

Are Motor Skills and Motor Inhibitions Impaired in Tourette Syndrome? A Review

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ABSTRACT: Tourette syndrome (TS) is a neurodevelopmental motor disorder described as an inability to inhibit unwanted motor movements. This article reviews research on the execution and inhibition of voluntary motor movements in TS. Over last two decades, a number of studies have addressed the structural and functional deficits associated with this syndrome. Only a limited number of studies have assessed the motor skills in these patients but have failed to reach any conclusive outcome. In the domain of response inhibition also, studies have reported arguable impairments in these patients. It is suggested that these conflicting results can be attributed to co-occurring comorbid conditions, the constraints posed by variable age groups, lack of control measures, and lack of specificity of domains addressed. This review will describe a way in which future research can be directed to increase our knowledge of this otherwise complex spectrum of disorders.

KEYWORDS: Tourette syndrome, voluntary motor movements, motor skills

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Introduction

Tourette syndrome (TS) is a disorder of childhood onset characterized by chronic motor and phonic tics. Tics are sudden, involuntary, recurrent, nonrhythmic motor movements or vocalizations occurring for a limited duration. Motor tics can be simple or complex, ranging from repetitive movements to coordinated action sequences. Verbal tics range from simple throat clearing to whole phrases, including repeated words or utterances, producing inappropriate or obscene utterances (coprolalia). TS is characterized by multiple motor tics and at least one vocal tic that persist for at least 1 year. The frequency, severity, and pattern of these tics often fluctuate over time. Along with these characteristic tics, TS is often marked by the presence of a number of co-occurring or comorbid conditions. These comorbid conditions include attention deficit hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD) and psychopathologies such as depression, anxiety, and other emotional dysregulations.¹ The prevalence estimates of TS in school-age children range from 1 to 10 per 1000 in the majority of cultures of the world. On account of the high prevalence rate and the wide spectrum of symptoms, TS gained momentum in empirical research, which was once considered to be a rare condition.

The fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in May 2013, classified Tourette's syndrome as a motor disorder that is listed

in the neurodevelopmental disorder category. Considering tics as an inability to inhibit unwanted motor movements, the question arises whether or not the intended voluntary movements are affected in TS.

The voluntary movements are the organized behavior responsible for the performance of a purposeful task. The motor movements reflect the capabilities of the motor systems to plan, coordinate, execute, and inhibit movements. The motor areas of the cerebral cortex integrate visual, proprioceptive, and other information to produce elaborate voluntary movements. Recent imaging studies in TS implicated structural and functional changes in different parts of cortico-striato-thalamocortical (CSTC) neural circuitry, projecting from diverse cortical areas to the basal ganglia, through the thalamus, and back to the cortex. Specifically, dysfunctions involving motor cortical areas are implicated in TS: for example, the heightened activation in premotor cortex and supplementary motor area,^{2–4} which are the key regions involved in planning and coordinating temporal sequences of action.⁵ Numerous studies have reported the structural and functional alterations in the motor networks in patients with TS. However, only a limited number of studies have assessed the manifestations of these deficits in the execution or inhibition of motor movements in this clinical population. The purpose of this article is to evaluate the current knowledge about the motor activity in clinical population with TS.



The aim of this review is to examine the current literature on motor activity in patients with TS in order to identify assessment procedures used to evaluate motor network alterations and to also discuss factors that probably contribute to the inconsistent findings among patients who suffer from this complex spectrum of disorder.

Methods

A PubMed literature search was performed of all articles from the year 1995 onward with the following terms: “motor movements”, “movement inhibition”, and “fine motor movements”. Inclusion criteria were studies on children and adults with TS. The titles and abstracts of all retrieved articles were reviewed, and papers that did not meet the above-mentioned criterion were excluded. In addition, a manual search was performed on the basis of the references found in the articles retrieved from PubMed.

Assessment Procedure

Each potentially relevant publication was then classified according to the patient sample, the assessment procedure used, and its aim. The majority of articles were investigations on the motor activity, while very few studies explored the execution of motor movement in terms of fine motor movements.

Motor Movement Execution

Motor skills are movements and actions of the muscles. Typically, these are categorized into two groups: gross motor skills and fine motor skills. Gross motor skills are involved in the movement and coordination of the arms, legs, and other large body parts. These participate in actions such as running, crawling, swimming, etc. Fine motor skills are involved in smaller movements that occur in the wrists, hands, fingers, feet, and toes. These participate in smaller actions such as picking up objects between the thumb and finger, writing carefully, and even blinking. The successful execution of a movement involves fine coordination of muscles.

The implication of primary motor structures in recent neuroimaging studies, along with the feature of tics as motor symptoms, would suggest that fine motor skills are impaired in patients with TS.^{6–8} On the other hand, clinical observations show that patients are able to suppress their tics during tasks requiring a certain degree of focused attention; for example, tics are often reported to be reduced while playing sports or music. Patients with TS are found among top athletes, professional piano players, and neurosurgeons. However, only a limited number of studies have investigated motor skills in patients with TS. There are eight studies in literature that directly assessed fine motor movements in this clinical population. Some of these studies found evidences of motor skill weakness and supported the presence of fine motor movement deficits.^{9–13} On the other hand, other studies reported contrary results (see Table 1).^{14–16}

The contrasting results of these studies can be due to the variations in the parameters studied. First, these studies have tried to assess the motor skill deficits using a variety of behavioral tasks, for instance, Purdue Pegboard, Beery Visual-Motor Integration (VMI) Test, the Rey–Osterreith Complex Figure Task (RCFT), finger tapping task, etc. These tasks markedly differ in the cognitive demands, mechanisms, and psychological processes involved. The reported inconsistency might also be due to different aspects of motor performance that was measured in the single studies, including visuo-motor integration and gross and fine motor skills. For example, Nomura et al¹² examined gross motor movements in patients with TS and reported slowness and clumsiness in movements while performing rapid alternations between inward and outward rotation of the arms (known as pronation and supination, respectively). However, skills needed to perform simple motor speed tasks seemed to be unimpaired in the patients with TS.¹⁵ In addition, Neuner et al¹¹ reported that fine motor skills in adult patients were task-dependent and found that steadiness and visuo-motor integration of fine motor skills but not precision and speed of movements were altered. Furthermore, patients with TS were not impaired in the performance of fast, goal-directed movements. Regarding overall force efficiency, patients with TS appeared to be superior when compared with matched adults.¹⁸

Interestingly, there is no agreement among studies relying even on same motor task called the Purdue Pegboard task that examines movement of hands, fingers, arms, and fingertip dexterity.^{9,13,14,19} Therefore, additional factors need to be considered for these variant observations. One possible hypothesis could be the effect of medication administered to patients, since these medications can influence the motor circuitry and thus motor movements. For instance, in the study by Bloch et al,⁹ one-half of the study sample was taking psychotropic medications at the time of neuropsychological testing. Although efforts were made to discern the effect of medication use, the possibility cannot be entirely dismissed. The effect of medication in this sample population can add a variability that is not a characteristic of this syndrome.

Studies often report motor function impairment in individuals with TS. However, the association of these deficits with TS versus co-occurring conditions has not been well understood due to the lack of adequate control conditions. These comorbid conditions can have differential role in the motor deficits. Sukhodolsky et al¹³ reported deficits in clinical population with pure TS as compared to the healthy matched controls; in contrast, in presence of ADHD as a comorbid condition, these deficits were no more significant than those of controls, suggesting that ADHD could be a possible compensatory mechanism in children with TS.

Also, neurodevelopment age could be an important reason for these mutually exclusive results. TS is a neurodevelopment

Table 1. Studies on motor skill weakness and fine motor movement deficits.

AUTHORS	NAME	PATIENT SAMPLE	AGE GROUP MEAN (SD)	TECHNIQUES AND TASKS	RESULTS
Nomura et al, 2003 ¹²	Neurology of Tourette's syndrome (TS) as a developmental dopamine disorder: a hypothesis	81 drug naive TS patients (70 males) with comorbidities	13.6 (5.8)	Neurological examination assessing pronation and supination, rigidity, posture, rotation and tilting effect	The clumsiness, rigidity, postural asymmetry, and abnormal tilting response
Bloch, Sukhodolsky, Leckman, and Schultz, 2006 ⁸	Fine motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome	32 children, with TS (ADHD excluded)	11.4 (1.5)	Purdue Pegboard, Beery Visual-Motor Integration (VMI) Test, Rey-Osterreith Complex Figure Task	Poor performance with the dominant and nondominant hand on the Purdue Pegboard test and VMI
Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, and Schultz, 2010 ¹³	Neuropsychological functioning in children with Tourette syndrome with and without attention deficit/hyperactivity disorder	56 children with TS-only, 45 with TS-plus-ADHD, 64 with ADHD and 71 healthy	11.37 (2.58)	Continuous Performance Test (CPT); Stroop test; Purdue Pegboard Task; Test of VMI	Only boys with TS-only but not girls were impaired in the dominant hand Purdue performance. TS-plus-ADHD were impaired on the sustained attention portion of the CPT
Neuner et al, 2012 ¹¹	Fine motor skills in adult Tourette patients are task-dependent	21 adults with TS (including comorbidities)	30.9 (10.09)	A motor performance test battery	Steadiness and visuo-motor integration of fine motor skills are altered but not precision and speed of movements
Eddy and Cavanna, 2014 ¹⁰	Set-shifting deficits: A possible neurocognitive endophenotype for tourette syndrome without ADHD	27 adults with uncomplicated TS	32.1 (12.57)	Digit Symbol Substitution Test	Impairments in response inhibition, fine motor control, set-shifting, and sustained attention
Georgiou, Bradshaw, Phillips, Cunningham, and Rogers, 1997 ¹⁵	Functional asymmetries in the movement kinematics of patients with Tourette's syndrome	12 patients with TS	30.8 (14)	Zig-zag movements with both hands to reach a target	No impairments in the performance of fast, goal directed movements
Buse et al, 2012 ¹⁴	Fine motor skills and interhemispheric transfer in treatment-naive male children with Tourette syndrome	27 treatment-naive males with "pure" TS	11 (1.16)	The Poffenberger paradigm; Finger tapping; The Purdue Pegboard task	No impairment of motor skills
Thomalla et al, 2014 ¹⁷	Memory and executive functions in adults with Gilles de la Tourette syndrome and chronic tic disorder	18 with TS with comorbid conditions	41 (12)	Purdue pegboard task	Fine motor skills intact



disorder with the most severe period of tic occurring at 10 years of age, followed by a decrease of symptoms. Until the adulthood, approximately 40% patients eventually become symptom-free, especially at rest.²⁰ This suggests that a compensatory or adaptive mechanism in these patients contributes to their motor alterations. Therefore, the variable sample age group could be a misleading factor when assessing the fine motor skills in TS. The empirical studies have often failed to control this crucial factor. For instance, Nomura and colleagues included a clinical sample ranging from 6 years to 41 years,¹² leading to a very heterogeneous sample population.

Motor Inhibition

The ability to inhibit unwanted behavior depending on the context is crucial for human social life. This includes both the inhibition of behavior driven by internal motivation in response to external stimuli and, depending on the context, the inhibition of planned and already prepared actions. Many studies have attempted to examine the inhibitory impairments in TS; however, the underlying mechanisms still remain unexplored. The presence of inhibitory impairment in patients with TS is debatable, and several studies have reported variable results (see Table 2).

Out of 25 studies on inhibition in TS, 12 reported the inhibitory deficits and impaired control of behavioral responses in different tasks^{21–23} and have argued that TS may be a result of an inhibitory dysfunction.¹⁸ On the contrary, other studies failed to find behavioral deficits in patients with TS when compared to control participants using behavioral inhibition or motor control tasks.^{24,25} Moreover, some studies even reported enhanced inhibitory performance in this clinical population. For example, patients with TS performed more accurately and faster than age-matched controls in an oculomotor switching task.²⁶ Other authors,²⁷ who found evidences of enhanced control of motor output in TS, argued that inhibition is increased, in order to achieve an adequate motor action. In accordance with these findings, Heise and colleagues²⁷ discussed increased inhibitory activation as a compensatory mechanism aimed at downregulating the abnormally high neuronal excitability.

As discussed above, an important yet understated fact that underlies the heterogeneity of the results is the type of task used to tap these inhibitions. Inhibitory processes work at various levels for a successful execution of a motor behavior and thus they may be distinguished in various categories.²⁸ Suppressing the internal stimuli could interfere with the current operations due to resource competition (interference control), or pre-potent or automatic responses (behavioral inhibition), or reflexive saccade (oculomotor inhibition). Previous studies have sought to address the inhibitory control using a variety of behavioral tasks, for instance the Stroop task, flanker task,^{24,29} Go-NoGo task,^{30–32} stop-signal task,³³ manual response switching task,^{25,27} and continuous performance task.³⁴ These tasks tap very different behavioral “inhibition”

mechanisms or processes that are impaired in TS. The Stroop task and flanker’s task are concerned with the executive or goal-directed inhibitory process that involves active cognitive control of a nontarget competing motor response. On the other hand, the Go-NoGo and stop-signal paradigm focus on inhibiting a pre-potent or primary motor response in compliance with changing cues, thus tapping the contextual change of motor behavior. However, although articles regularly target inhibition, the relation among the various meanings of inhibition is unclearly articulated.³⁵ The empirical studies lack a clear-cut discrimination of deficits in one type of inhibition versus the deficit in another and whether these inhibitory processes work in concert or operate separately.

Also, the employed tasks vary in the required cognitive demands for performing a successful inhibition. Jung et al²⁵ found that adolescents with TS exhibited enhanced cognitive control of motor output with increasing task difficulty. Another study,²² which employed a Go-NoGo task requiring the inhibition of a pre-potent action, reported that inhibitory control was intact in patients with TS. Though patients with TS had similar accuracy compared to controls, they responded significantly more slowly to correct Go trials than the controls. This suggested that patients with TS develop inhibitory adaptive strategies (overall increase in reaction times) in order to maintain high performance accuracy. In contrast to Eichele’s study, in speeded manual inhibition during Simon task, which induced similar conflict to pre-potent action, a deficient inhibitory control was reported in adults with TS.³⁶ The speeded response inhibition needing additional cognitive efforts for performing a task might explain the disagreement in the results.

However, surprisingly studies using the same task have little convincing evidences of inhibitory deficits, as these have produced mixed findings as well. Inhibitory control, when measured with the Go/NoGo task, was impaired in adults with TS^{32,37} and the Go/NoGo performance in children with TS was comparable to that of age-matched peers.^{38,39}

Variations in studies using same task, for example, Go/NoGo, could be explained on the basis of the difficulty level and variation of task. There are differences in the task specification of the Go/NoGo task applied. For example, in the task of Ozonoff et al,³⁸ the ratio of Go to NoGo stimuli is 50:50, whereas it is 83:17 in that of Hershey et al.³⁷ In Go-NoGo task, participants performed an action for frequent target stimuli (Go stimuli) and inhibited that action for infrequent nontarget stimuli (NoGo stimuli). If NoGo stimuli are relatively rare, then novelty effect is induced for these infrequent trials and this effect cannot be distinguished from inhibitory requirements.⁴⁵ Hence, it is crucial to have a rare NoGo stimuli to ensure that responses are pre-potent and response inhibition is difficult but crucial to control the effects of stimulus novelty.⁴⁶ This is even more important in TS, as patients were found to be impaired on tasks requiring the processing of novel stimuli.⁴⁷

Table 2. Studies on inhibition of voluntary motor movements.

AUTHORS	NAME	PATIENT SAMPLE	MEAN AGE (SD)	TECHNIQUE AND TASK	RESULTS
LeVasseur, Flanagan, Riopelle, and Munoz, 2001 ⁴⁰	Control of volitional and reflexive saccades in Tourette's syndrome	10 TS; comorbidities included On medication	11–55 years (14.9)	Oculomotor paradigms	Ability to inhibit or delay planned motor program is significantly impaired in Tourette's syndrome
Wylie, Claassen, Kanoff, Ridderinkhof, and van den Wildenberg, 2013	Impaired inhibition of prepotent motor actions in patients with Tourette syndrome	28 adults with persistent TS; without OCD or ADHD On medication	26.6 (13.5)	Speeded manual reactions Simon task	Deficient inhibitory control over prepotent motor actions in individuals with persistent TS
Hershey et al., 2004 ³⁷	Cognitive-pharmacologic functional magnetic resonance imaging in Tourette syndrome: a pilot study	8 medication-naïve adults	35.5 (13.5)	fMRI during Go-NoGo	Patient group had inhibitory deficits
Watkins et al., 2005 ³²	Executive function in Tourette's syndrome and obsessive-compulsive disorder	20 TS patients without OCS (included ADHD), 20 OCD patients On medication	TS: 31.5 (11.6)	Pattern and spatial recognition memory, attentional set-shifting, and a Go/NoGo	TS patients were impaired in spatial recognition memory, inhibition of prepotent response, and decision making
Eichele et al., 2010 ⁴¹	Go/NoGo performance in boys with Tourette syndrome	20 with TS including comorbidities	12.64 (2.05)	Behavioral Go-NoGo	Similar inhibitory control as similar accuracy in both groups. TS responded significantly slower than the controls. Eliminating ADHD and OCD patients from sample did not alter the results
Serrien, Orth, Evans, Lees, and Brown, 2005 ³¹	Motor inhibition in patients with Gilles de la Tourette syndrome: functional activation patterns as revealed by EEG coherence	10 with TS; two patients with comorbid conditions; No medication	28 (8)	EEG coherence during Go/NoGo	Gain in inhibitory frontomesial cortical networks is adaptively heightened in TS and is related to both voluntary movement and tic suppression
Roessner, Albrecht, Dechent, Baudewig, and Rothenberger, 2008 ³⁹	Normal response inhibition in boys with Tourette syndrome	22 medication-naïve boys pure TS	12.5 (1.5)	Go/NoGo task	The performance did not differ between boys with TS and healthy boys
Thomalla et al., 2014 ¹⁶	Costs of control: decreased motor cortex engagement during a Go/NoGo task in Tourette's syndrome	15 patients with pure Tourette's syndrome; Medication-naïve	34 (9)	fMRI Go/NoGo reaction time paradigm	TS patients had longer reaction times than healthy controls in Go trials and made more errors in total
Mueller, Jackson, Dhalla, Datsopoulos, and Hollis, 2006 ²⁶	Enhanced cognitive control in young people with Tourette's syndrome	9 patients with TS; ADHD excluded; under medication	13.1 (2.5)	Oculomotor switching task	TS individuals performed more accurately and faster than age-matched control in conditions where cognitive demands were maximal
Georgiou, Bradshaw, Phillips, Bradshaw, and Chiu, 1995 ²³	The Simon effect and attention deficits in Gilles la Tourette's syndrome and Huntington's disease	10 with TS; mixed comorbidities; under medication	31	S-R compatibility task	Patient experience difficulties in making attentional shifts, and in inhibiting inappropriate responses
Jackson et al., 2013 ⁴²	Motor excitability is reduced prior to voluntary movements in children and adolescents with Tourette syndrome	10 with TS without comorbid ADHD; on medication	14.4 (2.8)	TMS in conjunction with a manual choice reaction time task	Behavioral response–conflict task did not differ between groups. However, cortical excitability was significantly reduced in the TS group in the period immediately preceding finger movement

(continued)



Table 2. (Continued)

AUTHORS	NAME	PATIENT SAMPLE	MEAN AGE (SD)	TECHNIQUE AND TASK	RESULTS
Sheppard, Bradshaw, Georgiou, Bradshaw, and Lee, 2000 ¹⁸	Movement sequencing in children with Tourette's syndrome and attention deficit hyperactivity disorder	12 Pure TS under medication	11.9 (2.6)	Movement sequencing task	Movement sequencing impairment in TS
Sönke Johannes et al, 2003 ⁴³	Tourette syndrome and obsessive-compulsive disorder: Event-related brain potentials show similar mechanisms of frontal inhibition but dissimilar target evaluation processes	10 adults with TS (mixed comorbidities)	34.4 (33.7)	ERP during Stroop test	Frontal inhibitory mechanisms are altered alike in TS and OCD. However, the target detection and evaluation are intact in TS
Genevieve Thibault, O'Connor, Stip, and Lavoie, 2009 ⁴⁴	Electrophysiological manifestations of stimulus evaluation, response inhibition and motor processing in Tourette syndrome patients	15 adults with TS; comorbidity controlled; no medication	37 (8)	ERP during: Color word stroop; S-R compatibility task	TS participants showed appropriate capacity of motor inhibition
Eddy and Cavanna, 2014 ¹⁰	Set-shifting deficits: A possible neurocognitive endophenotype for Tourette syndrome without ADHD	Participants were 27 adults with uncomplicated TS; on medication	32.11 (12.57)	Digit Symbol Substitution Test	Patients with TS exhibited impairments on four measures assessing response inhibition, fine motor control, set-shifting, and sustained attention
Ozonoff, Strayer, McMahon, and Filloux, 1998 ³⁰	Inhibitory deficits in Tourette syndrome: a function of comorbidity and symptom severity	46 children with TS (23 without comorbidity, 23 with OCS and ADHD); under medication	11.9 (2.4)	Negative priming task	Pure TS performed similar to controls while patients with comorbid conditions; tended to perform less well than the control group. Also, with increased severity of symptomatology performance reduced significantly
Jung, Jackson, Parkinson, and Jackson, 2013 ²⁵	Cognitive control over motor output in Tourette syndrome	10 with "pure" TS (8 male, 2 female); under medication	13.5 (1.6)	fMRI during a manual response-switching task	Adolescents with TS exhibit enhanced cognitive control of motor output
Channon, Gunning, Frankl, and Robertson, 2006 ²⁴	Tourette's syndrome (TS): cognitive performance in adults with uncomplicated TS	20 with TS excluding comorbidities; under medication	31.05 (11.32)	Flanker task; sentence completion	TS is associated with only mild, circumscribed impairment
Channon et al, 2009 ³⁴	Tourette's syndrome (TS): Inhibitory performance in adults with uncomplicated TS	21 with pure TS; under medication	29.48 (11.44)	Stroop and flanker tasks and continuous performance task	TS group was found to be slower than the control group on most measures, but showed differential slowing under conditions with enhanced inhibitory demands on the combined Stroop-flanker and the incompatible CPT tasks
S. Johannes et al, 2001 ³³	Altered inhibition of motor responses in Tourette syndrome and obsessive-compulsive disorder	10 with TS including comorbid conditions	34.4 (14.3)	ERP in stop signal paradigm	Altered frontal inhibitory functions



There are prominent differences in the clinical sample population of TS in terms of clinical characteristics and associated comorbidities. Studies that reported finding executive function impairment in individuals with TS often do not exclude individuals with comorbid conditions such as ADHD or OCD (comorbidity is estimated to be ~50% and 40%, respectively). These conditions in absence of tics disorder had been previously associated with executive dysfunction.^{23,48} Surprisingly, relatively few studies have directly compared participants with different comorbid conditions of TS, and those that have, generally studied comorbid groups rather than comparing separate groups. One possibility is that some of the earlier clinical studies reporting negative results could not control all the comorbid factors because of the difficulty in recruiting participants with TS in the absence of comorbidities. By contrast, among studies carried out on individuals with “uncomplicated” or “pure” TS in which these comorbid conditions were excluded, no significant difference in cognitive and behavioral executive response inhibition between “pure” TS groups and matched controls was reported.^{10,24,30} For example, participants with pure TS showed no performance deficits on Go/NoGo,^{31,39} color-word Stroop, or Flanker tasks.³⁴ Similarly, Ozonoff et al³⁰ found normal inhibition effects in children with mild TS but impaired inhibition in children with TS and comorbid ADHD, thus suggesting that ADHD may contribute to the inhibitory deficits observed in TS.^{30,49,50} Developmental studies have revealed measurable and interesting age-related inhibitory changes. The inhibition process can be measured from the age of 7 years, although it is less variable in older children and adults.⁵¹ Speed of the inhibitory processes improves by about 50 ms from the age of ~7 years to the age of ~9 years, reaching a peak in young adulthood, and declining only slightly thereafter.² Specifically, the speed of processing go signal appears to be more strongly related to age than to the speed of processing the stop signal.^{28,52} Therefore, age can play a crucial role in the functioning of these inhibitory processes.

Discussion

This review of the literature has yielded a number of important results regarding motor activity in patients with TS. TS has been linked to cognitive and executive functioning impairment, but the recent empirical studies could not reach any conclusive outcome about the nature and course of these impairments. Inconsistencies are clearly present, which are attributable to the sensitivity of the task used to measure these motor processes, age of the patient, and wide spectrum of co-occurring or comorbid conditions.

There is a wide range of tasks employed to study the deficits related to TS. More often, clinical researchers adopt cognitive, psychological models but not always with a very clear rationale for selecting one paradigm over another. At other times, a disorder is studied with multiple paradigms, with a conclusion of a same global deficit. A more careful approach in

defining and exploring the specific inhibitory processes needs to be adopted. For instance, cognitive and motor inhibition relies on different neural substrates³⁰ and thus would indicate different domains of deficits.

An important factor to be considered for future research in TS is the specificity of deficits in patients with pure TS as opposed to ones with other comorbid conditions.⁵³ A more elaborate role of these confounding comorbid conditions can lead to a better understanding of this complex syndrome. As TS-like behaviors involve separate behavioral aspects (phonic and motor), these may show differential associations with the sub-types of ADHD, OCS, and response inhibition deficits. Studies have reported the lack of universality of these deficits. In order to learn more about TS, it seems necessary to focus on patients with pure TS. However, it is arguable that this may not be representative of the majority of patients within the Tourette spectrum. In fact, epidemiological evidence suggests that “pure” TS may be the exception rather than the rule.

Moreover, the influences of medication need to be controlled in these studies. Commonly prescribed drugs, such as dopamine antagonists and neuroleptics, are known to alter brain functions. Also, the stimulant medication prescribed to patients reduces the inhibitory deficits by reducing the time taken in the movement preparation and execution,¹⁸ thus adding to the discrepancies in the reported results. In order to learn about the natural disease state, investigations of neuronal function in TS require the study of patients excluding the effects of medication. This, however, reduces the feasibility and ethics of the study in clinical settings. A probable solution for this problem might be to include medication-naïve patients in order to minimize the influences of medication, if any.

TS has been described as a neurodevelopmental disorder occurring during early childhood, peaking its severity around the age of 9–12 years, followed by a decrease until the adult age, with approximately 40% eventually becoming symptom-free.²⁰ This suggests that compensatory processes occur over time to cope with the deficits presented by the syndrome. Thus, the age of the patients could be a sensitive measure in the outcome of these studies. Further studies should not only consider age-matched control group but also the homogeneity within the group. Thus the homogeneity in the age group would direct future research toward more reliably studies of the deficits associated with TS. Coherently, the male bias in TS prevalence stimulates the need to consider a developmental approach in TS. Significant sex differences were observed while performing task assessing motor skills in children with TS.¹³ Imaging studies have revealed sex-based differences in the thinning of brain regions particularly involved in TS, suggesting TS may have different developmental trajectories in males and females.⁵⁴ However, the majority of TS studies tend to include participants without considering the sex differences, or opt to include only males. Hence our understanding of TS may have been substantially biased toward males.



Additionally, given the normative sex differences in the general population,⁵⁵ directly comparing males and females with TS will be corrupted by potentially normal sex differences. Hence, it is also important to consider the sex-related behavioral differences and compare how males and females with TS differ respectively from the unaffected population.

There is also a growing body of evidence supporting the contribution of the psychosocial environment to the onset and natural course of tics and related symptoms.⁵⁶ The mixed results across studies may reflect heterogeneity in neurobiological development or personal experiences among patients with TS. A naïve approach for future research could be to investigate the association between TS with parental or close relationships.

Conclusion

In conclusion, there are many inconsistencies in the present empirical literature to make final considerations on the voluntary motor deficits in the patients with TS. Further controlled studies need to be undertaken in order to gain specificity regarding the unique deficits associated and to generalize a complex spectrum of disorders like TS. The neural mapping of motor deficits in TS could help plan efficacious studies focused on the causal role of these deficits in the disorder. Such work must address the fundamental issues of specific and differential aspects of the deficits in TS.

Author Contributions

Conceived and designed the experiments: NK, RT, PA, and CL. Analyzed the data: NK and CL. Wrote the first draft of the manuscript: NK and CL. Contributed to the writing of the manuscript: NK, RT, PA, and CL. Agree with manuscript results and conclusions: NK, RT, PA, and CL. Jointly developed the structure and arguments for the paper: NK, RT, PA, and CL. Made critical revisions and approved final version: NK, RT, PA, and CL. All authors reviewed and approved of the final manuscript.

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