks involving working memory [68], inhibition [57], and visuomotor integration [35], and patients with TS and comorbid ADHD exhibit impairment on tasks assessing planning and multitasking, while TS patients without ADHD do not [67,68].

Many researchers have failed to recognize the potential significance of comorbid conditions in relation to task performance, so many early studies did not adequately evaluate comorbidity [31,36,39,41], although a few investigations did differentiate between TS with ADHD and TS without ADHD [35,36]. On the whole, only more recent studies have attempted to control for any possible influence of comorbid ADHD on task performance [32,33,57,58,62,64]. Controlling for the influence of comorbidity could be particularly difficult if even subthreshold symptoms of disorders such as ADHD are associated with decrements in task performance. However, it may be argued that since the vast majority of patients with TS have comorbidities [25], focusing on cases of "uncomplicated" TS might not be informatory about TS as a whole.

Conclusions

The cognitive deficits exhibited by patients with TS are clearly not as striking as those shown by other patient groups with frontostriatal dysfunction [88], such as patients with Parkinson's disease or Huntington's disease. This may be because these disorders reflect different patterns of dysfunction affecting different frontostriatal pathways, in addition to the fact that the latter two disorders are degenerative and TS is not. Bornstein [41] suggested that a subgroup comprising approximately 20% of patients may exhibit impaired neuropsychological performance. There is, however, considerable evidence for deficits on tasks involving motor skills and visuomotor integration in TS, and reports of psychomotor slowing may extend to general cognitive slowing [89]. While evidence of motor sequencing deficits in TS [90] may implicate dysfunction of the dorsolateral prefrontal circuitry [91], the presence of such impairments is indeed debatable [92]. There is equivocal evidence for deficits in other abilities linked to dorsolateral prefrontal functioning such as fluency [93], planning [94], working memory [6], and cognitive flexibility [74], indicating that, overall, "uncomplicated" TS is unlikely to involve significant dysfunction within frontostriatal pathways involving this region. Indeed, it is unclear whether the reported deficits on these tasks, and on memory and attentional performance, are specifically attributable to TS due to the fact that so many of the samples tested contained patients with comorbidities. The adoption of a more conservative approach that rests on findings from studies of "uncomplicated" patients would lead to the conclusion that the only robust evidence of significant impairment revealed so far is in inhibitory performance on certain tasks.

One measure that may be particularly sensitive to "uncomplicated" TS is the Hayling test [95]. During each trial of this task, participants are asked to say a word to complete a sentence that is read to them. Each sentence strongly cues a particular word (e.g., "the dog chased the cat up the…"). The initiation (or baseline) section simply requires a word that "fits" the sentence, so participants can respond with the strongly cued word. For the inhibition section, the original version of the task instructs participants to simply complete the sentence with an unrelated word, although the participant may also be told that this word still makes sense. This task therefore requires the inhibition of a prepotent verbal response. However, Crawford et al. [62] noted that poor strategy use, as well as impaired automatic or inhibitory processes, could lead to poor performance on this task. Deficits in strategic or effortful processes, as suggested by Stebbins et al. [59], may not only account for their reported pattern of memory performance in TS but also account for deficits on tests such as the Hayling test, as found by Crawford et al. [62] and Channon et al. [58,64]. Such deficits would explain why patients may exhibit impairments on this inhibitory measure, but not on others (such as the Stroop test), and on the amount of variation apparent in performance across tasks and studies.

The Hayling test is associated with activity in the anterior cingulate cortex [82,96], as are the GNG task [97] and fluency tasks [92], which may also elicit impairment in TS. The anterior cingulate pathways may make an important contribution to performance on many tasks through inhibitory, attentional, and intentional processes, and are thought to be involved in response conflict processes and action monitoring [63,98]. There are reports of neurobiological changes in TS involving this region [99] that are possibly related to mild impairments in crucial attentional and inhibitory processes, which in turn contribute to the intermittent pattern of deficits observed on many tasks. We may tentatively conclude that while changes in dorsolateral prefrontal circuitry may lead to the greater executive deficits associated with symptoms of ADHD and while dysfunction of orbitofrontal circuitry may occur in OCD [100], dysfunction of the anterior cingulate circuit may lead to subtle, although significant, signs of higher cognitive impairment in TS.

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