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Dissociation between two aspects of procedural learning in Tourette syndrome: Enhanced statistical and impaired sequence learning

Running title: Hyperfunctioning in Tourette syndrome

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Abstract

Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder that primarily affects the cortico-basal ganglia-thalamo-cortical (CBGTC) circuitry and is characterized by motor and vocal tics. Previous studies have found enhancement in procedural memory, which depends on the CBGTC circuitry and plays an important role in the learning and processing of numerous motor, social, and cognitive skills and habits. Based on these studies, procedural hyperfunctioning in TS has been proposed. However, the neurocognitive mechanism underlying such hyperfunctioning is poorly understood. Here, we investigated how two aspects of procedural learning, namely 1) frequency-based statistical learning and 2) order-based sequence learning, are affected in TS. Twenty-one children with TS between the ages of ten and fifteen as well as 21 typically developing controls were tested on a probabilistic sequence learning task that enables the parallel assessment of these two aspects. We found that children with TS showed enhanced sensitivity to statistical information but impaired sequence learning compared to typically developing children. The deconstruction of procedural memory suggests that procedural hyperfunctioning in TS may be supported by enhanced sensitivity to statistical information. These results can provide a potential path for improving therapy methods and skill-oriented educational programs for TS.

Keywords: Tourette syndrome, sub-cortical structures, procedural memory, skill learning, basal ganglia, statistical learning

1. Introduction

Tourette syndrome (TS) or Tourette Disorder is a neurodevelopmental disorder characterized by several motor and at least one vocal tic for at least a one-year period, which cannot be accounted for other medical conditions or medications (American Psychiatric Association, 2013). TS can be marked by altered cognitive functions, including both impairments and enhancements (e.g., Mueller *et al*., 2006; Palminteri *et al*., 2011; Delorme *et al.*, 2015; Jung *et al.*, 2015; Yaniv *et al*., 2017; Takács *et al*., 2018; although comorbidities could have confounded some of the prior results, see Morand-Beaulieu *et al*., 2017). One of the areas where such enhancement has been found is procedural learning (and also accessing the already established procedural information), which underlies the learning of motor and cognitive skills (Walenski et al., 2007; Delorme *et al*., 2015; Palminteri *et al*., 2011; Dye et al., 2016; Takács *et al*., 2018). Based on these studies, it has been proposed that procedural hyperfunctioning exists in TS. The overlap between the neurobiological characteristics of TS and the neurophysiological underpinnings of procedural memory provides an opportunity to examine (1) the aspects of procedural functions and (2) the cognitive models of TS (Dye *et al.*, 2016; Shephard *et al*., 2018) at the same time. Here we aimed to examine how two aspects of procedural learning, namely statistical and sequence learning, are affected in TS and test whether these aspects contribute to the procedural hyperfunctioning proposed by previous studies.

The cognitive profile of TS has been thoroughly investigated, including executive functions (Channon *et al*., 2009; Yaniv *et al.*, 2017), social cognition (Eddy and Cavanna, 2013), and procedural memory (Channon *et al*., 2003; Marsh *et al.*, 2004). Results on the cognitive profile could be confounded by certain factors such as comorbidities (for a review, see Morand-Beaulieu *et al*. (2017). A crucial aspect of cognition is procedural memory, which contributes to the acquisition, storage, and use of implicit motor and automatic cognitive behaviors such as skills and habits (Ullman, 2004; Kaufman *et al*., 2010). Procedural memory is mediated mainly by the basal ganglia, particularly the striatum, and relies on the cortico-basal ganglia-thalamo-cortical (CBGTC) pathways (Poldrack and Packard, 2003; Doyon *et al*., 2009; Janacsek *et al.*, 2020). The basal ganglia are thought to contribute to the acquisition of skills and habits, whereas neocortical regions might be more important for processing skills after they have been automatized (Ullman, 2016). In TS, tics and habits are phenomenologically similar and share neural underpinnings (Conceição *et al*., 2017). It has been suggested that alterations in the frontostriatal regions and improper procedural learning mechanisms can explain the hyperkinetic profile of TS (Albin and Mink, 2006).

The exact brain mechanisms underlying TS are not yet fully understood. However, converging evidence suggests both structural and functional abnormalities in the basal ganglia, related frontal regions, and in the CBGTC pathways (Peterson *et al*., 1998; Stern *et al*., 2000; Mink, 2001; Albin *et al.*, 2003; Peterson *et al*., 2003; Albin and Mink, 2006; Maia and Frank, 2011). Tics may reflect abnormal habit-learning mechanisms, where improper stimulus-response associations are learned (Albin and Mink, 2006; Goodman *et al.*, 2014; Petruo *et al*., 2018). Abnormalities in the CBGTC loop support the hypothesis of altered habit-learning in TS. Tics may result from a heightened direct pathway activity relative to indirect pathway activity in the CBGTC loop (Mink, 2001; Maia and Frank, 2011).

These neurobiological alterations may lead not only to tics but also to enhancements in procedural learning (Walenski *et al*., 2007; Dye *et al.*, 2016). Most of the previous studies examining procedural learning in TS reported enhanced functions (Walenski *et al.*, 2007; Palminteri *et al*, 2011; Delorme *et al.*, 2015; Dye *et al*., 2016; Shephard *et al*., 2018; Takács *et al*., 2018), or at least intact functions (Channon *et al.*, 2003; Takács *et al*., 2017), with only two reporting impaired performance (Kéri *et al.*, 2002; Marsh *et al.*, 2004). The reason for the differences among these studies are not yet clear. The reason for the different results among these studies is not yet clear. Some prior studies involved only a handful of TS participants, which could have led to low statistical power failing to find group differences. Previous studies also diverse in terms of age (child or adult TS samples) and in terms of tic severity; both might be differently related to procedural learning. Relatedly, the presence of comorbidities could also confound the results. Another possibility is that previous studies tapped into different aspects of procedural memory and these aspects are differentially affected by TS. In the present study, we focused on this and investigated two aspects of procedural learning in TS.

Previous studies showing intact or enhanced procedural learning measured either sequence learning or language performance. One of the first studies using a sequence learning task to measure procedural memory in TS found no group differences between the TS and control groups (Channon *et al.*, 2003). Similarly, Takács *et al.* (2017) reported comparable learning performance between children with TS and typically developing peers using the Alternating Serial Reaction Time (ASRT) task. Shephard *et al.* (2018) examined sequence learning using the Serial Reaction Time (SRT) task in children with TS. Participants were assessed on two types of blocks: (1) sequence blocks containing stimuli following a predetermined sequence and (2) non-sequence blocks with random stimuli. Children with TS showed difficulties transitioning from sequence to non-sequence blocks, they showed greater disruption in accuracy compared to the control group. This result can imply that children with

TS overlearned the sequence in the task, which led to a more difficult transition. That is, children with TS showed procedural hyperfunctioning. In support of this, Takács *et al.* (2018) reported evidence of enhanced procedural learning in TS using the ASRT task. Children with TS made more prediction errors through learning than their typically developing peers, indicating enhanced sensitivity to the underlying regularities of the task. Moreover, procedural memory performance in TS had an early peak, and typically developing (TD) children did not exceed the level of TS performance throughout the task. The notion of procedural hyperfunctioning is further supported by studies with adult TS population, as well (Palminteri *et al.*, 2011; Delorme *et al.*, 2015). Palminteri *et al.* (2011) found that adults with TS showed enhanced reinforcement learning in a motor learning task. Furthermore, Delorme *et al.* (2015) found a higher rate of response to previously learned but devalued stimulus-response-outcome associations, which also suggest enhanced procedural functions.

Similar to the sequence learning results, procedural hyperfunctioning has also been found in language-based tasks. Two studies (Walenski *et al*., 2007; Dye *et al*., 2016) showed faster grammatical processes in TS on the morphological and phonological levels. Walenski et al. (2007) was the first study to demonstrate enhanced procedural functions in TS. In this study, children with TS showed faster producing of rule-governed past tenses compared to their typically developing peers (e.g., slip-slipped) while showing similar performance on producing irregular past tenses (e.g., bring-brought). Moreover, the naming of manipulated objects (e.g., hammer) was also "speeded" in TS, while naming of non-manipulated objects (e.g., elephant) was similar in the TS and control groups. These results support the procedural hyperfunctioning hypothesis in TS. Whereas producing regular past tenses and naming manipulated objects both rely on procedural memory, producing irregular past tenses and naming non-manipulated objects appear to be stored in declarative memory (Ullman, 2004). Another language-related study (Dye *et al*., 2016) further strengthens procedural hyperfunctioning in TS. This study showed "speeded" grammatical composition on a non-word repetition task in TS. Children with TS repeated non-words (e.g., "naichovabe") faster than typically developing peers, while in accuracy there was no difference between the groups. This type of phonological manipulation taps into decomposition, a procedural aspect of the language domain.

Procedural memory is a complex system and it supports several functions, such as learning sequences, probabilistic classification, and aspects of language, including grammar (Knowlton *et al*., 1994; Howard and Howard, 1997; Fiser and Aslin, 2001; Ullman *et al.*, 2020). Converging evidence suggests procedural hyperfunctioning in TS in both the acquisition of procedural information (such as in sequence learning; Palminteri *et al*., 2011; Delorme *et al*.,

2015; Takács *et al*., 2018) and the accessing of the already established procedures (such as in grammatical processing; Walenski *et al*., 2007; Dye *et al*., 2016). Importantly, acquiring procedural information is a complex function relying on multiple, parallel learning processes (Thiessen *et al*., 2013; Siegelman *et al.*, 2017; Maheu *et al.*, 2019; 2020). It is not yet clear which aspect of procedural learning supports the potential hyperfunctioning in TS.

Based on the previous studies, it is still unclear which aspects of procedural learning are affected in TS. Dye *et al.* (2016) suggest the importance of processing sequential information. Children and adults with TS may have enhanced sequence sensitivity, which leads to enhanced sequence learning and grammatical processing. Another significant aspect of procedural learning is processing of probabilistic information. The results of Takács *et al.* (2018), where children with TS showed enhanced learning on a probabilistic sequence learning task, suggest that enhanced sensitivity to probabilistic information may contribute to procedural hyperfunctioning. However, neither of these studies focused on contrasting these two aspects of procedural learning. Here, we designed a study to investigate how sensitivity to sequential vs. probabilistic information is affected in TS.

Crucially, the sensitivity to sequential information and to probabilistic information cannot be measured at the same time with most tasks. There is a paradigm, however, designed to distinguish these two learning processes. The cued version of the ASRT task (Howard and Howard, 1997; Németh *et al*., 2013) is able to measure both learning processes in parallel. Here, *statistical learning* refers to the acquisition of probabilistic (frequency) information. Participants learn the shorter-range relationship between visual stimuli that is primarily based on frequency (differentiating between more frequent and less frequent stimulus chunks). Additionally, *sequence learning* refers to the acquisition of order-based information. Thus, participants learn a series of stimuli that repeatedly occur in the same (deterministic) order, intermixed with random stimuli (resulting in an alternating sequence structure). From a theoretical perspective, it is important to note that at the level of transitional probabilities, statistical learning and sequence learning can be considered similar. Whereas statistical learning (as measured in the ASRT task) refers to the acquisition of second-order transitional probabilities that are less than one, sequence learning refers to the acquisition of second-order transitional probabilities that are equal to one. Despite the fact that both can be viewed as acquisition of transitional probabilities, a growing body of evidence suggests that they exhibit at least partially different characteristics both at behavioral and neural level (Howard and Howard, 1997; Németh *et al*., 2013; Kóbor *et al.*, 2018; Simor *et al.*, 2019). Shorter-range probabilistic information (i.e., *statistical learning*) is typically acquired incidentally and

relatively rapidly (Kóbor *et al.*, 2018; Simor *et al.*, 2019). In contrast, acquisition of the alternating sequence may occur either incidentally or intentionally with gradually improving performance in both cases (although an intentional learning condition typically results in faster sequence acquisition compared to an incidental learning condition) (Howard and Howard, 1997; Howard *et al.*, 2004; Simor *et al.*, 2019). Furthermore, statistical and sequence learning appear to have different electrophysiological characteristics, suggested by event-related potentials during learning (Kóbor *et al.*, 2018) as well as by neural oscillations during consolidation (Simor *et al.*, 2019).

The present study focuses on testing procedural hyperfunctioning in children with TS and investigates two aspects of procedural learning, namely, statistical learning and sequence learning using the ASRT task. Since previous ASRT studies showed that a cued, instructed version of the task results in relatively faster acquisition of the alternating sequence (e.g., Kóbor *et al.*, 2018; Simor *et al.*, 2019), enabling to measure statistical and sequence learning in the same time frame (i.e., within one learning session), we also chose this cued version in the current study. As previous research on TS and procedural learning did not provide first-hand evidence on these two aspects of procedural learning, we follow an exploratory approach to test which aspect is affected or may even support the procedural hyperfunctioning in TS.

2. Materials and methods

2.1. Participants

Twenty-seven children diagnosed with TS between the age of 10 and 15 were recruited through a regional child psychiatry hospital in Budapest, Hungary. They had been diagnosed with TS based on the DSM-V criteria (American Psychiatric Association, 2013). TS and any comorbidities have been diagnosed by a team of child psychiatrist, clinical psychologist and special education teacher following a minimum one-week-long stay and observation in the hospital. The TS children visit the hospital regularly later as well for check-ups and treatment. Hence, comorbidities have not been evaluated as a part of the present study but were previously diagnosed in the hospital. Children with comorbid psychiatric or neurodevelopmental disorders were excluded from the analysis except for the ones with comorbid attention deficit hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD) since the presence of these disorders are common in TS (Robertson, 2015). Three children were excluded from the analyses due to comorbid disorders: one child had comorbid depression, OCD, and ADHD, one child had comorbid depression, anxiety disorder, and ADHD, and one child had comorbid autism spectrum disorder and ADHD. Moreover, medication was also an exclusionary criterion.

From the recruited 27 participants, five participants were taking medication during the time of testing. Out of the five participants, two of them had some comorbid diagnoses other than ADHD or OCD. Therefore, additional three participants were excluded from the analyses due to medication. In sum, we excluded six participants due to comorbid diagnoses and medication and data of 21 children with TS (18 boys and three girls) were analyzed. In this final sample, three children met the criteria for comorbid ADHD and one child was diagnosed with comorbid OCD and ADHD.

Ninety-nine typically developing (TD) children participated in the study from local schools. From the TD group, we matched 21 children one-to-one to the TS children based on sex and age. If more than one TD participant met the matching criteria for a participant with TS, we selected the one who was closest to the participant with TS in age measured in months and were in the same school grade. The individuals in the pairs did not differ more than six months in age and were in the same school grade. None of the matched TD children had any psychiatric, neurological, or neurodevelopmental disorders according to parental reports. All participants were native Hungarian speakers, and they had normal or corrected-to-normal vision. Table 1 summarizes the descriptive characteristics of the groups alongside with other cognitive measurements often reported in TD (Robertson *et al.*, 2017).

The experiment composed of two sessions on the same day with a 5-hour delay between them. In this study, we report only the first part of the experiment analyzing the learning phase of the procedural learning task. Parents of all participants were asked to complete the Strength and Difficulties Questionnaire (SDQ; Goodman, 1997) to measure hyperactivity, emotional difficulties, conduct, and peer problems. Caregivers of all participants provided written consent and children assented to participate in the study before testing. The study was approved by the local institutional research ethics committee and was conducted in accordance with the Declaration of Helsinki.

Table 1. Descriptive data of the participants and performance on the cognitive measurements.

	Group					
	TD (n = 21)		TS (n = 21)			
	M	*SD*	*M*	*SD*	*t*	*p*
Age in months	149.38	16.98	148.43	16.41	0.19	0.85
School grade	6.00	1.34	5.90	1.34	0.61[1]	0.96

SDQ total score	8.38	4.64	11.42	6.41	-1.73	0.09
YGTSS total score	–	–	17.43	8.12	–	–
WCST perseverative error (%)	16.42	8.64	16.02	7.53	0.16	0.87
Phonemic verbal fluency	10.76	3.03	10.17	2.74	0.67	0.51
Semantic verbal fluency	19.79	5.30	18.74	3.40	0.76	0.45
Counting span	3.38	0.60	3.67	0.97	-1.11	0.28

Note. The neuropsychological tests are well-known tasks for measuring executive functions. Wisconsin Card Sorting Task (Berg, 1948; Mueller and Piper, 2014) was used to measure cognitive flexibility. A higher percentage of perseverative errors indicate worse cognitive flexibility. Phonemic and semantic verbal fluency (Strauss *et al*., 2006; for Hungarian version, see Tánczos *et al*., 2014*a*, *b*) measures the central executive component of the working memory model. Here, verbal fluency is measured by the number of correct words. The counting span task (Case *et al.*, 1982) is a complex working memory task. Participants' counting span capacity is calculated by the highest set size they were able to recall in the correct order. SDQ = Strength and Difficulties Questionnaire. YGTSS = Yale Global Tic Severity Scale. WCST = Wisconsin Card Sorting Task. [1]G-test was used instead of Chi-square test as the assumptions of Chi-square test were not met.

2.2. Tasks

2.2.1. Alternating Serial Reaction Time (ASRT) task

Statistical and sequence learning was measured by the cued version of the Alternating Serial Reaction Time (ASRT) task (Németh *et al.*, 2013). In this task, a target stimulus (either a dog's head or a penguin) appeared in one of the four equally spaced, horizontally arranged possible locations (empty circles). Participants were instructed to press the corresponding key on the keyboard (Z, C, B or M) as accurately and as fast as they could. The stimulus remained on the screen until the participants responded, then, after a 120-ms-long delay, the next target appeared.

The presentation of the stimuli followed an 8-element alternating sequence where pattern and random elements alternated with each other (e.g., 1-r-2-r-4-r-3-r, where numbers represent the locations from left to right and 'r' indicates a randomly selected location). In the cued ASRT task, the pattern and random elements are visually distinguishable, pattern elements are indicated by the dog's head and random elements are indicated by the penguins. Participants

were informed about the presence of the sequence structure, they were told that the dogs always follow a predetermined pattern, while penguins appear randomly in one of the possible locations. They were instructed to find the pattern of the dog's appearance to improve their performance. The alternation of pattern and random elements creates six unique sequence permutations: 1-r-2-r-3-r-4-r, 1-r-2-r-4-r-3-r, 1-r-3-r-2-r-4-r, 1-r-3-r-4-r-2-r, 1-r-4-r-2-r-3-r, and 1-r-4-r-3-r-2-r. Note that each of these six permutations can start at any location (e.g., 1-r-2-r-3-r-4-r and 2-r-3-r-4-r-1-r are identical sequence permutations). One of the permutations were selected to each participant and it was counterbalanced across participants in each group.

The structure of the ASRT task results in some runs of three successive elements – referred to as *triplets* – more frequent than others. If the sequence is 1-r-2-r-4-r-3-r, triplets such as 1-X-2, 2-X-4, 4-X-3, 3-X-1 (X indicates the middle element of the triplet) occur often since their last element can be either pattern or random. However, 3-X-2 or 4-X-2 occur less frequently as the third element could only be random. The more frequent triplet types are labeled as "high-frequency" triplets, while the latter types are labeled as "low-frequency" triplets (Howard & Howard, 1997; Németh et al., 2013). The labels also refer to the transitional probabilities inside the triplets meaning that the third element of a high-frequency triplet is highly predictable from the first element of the triplet (with 62.5% probability). In case of the low-frequency triplet, the predictability of the final element is lower (12.5%).

Furthermore, each element can be categorized by their structure, meaning whether they are pattern or random elements (note that these are differentiated by visual cues). We can distinguish high-frequency triplets with the last element being a pattern element and high-frequency triplets with the last element being a random element. The last element of a low-frequency triplet can only be a random element as pattern elements always appear with high probability.

Previous studies have shown that participants perform differently on the different triplets. Participants show faster performance on the high-frequency triplets compared to the low-frequency ones (e.g., Howard and Howard, 1997; Janacsek *et al.*, 2012; Takács *et al.*, 2018), and they also show faster performance on pattern triplets compared to the random ones (e.g., Howard and Howard, 1997; Kóbor *et al.*, 2018; Simor *et al.*, 2019). Therefore, we can differentiate three trial types: (1) trials that belongs to the predetermined sequence and are the last element of a high-frequency triplet called *pattern* trials, (2) trials that appear randomly and also are the last element of a high-frequency triplet called *random high* trials, and (3) random elements that appear as the final element of a low-frequency triplet labeled as *random low* trials.

Different performance on these trial types can help differentiating the two aspects of procedural learning, sequence learning and statistical learning (Howard and Howard, 1997; Németh *et al.*, 2013). Sequence learning is measured by the difference in reaction times between pattern and random high elements. These elements share the same statistical properties as they both correspond to the last element of a high-frequency triplet, but they differ in sequence properties as one of them is part of the predefined sequence while the other appears randomly. Therefore, faster response to the pattern compared to the random high trials indicates greater sequence learning. To assess statistical learning, we compare the reaction times between random high and random low trials. Here, the elements share the sequence structure (both are random) but differ in statistical properties as they correspond either to the final element of a high-frequency or a low-frequency triplet. Therefore, greater statistical learning is defined as faster reaction time to random high than to random low elements. To sum up, statistical learning grasps purely frequency-based learning, whereas sequence learning shows the acquisition of order information. The structure of the ASRT task and the quantification of the underlying learning mechanisms illustrated in Fig. 1.

The task consisted of 20 1-minute-long blocks, each block contained 85 trials. Each block started with 5 random trials for practice, then the unique 8-element alternating sequence was presented 10 times. After each block, awareness of the sequence structure was measured. Participants were instructed to type the order of the dog's head using the corresponding keys. The sequence report lasted until the participants produced 12 consecutive responses, ideally, the given 4-element sequence three times. This method allowed us to determine the duration (in terms of blocks) participants needed to discover the sequence as defined by consistently reporting the given sequence with an at least 70% accuracy from that point. We labeled this variable as the *timing of the discovery* of the sequence. We also quantified the average knowledge about the sequence formed by the end of the task. We used each reported sequence after the last five blocks and calculated how many responses out of the 12 was correct after each block. Then the mean of these percentile variables was calculated for each participant. We labeled this average of the reports as *explicit knowledge*.

A

Sequence structure: e.g., 1 – r – 2 – r – 4 – r – 3 – r

P	r		P	r		P	r		P	r		P	r		P	r		P	r		P	r		P
1	1	2	2	1	2	4	1	2	3	1	2	1	1	2	2	1	2	4	1	2	3
	3	4		3	4		3	4		3	4		3	4		3	4		3	4				

B

	Structure: P-r-P (the last element is always pattern)	Structure: r-P-r (the last element is always random)	
High-frequency triplets (62.5% of all trials)	3-4-**1** (50%)	3-4-**1** (12.5%)	Sequence learning: pattern high – random high
Low-frequency triplets (37.5% of all trials)	never occurring (always high)	3-4-**2** (12.5%) 3-4-**3** (12.5%) 3-4-**4** (12.5%)	
			Statistical learning: random high – random low

Figure 1. An example of sequence structure, (A) triplet types and the underlying learning mechanisms (B) in the cued Alternating Serial Reaction Time (ASRT) task. In the example of the alternating sequence structure (A), numbers indicate pattern elements and 'r' indicates a randomly selected location. The alternating sequence makes some runs of three consecutive elements more frequent than others. Based on the structure, among high-frequency triplets, we can differentiate pattern high triplets (with red shading in Fig1A and red font in Fig1B) and random high triplets (with gold shading in Fig1A and gold font in Fig1B). Low-frequency triplets can only end with a random element (random low triplets, with blue shading in Fig1A and blue font in Fig1B). Statistical learning is quantified by contrasting the reaction time of the random high and random low triplets (gold vs. blue, the right column of the table). Sequence learning is quantified by contrasting the reaction time of the pattern high and random high triplets (red vs. gold, the top row of the table). Adapted from Németh *et al.*, 2013.

2.2.2. Yale Global Tic Severity Scale (YGTSS)

Tic severity was measured by the Yale Global Tic Severity Scale (Leckman, 1989), which is a reliable and conventional measurement of tic severity. YGTSS is a semi-structured interview, which rates motor and vocal tics based on their number, frequency, complexity, intensity, and interference with everyday life on a scale of zero to five for motor and phonic tics individually. The Total Score reported here consists of the motor and phonic scores with a maximum score of 50. Tic severity was measured regarding symptoms in the last week.

2.3. Data analysis

Statistical analysis of the ASRT task was based on previous studies (Németh *et al*., 2013; Kóbor *et al*., 2018; Simor *et al*., 2019). The 20 1-minute-long blocks were collapsed into four epochs, each containing five blocks. Each trial was categorized as the final element of a *pattern high*, *random high* or *random low* triplet. Two types of low-frequency triplet were excluded from the analysis, repetitions (e.g., 222, 444) and trills (e.g., 121, 242), since participants often show pre-existing response tendencies to these items (Song *et al*., 2007*a*, *b*). The median of RT data (for correct responses) was calculated for each participant in each epoch, separately for the three types of triplets. We also calculated learning scores separately for each epoch for the two types of underlying learning processes. Statistical learning scores were calculated as the difference in RT between random high and random low triplets, while sequence learning scores were calculated as the difference in RT between pattern high and random high triplets.

To examine the two learning mechanisms, RT data were analyzed in a mixed design ANOVA across the four epochs. Statistical learning was quantified with a mixed-design ANOVA with FREQUENCY (random high-frequency and random low-frequency triplets) and EPOCH (1-4) as within-subjects factors and GROUP (TS and TD) as a between-subjects factor. Sequence learning was also quantified with a mixed-design ANOVA with ORDER (pattern high-frequency and random high-frequency triplets) and EPOCH (1-4) as within-subjects factors and GROUP (TS and TD) as a between-subjects factor. To test for post hoc pairwise comparisons, we used LSD (Least Significance Difference) tests. The Greenhouse-Geisser epsilon correction was used when necessary. As a measure of effect size partial eta-squared (η^2_p) is reported.

3. Results

To compare **statistical learning** among the TS and TD groups, we conducted a mixed-design ANOVA on the RT (see Data analysis). The ANOVA revealed a significant FREQUENCY main effect ($F(1, 40) = 71.4$, $p < .001$, $\eta^2_p = 0.64$), meaning that RTs were faster on random high-frequency triplets compared with random low-frequency triplets. The main effect of EPOCH was also significant ($F(3,120) = 44.90$, $p < .001$, $\eta^2_p = 0.53$), indicating that, over groups, participants became faster with practice on both random high and random low-frequency triplets. The FREQUENCY*GROUP interaction was at the trend-level ($F(1, 40) = 3.31$, $p = .076$, $\eta^2_p = 0.076$), while FREQUENCY*EPOCH*GROUP interaction was significant ($F(3, 120) = 2.96$, $p = .035$, $\eta^2_p = 0.07$), indicating that the time course of statistical learning

was different between the groups (see Fig. 2). Follow-up analysis on the statistical learning score revealed a difference in the first epoch between the groups: The TS group showed higher learning than the TD group (TS: *M* = 27.38 ms, *SD* = 31.45 ms; TD: *M* = -0.79 ms, *SD* = 28.91 ms; *p* = .004; see Fig. 2C). There was no difference in learning in the remaining epochs (all *p*s > .203). The main effect of GROUP and other interactions were not significant (all *p*s > .291). In order to investigate whether the inclusion of ADHD and OCD comorbidities in the TS group could confound the results, we conducted the same analysis as above on the 17 children with TS without any comorbidities and the matched TD group. The analysis showed the same results as described above, indicating that the inclusion of TS participants with ADHD and OCD comorbidities does not confound the results (see Supplementary Material).

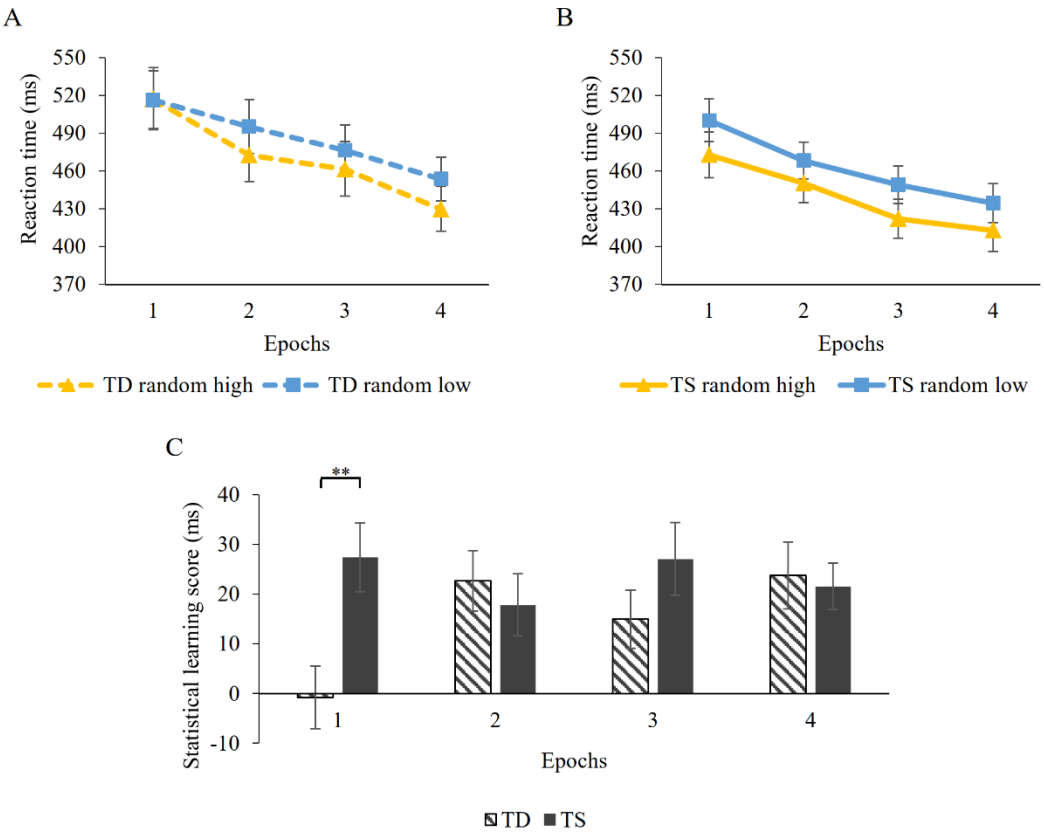

Figure 2. Statistical learning in the TD (A) and TS group (B). Dashed lines represent the TD group, continuous lines represent the TS group. Blue lines with square symbols indicate the reaction time (ms) on the random low triplets, gold lines with triangle symbols indicate the reaction time (ms) on the random high triplets. Statistical learning is indicated by the distance between the blue and gold lines. (C) Statistical learning score in the TD and TS group. Dashed bars represent the TD group, filled bars represent the TS group. Statistical learning score is computed by extracting reaction time of the random high triplets from reaction time of the

random low triplets, separately in each epoch. Higher learning score indicates better learning. Error bars denote standard error of mean. **$p < .01$.

To further examine the difference in statistical learning in the first epoch of the task between the TS and TD groups, we performed an additional analysis focusing on block-level data. We conducted a mixed design ANOVA with FREQUENCY (random high-frequency and random low-frequency triplets) and BLOCK (1-5) as within-subjects factors and GROUP (TS and TD) as a between-subjects factor. The main effect of FREQUENCY was significant ($F(1, 40) = 8.70$, $p = .005$, $\eta^2_p = 0.17$), participants showed faster RTs on the random high-frequency triplets compared to the random low-frequency triplets. The main effect of BLOCK was also significant ($F(4, 160) = 2.66$, $p = .035$, $\eta^2_p = 0.063$), suggesting reaction times became faster on both triplets with practice in both groups. The FREQUENCY*GROUP interaction was significant ($F(1, 40) = 14.24$, $p = .001$, $\eta^2_p = 0.263$), the TS group showed faster RTs to random high-frequency triplets than random low-frequency ones overall in the first epoch ($M = 32.30$, $SD = 32.86$), while the TD group did not show learning in the first epoch ($M = -3.96$, $SD = 29.31$). Crucially, FREQUENCY*BLOCK*GROUP interaction was marginally significant ($F(4, 160) = 2.17$, $p = .074$, $\eta^2_p = 0.05$). The post hoc analysis revealed that the TD group showed similar RTs on random high-frequency and random low-frequency trials in four out of five blocks (ps > .206), and even marginally *faster* responses on random-low frequency compared to random-high frequency triplets in the remaining block (i.e., the opposite direction than expected for statistical learning; $p = .073$), suggesting that the TD group did not acquire the statistical knowledge in Epoch 1. In contrast, the TS group showed comparable RTs on both trial types only in the first block ($p = .949$), and showed marginally significant (Blocks 2 and 4, ps < .084) or significant (Blocks 3 and 5, ps < .026) statistical learning in the remaining blocks. This block-wise analysis provides evidence that the difference between the TD and TS groups in the epoch-wise analysis on statistical learning is not due to pre-existing response tendencies. Instead, it suggests that the TS group acquired the statistical knowledge gradually albeit early in the task (around Blocks 2-3), while the TD group required more practice to achieve a similar level of knowledge as the TS group (observed in the later epochs).

To investigate **sequence learning,** we also used a mixed design ANOVA on the RT (see Data analysis). The main effect of ORDER was significant ($F(1, 40) = 8.35$, $p = .006$, $\eta^2_p = 0.17$), suggesting that participants showed faster RTs on pattern high-frequency triplets compared with random high-frequency ones. The main effect of EPOCH was also significant ($F(2.3, 90.1) = 42.33$, $p < .001$, $\eta^2_p = 0.51$), indicating that participants became faster with

practice on both triplets. The significant ORDER*GROUP interaction ($F(1, 40) = 4.93$, $p = .032$, $\eta^2_p = 0.11$) suggests that the two groups differed in the RT difference between the triplets. Follow-up analysis on the learning scores showed that the TD group learned to differentiate between pattern high and random high-frequency triplets, but the TS group showed similar RTs on both triplets (TD: $M = 38.46$ ms, $SD = 66.11$ ms; TS: $M = 5.04$ ms, $SD = 19.71$ ms) (see Fig. 3). The EPOCH*GROUP interaction was at the trend-level ($F(2.3, 90.1) = 2.67$, $p = .068$, $\eta^2_p = 0.063$), other main effects or interactions were not significant (all ps > .223). We conducted the same analysis as above on the TS group without any comorbitidies and the matched TD group to investigate whether comorbidities could confound the results. The analysis without comorbidities showed identical results as the analysis involving TS participants with ADHD and OCD comorbidities (see Supplementary Material).

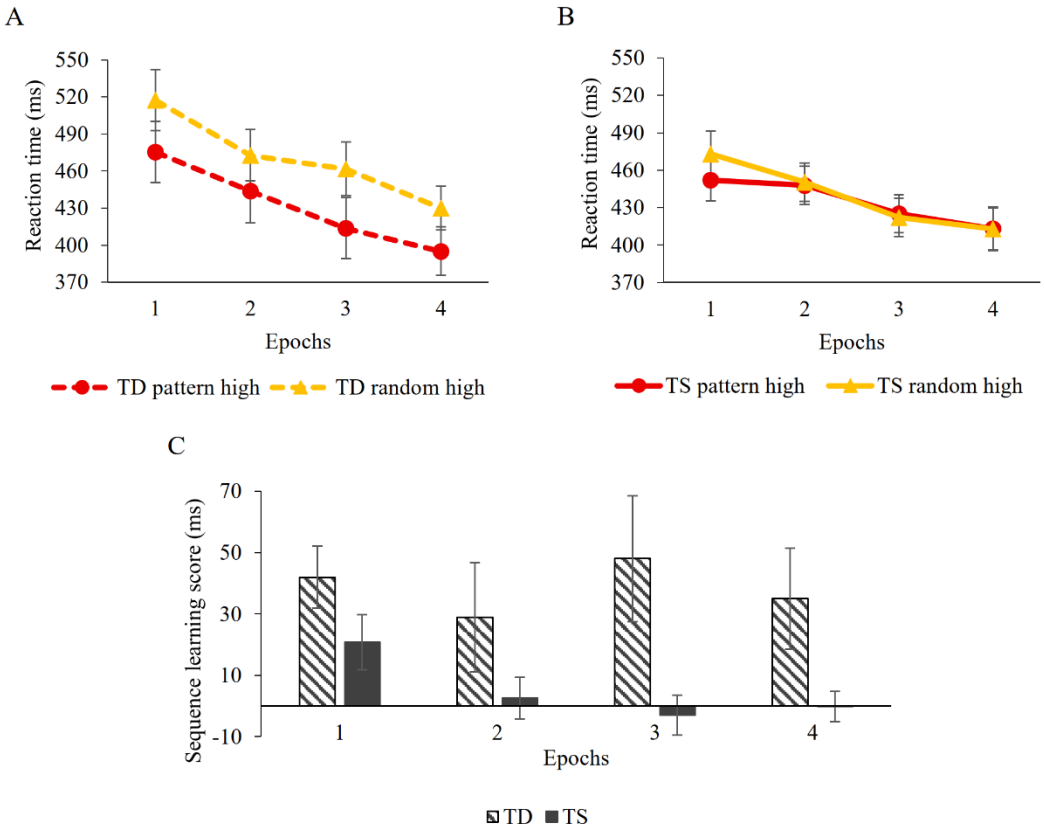

Figure 3. Sequence learning in the TD (A) and TS group (B). Dashed lines represent the TD group, continuous lines represent the TS group. Red lines with circle symbols indicate the reaction time (ms) on the pattern high triplets, gold lines with triangle symbols indicate the reaction time (ms) on the random high triplets. Sequence learning is indicated by the distance between the red and gold lines. (C) Sequence learning score in the TD and TS group. Dashed

bars represent the TD group, filled bars represent the TS group. Sequence learning score is computed by extracting reaction time of the pattern high triplets from reaction time of the random high triplets, separately in each epoch. Higher learning score indicates better learning. Error bars denote standard error of mean.

To evaluate the relationship between tic severity and procedural learning in the TS group, we correlated statistical and sequence learning scores with the YGTSS total score. First, we investigated **the relation between statistical learning and tic severity**. One participant showed extremely high statistical learning score according to Tukey's (1977) criterion (more than 1.5 times the interquartile range) and was an outlier with regard to the relation of statistical learning and tic severity. We excluded this participant from the correlation analysis. The analysis revealed a negative relationship at the trend-level (r = -.43, p = .06), suggesting better statistical learning in children with less severe tics (Fig. 4A). The **correlation between sequence learning and tic severity** was not significant (r = .18, p = .44; Fig. 4B).

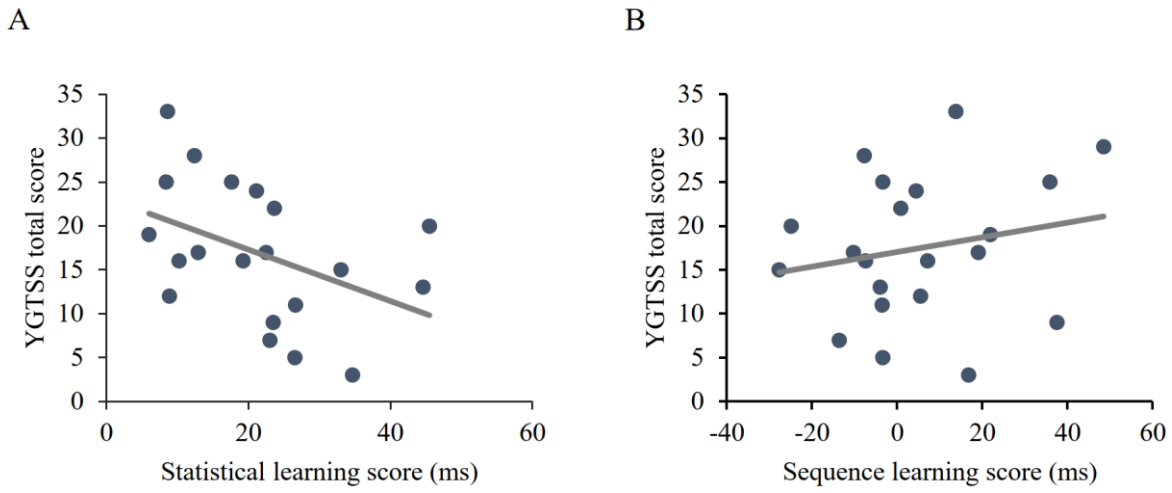

Figure 4. Correlation between (A) YGTSS total score and statistical learning score and (B) between YGTSS total score and sequence learning score. YGTSS = Yale Global Tic Severity Scale. Statistical learning score is the difference in RT between random high and random low-frequency triplets. Sequence learning score is the difference in RT between pattern high and random high-frequency triplets.

In order to check whether participants followed the instruction to find the predetermined 4-element sequence of the pattern stimulus' (dog's head) appearance, we asked them to report the sequence of the dog's head after each block. According to the results, explicit knowledge

about the sequence was present early in the task, the timing of discovery was around the 6th block, and it did not differ between the TS and TD groups ($t(34) = 0.199$, $p = .843$; $M_{TS} = 5.61$, $SD_{TS} = 6.55$; $M_{TD} = 6.05$, $SD_{TD} = 6.82$). Explicit knowledge of the sequence also suggests that the participants followed the instructions, the mean explicit knowledge score in the last epoch was 89% (*SD* = 20%) in the TS and 79% (*SD* = 29%) in the TD group. Moreover, we found no significant difference between the groups ($t(40) = -1.25$; $p = .218$), suggesting that similar explicit knowledge emerged in the groups about the predetermined sequence structure.

4. Discussion

The goal of the present study was to examine how two aspects of procedural learning, namely statistical and sequence learning, are affected in TS, and test whether these aspects contribute to the procedural hyperfunctioning observed in previous studies. We used the cued version of the Alternating Serial Reaction Time task, which allowed us to examine the two aspects simultaneously, in the same experimental design. We found enhanced sensitivity to statistical information in TS, while the TS group showed impaired sequence learning. Furthermore, executive functions and working memory capacity did not differ between the groups (Table 1).

4.1. Sensitivity to statistical information

Children with TS showed enhanced sensitivity to statistical information compared to their typically developing peers. This result is in line with previous studies showing speeded processing on tasks tapping into procedural learning and memory (Walenski *et al.,* 2007; Dye *et al.,* 2016; Shephard *et al.,* 2018; Takács *et al.,* 2018). In the present study, the enhanced sensitivity to statistical information was more prominent at the beginning of the task. The steepness of the learning curve is a sensitive index of how learning occurs in a specific group (Barnes *et al.,* 2010). Prior studies on neurotypical population showed that statistical learning reach a plateau early, hence, probabilistic information is learned rapidly and then remains stable (Kóbor *et al.,* 2018; Simor *et al.,* 2019). Our results showed the same pattern in both groups, however, it happened faster in the TS than in the TD group. Similar pattern was reported in the study of Takács *et al.* (2018), in which children with TS showed better learning at the end of the first learning session than their TD peers. The study of Takács *et al.* (2018) employed a probabilistic sequence learning task, in which participants acquire probabilistic information in an incidental manner. In that task version with non-cued stimuli, learning may occur in a slower pace than in the cued version of the task (note that the knowledge of statistical information

remains consciously inaccessible to participants even in the cued version of the task; for more details, see Simor *et al.,* 2019). Thus, faster procedural learning in TS can be found in both non-cued and cued learning situations, and in a more speeded manner in the latter case.

Our result is in line with previous studies that used tasks with probabilistic sequence structure (Shephard *et al*., 2018; Takács *et al*., 2018). While these tasks were linked to procedural learning processes, it was not clear whether sensitivity to sequential or to probabilistic information (statistical learning) led to the enhanced performance. According to the results of the present study, enhanced sensitivity to probabilistic information may contribute to procedural hyperfunctioning. This is in line with the notion of procedural hyperfunctioning in TS, supported by Takács *et al.* (2018) and Shephard *et al.* (2018). The probabilistic sequence learning measured by the study of Takács *et al.* (2018) and statistical learning investigated in the present study are highly similar, as both require the acquisition of frequency-based information. Moreover, in the study of Shephard *et al.* (2018), children with TS showed difficulties with transitioning from sequence to non-sequence blocks in the SRT task, indicating hyperlearning.

Sensitivity to statistical information might also explain the results of studies showing enhanced performance on language-based tasks (Walenski *et al*., 2007. Dye *et al*., 2016). The acquisition of complex probabilistic regularities (extraction of 2nd order non-adjacent transitional probabilities) has been found to be crucial in language acquisition and processing (Saffran *et al*., 1996; Thompson and Newport, 2007; Conway *et al.*, 2010; Misyak *et al.*, 2010; Németh et al., 2011). We can see this, for instance, in studies showing that transitional probabilities between pairs of syllables are essential in the detection of word boundaries (Saffran *et al*., 1996). Processing statistical information is also part of syntactic processing, as transitional probabilities between word-like units help to detect phrase boundaries (Thompson and Newport, 2007). Moreover, processing of non-adjacent dependencies and individual differences in statistical learning are associated with differences in language ability (Misyak *et al*., 2010). Németh *et al.* (2011) also found evidence for the relation of statistical learning (with non-adjacent dependencies) and sentence processing in healthy adults. Kidd (2012) also reported an empirical demonstration of the association between statistical learning and syntactic processing in children. These results suggest that the processing of statistical information is important in language acquisition and language processing from infancy to adulthood.

Therefore, the "speeded grammatical processing" seen in children with TS (Walenski *et al*., 2007; Dye *et al*., 2016) could reflect their enhanced sensitivity to statistical information. In detail, the non-word repetition task used in the study of Dye *et al.* (2016) involves rule-governed

(de)composition of the non-words. Participants do not simply repeat the non-words, they separate them into phonological segments then attempt to reconstruct them. This process is influenced by the phonotactical constraints of the language (see e.g., Coady and Evans, 2008). Acquiring and using phonotactical constraints within words requires detecting and using transitional statistics, i.e., statistical learning. Moreover, the faster production of regular past tenses in TS (Walenski *et al.*, 2007) can also reflect enhanced sensitivity to statistical information, as rule-governed composition of morphemes also involves transitional statistics. However, it is not clear how enhanced sensitivity to probabilistic information can explain the speeded tool but not animal naming in TS (Walenski *et al.*, 2007). It might be possible that better statistical learning has an additive effect, which can be generalized to tool naming (and perhaps to other procedural functions), but further studies are warranted to investigate this notion.

One can argue that other alternative explanations may better explain the group differences found in the present study. One such alternative explanation could be a general "speeded processing" in TS, that could be captured by generally faster reaction times, irrespective of the stimulus types. However, generally faster reaction times cannot alone explain the accumulating evidence of procedural hyperfunctioning in TS. Takács *et al.* (2018) found that children with TS showed more prediction errors indicating enhanced procedural functions, while in the study of Shephard *et al.* (2018) children with TS showed difficulties with the transition from sequenced to non-sequenced learning. None of these learning measures are directly related to "speeded processing". Furthermore, general "speeded processing" cannot explain the findings of Walenski *et al.* (2007). If children with TS had overall faster response times, it would have manifested not only in producing regular past tenses and tool naming (related to procedural functions) but also in producing irregular past tenses and animal naming (related to declarative functions) (Walenski *et al.*, 2007). However, the study of Walenski *et al.* (2007) showed no differences between the TS and TD groups in response times related to declarative functions, suggesting that general "speeded processing" cannot explain their results. Moreover, our current results also do not support generally faster processing or response execution as we did not find a difference between the TS and the control group in average reaction times (indicated by the non-significant main effect of Group; see Results). Note that the general "speeded processing" notion detailed above is different from the Clinical Extension Hypothesis, introduced in the study of Dye *et al.* (2016). This hypothesis proposes that neurobiological alterations in TS might result in speeded performance supported by processes related to the neurobiological alterations.

4.2. Sensitivity to sequential information

Our results indicate impaired sequence learning in TS as children did not differentiate between pattern high-frequency and random high-frequency triplets. Similar alterations have been demonstrated in previous studies of motor learning in TS (Stebbins *et al*., 1995; Avanzino *et al*., 2011; Palminteri *et al*., 2011). Avanzino *et al.* (2011) found impaired performance in TS children on a sequential single-hand finger-tapping task. Similarly, Stebbins *et al.* (1995) reported deficits in a motor learning task in TS. Furthermore, in the study of Palminteri *et al.* (2011), TS and TD showed different performance in a motor skill learning task, where triplets were associated with different outcomes: high reward or minimal reward. While participants with TS showed enhanced learning in the high reward condition, the group difference was reversed when only minimal reward was present. Therefore, possible sequence learning impairment can be modified or even masked by other involved processes such as the reward system. In our study, the task was designed to clearly differentiate between sequence learning and sensitivity to probabilistic information.

Accumulating evidence based on neurotypical population suggests a dissociation between statistical learning (processing of frequency-based information) and sequence learning (processing of serial order information). First, previous studies suggested at least partially different developmental trajectories of statistical and sequence learning (Németh *et al*., 2013). Second, while statistical information is typically acquired relatively rapidly and incidentally, sequence learning seems to occur with gradually improving performance, irrespective of whether it occurs incidentally or intentionally (at least, when measured with the ASRT task; Howard and Howard, 1997; Howard *et al.*, 2004; Simor *et al*., 2019). Furthermore, they are distinguishable on the neural level as suggested by event-related potentials during learning (Kóbor *et al*., 2018) and by neural oscillations during consolidation (Simor *et al*., 2019). The present study further supports the notion of multifactorial procedural learning, as we found a dissociation between two aspects of learning in the clinical group: the TS group showed enhanced statistical learning and impaired sequence learning on the ASRT task. It is possible that the two aspects of learning compete with one another in TS. Therefore, having enhanced processing on one of them results in having a disadvantage on the other. Future studies are warranted to test this possibility.

Note that we used a cued version of the ASRT task since previous studies showed relatively faster acquisition of the alternating sequence in this task version (e.g., Kóbor *et al.*, 2018; Simor *et al.*, 2019), enabling to measure statistical and sequence learning in the same

time frame (i.e., within one learning session). Consequently, while statistical learning occurred incidentally in the current study, sequence learning could have been supported by incidental as well as intentional learning processes. The intention to learn may have interfered with the acquisition of the alternating sequence selectively in the TS group but not in the TD group. This interpretation, however, seems unlikely. Both groups showed similar working memory and executive function capacity (see Table 1), suggesting similar cognitive resources that are required to follow the instructions in the task. Indeed, both groups acquired similar level of explicit knowledge about the sequence (as measured by the *sequence reports* after each block). The weaker performance in the TS group appeared to be limited to weaker sequence learning as measured by the reaction time *learning scores*. Additionally, the fast pace of the task (typical responses under 500 ms) makes it difficult for the consciously accessible sequence knowledge to substantially influence participants' response times, leading to at least somewhat dissociable measures (Horváth *et al.,* 2018). In this view, the sequence report may serve as a more explicit measure of sequence knowledge, and the reaction time learning scores may reflect a more implicit, incidental measure of sequence knowledge, even in an intentional learning situation. This pattern of findings suggests that, even though participants performed a cued version of the task and had intention to learn the alternating sequence, the TS group's weaker performance may be selective to the implicit measure of sequence acquisition, irrespective of whether learning occurs incidentally or intentionally. Nevertheless, future studies are needed to directly test this possibility.

4.3. Procedural functioning and symptom severity in TS

We tested the spectrum of tic severity using the Yale Global Tic Severity Scale. Sensitivity to statistical information showed marginally significant negative correlation with the severity of tics, indicating that enhanced sensitivity to statistical information can emerge in conjunction with less severe tics. Besides tic severity, premonitory urges could also relate to sensitivity to statistical information. Premonitory urges are described as a feeling of tightness or tension resulting in discomfort or distress and only can be relieved by performing specific tics (Robertson *et al.*, 2017). However, the relation between premonitory urges and tics is not deterministic, tics can be present without premonitory urges. It has been shown that premonitory urges are associated with interoceptive awareness (Ganos *et al.*, 2015). Interoceptive information is processed implicitly. Being highly sensitive to implicit statistical information could lead to being more aware of or sensitive to premonitory urges. The relation between procedural hyperfunctioning and sensitivity to premonitory urges may also converge

on the neural level as supplemental motor area is important in both processes (Peterson *et al*., 1999; Grafton *et al.*, 2002; Conceição *et al*., 2017;). Future studies should explore this connection between sensitivity to statistical information and to premonitory urges, especially considering the importance of premonitory urge detection in therapy (see habit reversal training, Piacentini and Chang, 2005).

4.4. Limitations and clinical implications

The finding of the present study is limited to a specific TS population, namely, those with less severe symptoms and without comorbidities. In our study, participants with TS are characterized with mild to moderate symptoms, indicated by the YGTSS. Future studies should test whether procedural hyperfunctioning is present in children with severe symptoms. Additionally, most of the children in the clinical group had TS without comorbidities (only 3 children had comorbid ADHD and 1 comorbid ADHD and OCD), therefore, sensitivity to statistical information seems to be specific to TS. Comorbidities can contribute to a greater interindividual variability in procedural functions and may mask the differences specifically related to TS. Future studies are warranted to examine sensitivity to statistical information in subgroups of TS population, such as TS with specific comorbidities. Future investigations also seem to be warranted on whether these findings extend to disorders with similar neurocognitive profiles as TS, such as OCD (Roth *et al*., 2004).

Our study has both clinical and educational implications. Procedural memory plays an important role in skill acquisition, such as sports, language, or even social skills (Lieberman, 2000; Kaufman *et al*., 2010; Frith and Frith, 2012). Strong skill-based competencies in TS could help reduce the disadvantages related to the disorder. Moreover, skill-based training using frequency-based information might also help in reducing behavioral symptoms and learning disadvantages. Future studies are needed to develop such training methods or improve already existing ones, and to test their effects in practice.

4.5. Conclusion

In the present study, our aim was to investigate two aspects of procedural learning, namely statistical and sequence learning, and test whether these aspects of learning contribute to the procedural hyperfunctioning in TS proposed by previous studies. Our results showed further evidence for enhanced procedural functions in TS with a heightened sensitivity to statistical information, while sequence learning was impaired in TS. These results suggest that

sensitivity to frequency-based information may contribute to the procedural hyperfunctioning in TS, shedding light on a cognitive advantage in TS.

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Competing interest

The authors report no competing interest.

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Supplementary materials

Dissociation between two aspects of procedural learning in Tourette syndrome: Enhanced statistical and impaired sequence learning

Running title: Hyperfunctioning in Tourette syndrome

1. Supplementary data analyses on sample without comorbid diagnoses

In order to check whether comorbidities could confound the results or explain the procedural advantage reported in the manuscript, we have run the same analyses as described in the manuscript on the 17 children with TS without any comorbidities and their matched controls.

1.1 Supplementary Results

We ran a mixed design ANOVA on RT data across the four epochs. Statistical learning was quantified with a mixed design ANOVA with FREQUENCY (random high-frequency and random low-frequency triplets) and EPOCH (1-4) as within-subjects factors and GROUP (TS and TD) as a between-subjects factor. Sequence learning was also quantified with a mixed design ANOVA with ORDER (pattern high-frequency and random high-frequency triplets) and EPOCH (1-4) as within-subjects factors and GROUP (TS and TD) as a between-subjects factor. To test for post hoc pairwise comparisons, we used LSD (Least Significance Difference) tests.

As for **statistical learning**, the main effect of FREQUENCY was significant ($F(1, 32) = 56.11$, $p < .001$, $\eta^2_p = 0.637$), indicating that RTs were faster on random high-frequency triplets than on random low-frequency ones. The main effect of EPOCH was also significant ($F(3, 96) = 42.16$, $p < .001$, $\eta^2_p = 0.569$), meaning that over groups, participants became faster with practice on both triplets. Crucially, the FREQUENCY*EPOCH*GROUP interaction was significant ($F(3, 96) = 3.50$, $p = .018$, $\eta^2_p = 0.099$), meaning that the time course of statistical learning was different between the groups. Similarly to the results presented in the manuscript, follow-up analysis revealed a difference in the first epoch between the groups: The TS group showed higher learning than the TD group (TS: $M = 28.14$ ms, $SD = 28.95$ ms; TD: $M = -3.47$ ms, $SD = 29.55$ ms). There was no difference in the remaining epochs (all ps > .397). The main effect of GROUP and other interactions were not significant (all ps > .102).

As for **sequence learning**, the main effect of ORDER was significant ($F(1, 32) = 8.90$, $p = .005$, $\eta^2_p = 0.218$), meaning that participants showed faster RTs on the pattern high-frequency triplets compared with the random high-frequency triplets. The main effect of EPOCH was significant as well ($F(3, 96) = 44.35$, $p < .001$, $\eta^2_p = 0.581$), suggesting that participants showed faster RTs with practice over both triplets. Similarly to the results in the manuscript, the ORDER*EPOCH interaction was significant ($F(3, 96) = 5.02$, $p = .032$, $\eta^2_p = 0.136$), meaning that the groups differed in the RT difference between the triplets. Follow-up analysis on the learning scores suggests that while the TD group learned to differentiate between the triplets, the TS group showed similar RTs on both triplets (TD: $M = 46.65$ ms, $SD = 71.27$ ms; TS: $M = 6.63$ ms, $SD = 18.51$ ms). The EPOCH*GROUP interaction was significant ($F(2.0, 65.9) = 3.77$, $p = .027$, $\eta^2_p = 0.106$), other main effects or interactions were not significant (all ps > .253).

To summarize, analyses without comorbidities showed *identical result as our original analyses*, indicating that the inclusion of participants with ADHD and OCD comorbidities in the TS group explains neither the procedural enhancement, nor the results of sequence learning.