Title: Is procedural memory enhanced in Tourette syndrome? Evidence from a sequence learning task

Running title: Procedural memory in Tourette syndrome

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Abstract

Procedural memory, which is rooted in the basal ganglia, underlies the learning and processing of numerous automatized motor and cognitive skills, including in language. Not surprisingly, disorders with basal ganglia abnormalities have been found to show impairments of procedural memory. However, brain abnormalities could also lead to atypically enhanced function. Tourette syndrome (TS) is a candidate for enhanced procedural memory, given previous findings of enhanced TS processing of grammar, which likely depends on procedural memory. We comprehensively examined procedural learning, from memory formation to retention, in children with TS and typically developing (TD) children, who performed an implicit sequence learning task over two days. The children with TS showed sequence learning advantages on both days, despite a regression of sequence knowledge overnight to the level of the TD children. This is the first demonstration of procedural learning advantages in any disorder. The findings may further our understanding of procedural memory and its enhancement. The evidence presented here, together with previous findings suggesting enhanced grammar processing in TS, underscore the dependence of language on a system that also subserves visuomotor sequencing.

The procedural memory system underlies the learning, storage, and use of implicit cognitive and perceptual-motor skills and habits (Goodman, Marsh, Peterson, & Packard, 2014; Poldrack et al., 2001; Poldrack & Foerde, 2008; Ullman, 2004, 2016). Evidence suggests that the system is multifaceted in that it supports numerous functions that are performed automatically, including sequences, probabilistic categorization, and grammar, and perhaps aspects of social skills (Fiser & Aslin, 2001; J H Howard & Howard, 1997; Lieberman, 2000; Mayor-Dubois, Zesiger, Van der Linden, & Roulet-Perez, 2015; Poldrack & Foerde, 2008; Pothos, 2007; Ullman, 2016). Thus, procedural memory offers an important construct for studying interactions between language, sensory, and motor processes. It has been suggested that prediction-based mental simulations underlie this wide range of processes (Barsalou, 2008).

The procedural system relies on a brain network which is rooted in frontal/basal-ganglia circuits (Doyon et al., 1998, 2009; Stillman et al., 2013; Ullman, 2016). Not surprisingly, impairments of procedural memory have been found in a wide range of developmental and adult-onset disorders with basal ganglia abnormalities (e.g., attention deficit hyperactivity disorder: Barnes, Howard, Howard, Kenealy, & Vaidya, 2010; Parkinson's disease: Clark, Lum, & Ullman, 2014; obsessive compulsive disorder: Kathmann, Rupertseder, Hauke, & Zaudig, 2005; specific language impairment: Lum, Conti-Ramsden, Morgan, & Ullman, 2013; dyslexia: Lum, Ullman, & Conti-Ramsden, 2013).

Despite the basal ganglia abnormalities found in Tourette syndrome (TS), this disorder may be different. TS, which has prevalence rate of about 0.85% to 1% (M. M. Robertson, 2015a), is a neurodevelopmental disorder characterized by at least one vocal tic and multiple motor tics, which are not explained by medications or another medical condition (DSM-5,

American Psychiatric Association, 2013). The tics in TS are fast, abrupt, recurrent, and semi-voluntary (DSM-5, American Psychiatric Association, 2013). The disorder is associated with alterations of the basal ganglia and closely connected cortical regions (especially motor and other frontal cortices), which seem to lead to tics at the behavioral level (Albin & Mink, 2006; Müller-Vahl et al., 2009, 2014).

Apart from motor tics, other motor alterations have been also found in TS. These include fine-motor coordination deficits (Bloch, Sukhodolsky, Leckman, & Schultz, 2006), slower execution of simple motor series (Avanzino et al., 2011), and a lack of bimanual asymmetry in drawing (Georgiou, Bradshaw, Phillips, Cunnington, & Rogers, 1997). However, motor impairments alone cannot explain the altered cognition and behavior in TS (Goodman et al., 2014; M. M. Robertson, 2015b). Similarly to other movement disorders (Cardona et al., 2014), individuals with TS also show alterations in executive function (Jung, Jackson, Parkinson, & Jackson, 2013), language (Dye, Walenski, Mostofsky, & Ullman, 2016; Walenski, Mostofsky, & Ullman, 2007), and memory processes (Crawford, Channon, & Robertson, 2005; Dye et al., 2016; Kéri, Szlobodnyik, Benedek, Janka, & Gádoros, 2002; Marsh et al., 2004; Palminteri et al., 2011; Ullman & Pullman, 2015).

Interestingly, alterations of procedural memory have been proposed as one of the neurocognitive underpinnings of tics in TS (Goodman et al., 2014; Kéri et al., 2002; M. M. Robertson, 2015b). Moreover, procedural memory is an ideal avenue to study mental simulations, which play a role in various motor and cognitive processes (Barsalou, 2008). Nevertheless, to our knowledge only four studies of TS have examined the learning of cognitive or perceptual-motor skills in tasks that depend on procedural memory (Channon, Pratt, & Robertson, 2003; Kéri et al., 2002; Marsh et al., 2004; Takács et al., 2017). These have yielded mixed results, with two reporting impaired learning (Kéri et al., 2002; Marsh et

al., 2004) and two finding normal learning (Channon et al., 2003; Takács et al., 2017). We are not aware of any studies that have comprehensively examined the broader process of learning in procedural memory in TS, from initial memory formation through overnight retention – despite the fact that retention is the goal of skill learning, and such a delay appears to be critical for consolidation, that is, the stabilization of memories (Breton & Robertson, 2014; E. M. Robertson, 2009).

Despite the absence of studies examining procedural learning and retention in TS, two studies have probed already-established, i.e., previously-learned, procedures (Dye et al., 2016; Walenski et al., 2007). Both of these examined a key aspect of cognition that has been linked to procedural memory, namely grammar (Ullman, 2004, 2016). Despite grammatical deficits in various other disorders affecting the basal ganglia, such as Parkinson's disease, Huntington's disease, and specific language impairment (Ullman et al., 1997; Ullman & Pierpont, 2005), both of these TS studies reported *faster* rule-governed grammatical processing in children with TS than typically developing (TD) children (with no differences in accuracy). One study found speeded processing of regular past-tense forms, whose rule-based composition has been linked to procedural memory, but not of irregular past-tenses, which appear to be stored in declarative memory (Walenski et al., 2007). This study also reported, in the same children with TS, speeded naming of manipulated objects (e.g., hammer), which rely on procedural knowledge (how to manipulate the object), but not of non-manipulated objects (e.g., elephant). A more recent study observed speeded repetition of non-words (e.g., "naichovabe"), which was explained by the speeded grammatical composition of phonological segments (Dye et al., 2016). Both studies suggested that the findings may be explained by speeded procedural processing, due to some sort of enhancement of procedural memory in TS (Dye et al., 2016; Walenski et al., 2007). Thus, understanding procedural

memory in TS may shed light on the dependence of language on non-linguistic neurocognitive correlates.

What might account for the previously-observed pattern of procedural learning and processing? One possibility is that the learning of procedures in the disorder remains normal or even impaired, but after they are learned, their processing may be speeded, perhaps due to mechanisms that underlie processing but not learning. However, another possibility is that procedural learning (perhaps in addition to processing) is enhanced in TS, but that previous studies of procedural learning in TS used tasks that might be learned in part in other memory systems, such as declarative memory (Kéri et al., 2002; Marsh et al., 2004), or may have had insufficient power due to few subjects (Channon et al., 2003; Takács et al., 2017). Additionally, since grammar involves sequences, which might have privileged status in procedural memory (Hsu & Bishop, 2014; Krishnan, Watkins, & Bishop, 2016), it is possible that sequence learning, in particular, might be enhanced in TS. Indeed, the two studies finding impairments in TS examined non-sequence procedural learning (Kéri et al., 2002; Marsh et al., 2004).

The present study was designed to test the hypothesis that procedural learning and/or retention of sequences may in fact be enhanced in TS. We tested 21 children with TS and 21 TD children on the Alternating Serial Reaction Time (ASRT) task. This widely-employed task probes the procedural learning of visuomotor sequences with continuous measurements – allowing one to detect exactly when any group differences in learning might emerge – with no known dependence on declarative memory (J H Howard & Howard, 1997; Song, Howard, & Howard, 2007a). Crucially, we examined not only initial learning, but also retention, which together were examined in two sessions given on subsequent days. Finally, in order to test whether enhanced sequence learning might be specific to procedural memory, rather than a

broader learning or memory effect, and to exclude the possibility that learning in this task depends on declarative memory, we also tested declarative memory in both groups.

Materials and Methods

Participants and procedure

Thirty-four children with TS (30 boys and 4 girls) between the ages of 8 and 15 years were recruited from Vadaskert Child Psychiatry Hospital in Budapest, Hungary. Children had been diagnosed with TS by both a licensed clinical psychologist and a board-certified child psychiatrist at the hospital, according to the DSM-IV-TR criteria (American Psychiatric Association, 2000). None of the TS children were on medication for the disorder when they were tested. Children with comorbid neurodevelopmental or psychiatric disorders were excluded — specifically those with specific language impairment, learning disorder (dyslexia and dyscalculia), conduct disorder, or major depression. Co-morbid attention deficit hyperactivity disorder and obsessive-compulsive disorder were not exclusionary criteria, since these disorders are common in children with TS.

Twenty-six TD children were recruited from local schools (20 boys and 6 girls, see Table 1). They ranged between 8 and 14 years of age, and had no known psychiatric, neurological, or neurodevelopmental disorders, according to school psychologists and the SDQ (see below).

From these TS and TD children, we selected 21 from each group that were matched on sex (16 males and 5 females in each group) and age. The 21 TS and 21 TD children were matched one-to-one based on the basis of both school grade and age, with both individuals in each pair being in the same grade and differing in age by no more than six months. Five of the

21 children with TS had comorbid ADHD, and one had comorbid OCD. All participants were native speakers of Hungarian.

All participants (TD and TS) had normal or corrected-to-normal vision, and normal hearing. Parents of all participants were asked to fill in the Strengths and Difficulties Questionnaire (Goodman, 1997) (SDQ, see Table 1) to estimate potential psychiatrically relevant symptoms, including hyperactivity, emotional symptoms, conduct problems, and peer difficulties. Parents of all participants signed an informed consent form, and did not receive financial compensation for their participation. Ethical permission was obtained by the national United Ethical Review Committee for Research in Psychology.

Based on their consents, the partner hospital made accessible, for 15 of the 21 children with TS, the scores from the Yale Global Tic Severity Scale (YGTSS, see Table 1) (Leckman et al., 1989), which rates motor and phonic tics in TS. We report Total Score of the questionnaire, which consists of severity of motor and phonic tics, without the subjective impairment rates. Story and word-list learning assess learning in declarative memory.

The experiment consisted of two sessions, for both the TS and the TD groups. The first session (Session 1) took place in the afternoon of the first day, whereas the second session (Session 2) took place the next morning, after a 16 hour delay. The ASRT task was given both days, with 20 blocks in each day. The tasks probing declarative memory (story learning and word-list learning) were given only in the first session.

Tasks

Procedural learning task: the Alternating Serial Reaction Time (ASRT) task

Sequence learning was measured by the Alternating Serial Reaction Time (ASRT) task (J H Howard & Howard, 1997; Nemeth et al., 2010; Song, Howard, & Howard, 2007b;

Virag et al., 2015). This widely-used version of the serial reaction time (SRT) task allows for continuous measurement of sequence learning. Converging evidence suggests that this learning occurs in procedural memory: sequence learning in serial reaction time and related tasks is linked to frontal/basal-ganglia circuits, in particular when it is implicit (Clark et al., 2014; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Vakil, Kahan, Huberman, & Osimani, 2000)(Stillman et al., 2013), and learning in the ASRT task is highly implicit, with no evidence across multiple studies of any explicit knowledge, either in adults (J H Howard & Howard, 1997; Nemeth et al., 2010; Romano, Howard, & Howard, 2010; Song et al., 2007a) or children (Barnes et al., 2010; Janacsek, Fiser, & Nemeth, 2012; Nemeth, Janacsek, & Fiser, 2013).

In this task, a target stimulus (a dog's head) appeared in one of four possible locations (empty circles) on the screen, in a horizontal arrangement. Participants were asked to press the corresponding key (Z, C, B and M on a QWERTY keyboard, representing the four locations on the screen) as quickly and accurately as they could. Each stimulus remained on the screen until the participant pressed the key corresponding to the target. Following the response, and a subsequent delay of 120 ms, the next target appeared.

The basic trial sequence consisted of eight elements, in which random trials alternated with pattern trials (e.g., 1r2r3r4r). Six sequence patterns were counterbalanced across participants in each participant group: 1r2r3r4r, 1r2r4r3r, 1r3r2r4r, 1r3r4r2r, 1r4r2r3r, and 1r4r3r2r, where 1-4 indicate the target locations from left to right, and r indicates a randomly selected position out of the four possible ones. This structure results in some of the three consecutive elements (henceforth referred to as Triplets) occurring more frequently than others (J H Howard & Howard, 1997; Nemeth et al., 2010). The former ones are referred to as high-frequency triplets, occurring in 62.5% of all trials, while the latter ones are referred to as

low-frequency triplets, occurring in 37.5% of all trials. Note that each item was categorized as the third element of either a high- or low-probability triplet. Two types of low-frequency triplets were eliminated from analysis, repetitions (e.g., 111, 444) and trills (e.g., 121, 242), since participants often show pre-existing response tendencies to these items, which moreover occur infrequently (D. V Howard et al., 2004; Song et al., 2007a, 2007b). The task had 20 blocks, each consisting of 85 trials (presentations of the dog's head, with their corresponding key presses). In each block, the first 5 trials were randomly positioned, and were for practice purposes only (not analyzed further), after which the 8-element alternating sequence was repeated 10 times. Participants were allowed to take a brief break between each block.

Accuracy and reaction times (RT) of the responses to these items constituted the dependent measures (J H Howard & Howard, 1997; Nemeth et al., 2010; Song et al., 2007a). In the ASRT task, the key measures of *sequence learning* is operationalized as increasing differences in RTs or accuracy between high- and low-frequency triplets over the course of the task (J H Howard & Howard, 1997; Song et al., 2007a). Sequence learning or knowledge is often also operationalized as differences between high- and low-frequency triplets at any given point in time during the task (Barnes et al., 2010; D. V Howard et al., 2004; Nemeth, Janacsek, Király, et al., 2013). In accuracy, this difference is often a result of decreasing accuracy for low-frequency triplets, while performance for the high-frequency ones remains stable, with a high accuracy. It has been suggested that this pattern (Curran, 1997; Feeney, Howard, & Howard, 2002; J H Howard & Howard, 1997; D. V. Howard & Howard, 2001; Schvaneveldt & Gomez, 1998) may be explained by the acquisition of high- vs. low-frequency regularities (D. V Howard et al., 2004; Song et al., 2007a, 2007b). In particular, as participants learn the high-frequency triplets, they may make more errors on low-frequency triplets because they increasingly predict the last element of a high-frequency rather than that of a low-frequency triplet. Thus, this increasing accuracy difference between high- vs. low-

frequency triplets is taken to indicate probabilistic sequence learning (Curran 1997; Howard and Howard 1997, 2001; Feeney et al. 2002; Howard et al. 2004; Song et al. 2007a, 2007b; Csábi et al. 2016).

Declarative learning tasks: story learning and word-list learning

Learning in declarative memory was measured with two tasks: a story learning task and a word-list learning task (see Table 1). We used the Hungarian version of "The War of the Ghosts" test as a story learning task (Csábi, Benedek, Janacsek, Katona, & Nemeth, 2013). In this test, participants were asked to listen to a short story that consists of 36 sentences. They were asked to recall it as best as possible both immediately after listening to it (immediate story recall) and again 15 minutes later (delayed story recall). According to standard scoring procedures (Gauld & Stephenson, 1967), in each recall test each sentence is worth 1 point for verbatim recall and 0.5 points for a non-verbatim response that retained the 'core' information of the sentence (Csábi et al., 2013; Gauld & Stephenson, 1967). Additionally, to capture how much of the knowledge that was actually learned immediately was then later retained (or forgotten) after the 15 minute delay, we also computed a difference score between delayed story recall and immediate story recall (Csábi et al., 2013).

In the word-list learning task (Strauss, Sherman, & Spreen, 2006), participants were visually presented with a list of 15 Hungarian nouns, each of which was shown on the screen for 5 seconds. Immediately after three presentations of this list participants were asked to recall it as accurately as possible (immediate word-list recall). Fifteen minutes later, they were asked again to recall the list (delayed word-list recall). In each recall test, each correctly recalled word is worth 1 point regardless of its position in the original word list. Similarly to

the story recall task, we calculated a difference score between delayed word-recall and immediate word-list recall.

Statistical Analysis

Since the present paper focuses on procedural learning in TS, as measured by the ASRT task, here we describe the statistical analyses of this task. See the Results section for the (simpler) analyses for the other tasks.

The statistical analyses of the ASRT task were based on previous studies (J H Howard & Howard, 1997; Nemeth et al., 2010; Romano et al., 2010; Song et al., 2007b). The entire ASRT task over both sessions was collapsed into 8 epochs (four in each session), each of which consisted of 5 blocks (James H. Howard, Howard, Japikse, & Eden, 2006; Nemeth et al., 2010; Nemeth, Janacsek, Király, et al., 2013). Mean accuracy (percentage of correct responses) and medians of RT data (for correct responses) were calculated for each participant and each epoch, separately for high- and low-frequency triplets. We also calculated sequence knowledge scores as the difference in RT or the difference in accuracy between low- and high-frequency triplets, separately for each epoch.

To examine probabilistic sequence learning across the two groups, accuracy and RT data were analyzed in a mixed design ANOVA on the 8 epochs of Session 1 and 2, with TRIPLET (2: high vs. low) and EPOCH (1–8) as within-subjects factors, and GROUP (TS vs. TD) as a between-subjects factor. As follow-up analyses, we conducted mixed design ANOVAs on the sequence knowledge scores (i.e., accuracy or RT differences between high- and low-frequency triplets; see above), with EPOCH (1-8) as a within-subject factor, and GROUP (TS vs. TD) as a between-subject factor. Note that GROUP*EPOCH interactions may indicate fatigue or other general task effects, which are not of interest here. Instead, a GROUP*EPOCH*TRIPLET interaction crucially reveals group differences in sequence

knowledge over time, that is, in sequence learning. We also followed up on the ANOVAS with LSD (Least Significant Difference) tests for post hoc pair-wise comparisons. The Greenhouse-Geisser epsilon correction was applied when necessary. Here we report η_p^2 effect size index for ANOVA main effects and interactions. Significance was assessed with $\alpha = .050$. All *p*-values are reported as two-tailed.

Results

Both accuracy and reaction times (RTs) were acquired, as both have been found to reflect sequence learning in ASRT (Csábi et al., 2016; Song et al., 2007a, 2007b). However, when both measures are reported (not always the case), accuracy appears to be a more reliable indicator of sequence learning, including group differences in learning (Hedenius et al., 2013; James H. Howard et al., 2006; Song et al., 2007a, 2007b) – not surprisingly, since accuracy may be a particularly good indicator of prediction errors (Hedenius et al., 2013; D. V Howard et al., 2004; Song et al., 2007a), a key index of learning in procedural memory (J H Howard & Howard, 1997; Song et al., 2007a, 2007b). Thus in the present study, group differences were expected particularly in accuracy.

Analyses of Variance (ANOVAs) on RT (see Methods), with the factors GROUP (2 levels: TS and TD), TRIPLET (2 levels: low-frequency and high-frequency triplets), and EPOCH (8 levels: 4 epochs in session 1 and 4 in session 2), yielded the following pattern: significant TRIPLET and EPOCH*TRIPLET effects, indicating sequence learning over both groups, but no main effects or interactions involving GROUP, suggesting no group differences in sequence learning with RT as the dependent measure (see Supplementary Table 1 and Supplementary Figure 1).

Analyses of accuracy revealed a different pattern. Figure 1A shows accuracy data for the low- and high-frequency triplets as a function of the 8 epochs, for each group. Sequence knowledge scores for accuracy (difference in accuracy between low- and high-frequency triplets; see Methods) for each group are presented in Figure 1B. Most importantly, there were three significant effects involving GROUP (see Table 2).
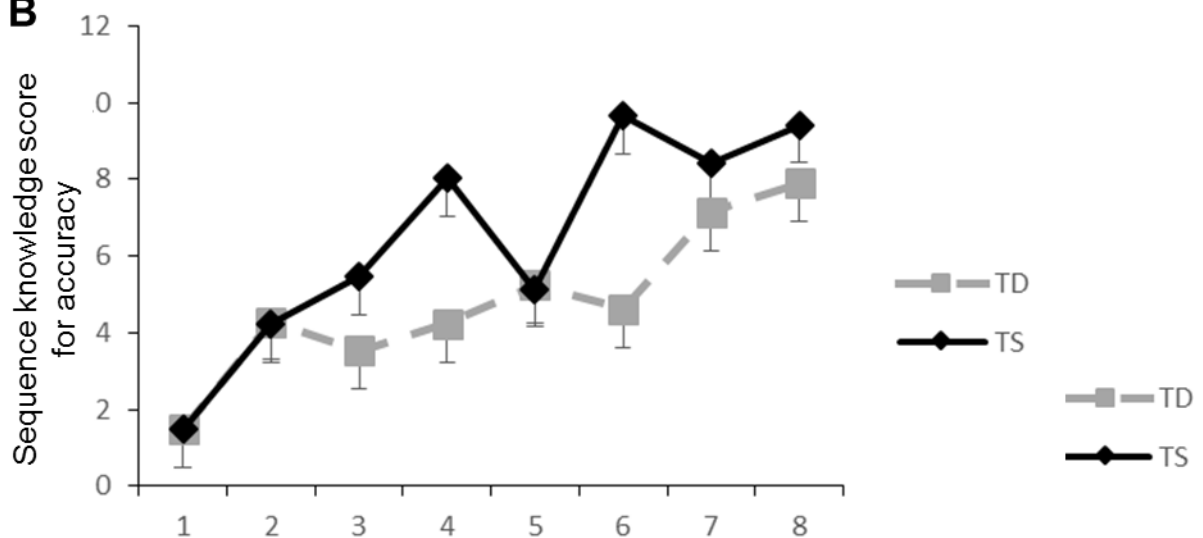
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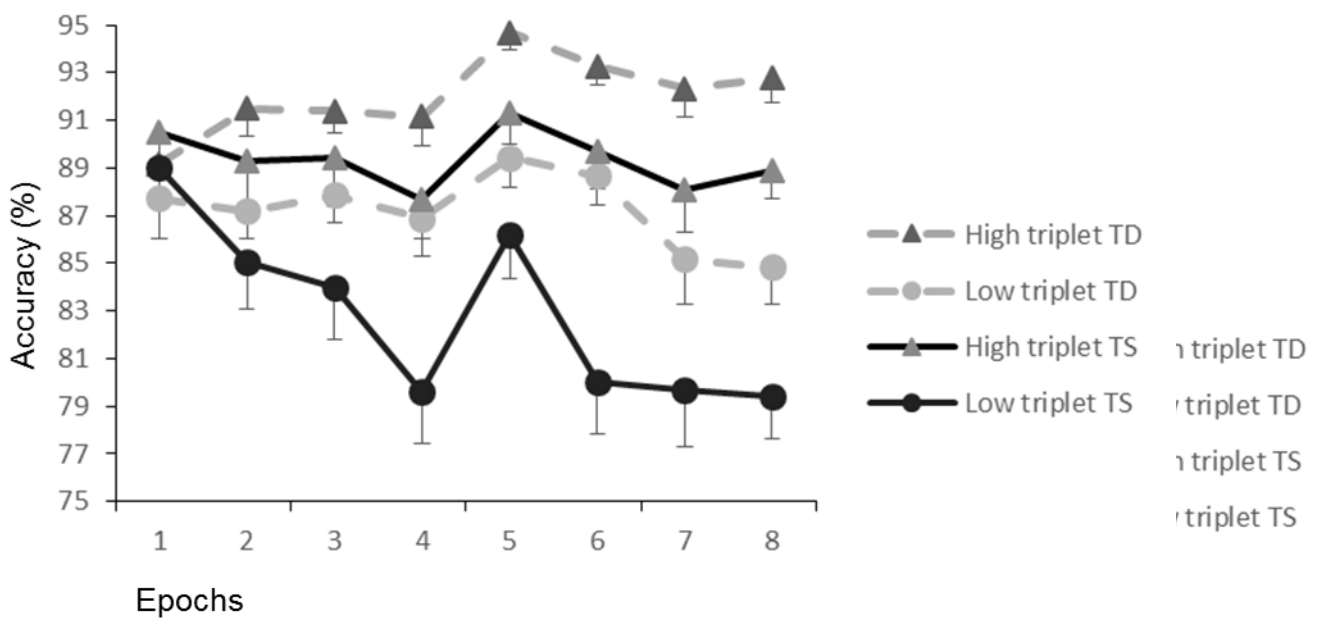
B

Figure 1: (A) Accuracy data by triplet type (high- vs. low frequency triplets) as a function of epoch (1–8), for each group. (B) Accuracy sequence knowledge score (difference between high- and low-frequency triplets) as a function of epoch, for each group. Please see Results and Note to Table 1, including regarding the pattern of change in low- vs. high-frequency triplets. TD = typically developing; TS = Tourette syndrome. Error bars denote standard error of the mean. Vertical line with diagonal pattern represents 16 hour delay.

A main effect of GROUP indicated that the TD children were better overall than the children with TS, while a GROUP*EPOCH interaction suggested that practice had overall different effects in the two groups. Crucially, a significant GROUP*EPOCH*TRIPLET interaction qualified both of these effects, and revealed that the time course of sequence learning was different between the groups. As can be seen in Figure 1A, the low-frequency triplets decrease more in the TS than TD group, consistent with greater sequence learning in the children with TS than the TD children (see Table 2). Indeed, follow up analyses on the sequence knowledge scores confirmed that the children with TS had greater sequence knowledge than the TD children, both in the last epoch of Session 1 (epoch 4: TS: $M =$ 8.05%, $SD = 1.2$%; TD: $M = 4.24$%, $SD = 1.2$%; $p = .032$) and in the second epoch of Session 2 (epoch 6: TS: $M = 9.67$%, $SD = 0.9$%; TD: $M = 4.62$%, $SD = 0.9$%; $p = .001$). No other epoch showed a group difference in sequence knowledge scores ($ps > .406$).

Importantly, unlike in some studies (Roth, Baribeau, Milovan, O'Connor, & Todorov, 2004), there was absence of a group difference of sequence knowledge at the beginning of the task, indicating that the observed group differences in later epochs was due to *learning*, not to a baseline difference between the groups.

To investigate overnight retention, in particular the possibility of consolidation atypicalities in TS, we had planned to compare performance (both with RTs and accuracy as dependent measures) between the end of Session 1 (epoch 4) and the beginning of the Session 2 (epoch 5); that is, before vs. after the 16-hour delay. However, reliable testing of group differences in consolidation requires an equivalent level of knowledge prior to consolidation, since differences in such knowledge can alone be responsible for overnight changes in performance (Hauptmann, Reinhart, Brandt, & Karni, 2005; Wilhelm, Metzkow-Mészàros, Knapp, & Born, 2012). Since the children with TS showed greater sequence knowledge than the TD children at the end of Session 1, such comparisons would not be appropriate for the examination of consolidation differences between the groups. The analyses are nevertheless presented in the Supplementary Results from Retention Analyses for interested readers.

Finally, unlike in the ASRT task, the children with TS and the TD children did not differ on any measure of declarative memory, that is, in the story recall and word-list learning tasks (Table 1; see Methods for specifics on the tasks). To examine possible associations between sequence knowledge and declarative memory, we also performed correlations between ASRT sequence knowledge accuracy scores and accuracy in the story recall and word-list learning tasks. There were no significant correlations between mean sequence knowledge scores for either Session 1 or Session 2 and any of the six measures of declarative learning (immediate, delayed, or retention for either story learning or word-list learning), even without correction for multiple comparisons (ps > .33).

Table 1: Participant information and performance on the tests of declarative memory.

	Group					
	TD (*n* = 21)		TS (*n* = 21)			
	M	*SD*	*M*	*SD*	*t*	*p*
Age in months	137.43	17.52	138.10	18.27	0.216	.831
School grade	5.38	1.56	5.52	1.78	3.11*	.896
SDQ Total problem	14.58	7.53	13.89	2.00	0.121	.904
YGTSS Total score	-	-	26.45	5.32	-	-
Story learning: immediate recall	10.60	3.49	11.17	4.18	- 0.481	.633
Story learning: delayed recall	10.10	3.62	10.83	4.42	-0.592	.557
Story learning: difference score	-0.50	2.07	-0.33	1.44	0.302	.764
Word-list learning: immediate recall	7.81	2.27	8.14	2.10	- 0.493	.625
Word-list learning: delayed recall	6.00	2.26	6.38	2.54	0.514	.610
Word-list learning: difference score	-1.81	1.60	-1.76	1.87	0.089	.930

Note: SDQ: Strengths and Difficulties Questionnaire (Total problem); YGTSS: Yale Global Tic Severity Scale (Total score). The children with TS and the TD children did not differ on either the story learning test or the word-list learning test, on either immediate or delay recall, indicating intact declarative memory in TS. Underscoring normal declarative memory in TS, the TS and TD groups also did not differ on the difference scores (delayed – immediate recall) on either test. *P*-values below .050 are **boldfaced.** *: Exact significance test was selected for Pearson's chi-square since the assumptions for a chi-squared test (at least 80% of the expected counts are more than five and all expected counts exceed one) were not met.

Table 2: Results from ANOVAs performed on all 8 epochs on ASRT accuracy data.

Effect	*F*	*p*	η_p^2
GROUP	5.135	**.029**	.114
EPOCH	3.686	**.001**	.084
TRIPLET	146.94	**< .001**	.786
GROUP*EPOCH	2.429	**.020**	.057
EPOCH*TRIPLET	121.1	**< .001**	.232
GROUP*TRIPLET	3.270	.078	.076
GROUP*EPOCH*TRIPLET	2.05	**.049**	.049

Note: The ANOVA on accuracy on all 8 epochs yielded the following pattern. The main effect of GROUP was significant, indicating that TD children were better overall in their accuracy than the children with TS (TD: $M = 89.62\%$, $SD = 1.1\%$ vs. TS: $M = 86.11\%$, $SD = 1.1\%$). There was a main effect of EPOCH, due to accuracy decreasing over the course of practice (1st epoch: $M = 91.43\%$, $SD = 0.7\%$ vs. 8th epoch: $M = 82.7\%$, $SD = 1.1\%$, see Figure 1). Note that this decrease in accuracy over the course the task is often observed, especially for low-frequency triplets (see just below). The main effect of TRIPLET was also significant, such that participants, across both groups, were more accurate on high-frequency than low-frequency triplets ($M = 90.70\%$, $SD = 0.7\%$ vs. $M = 85.0\%$, $SD = 0.9\%$). The GROUP*EPOCH interaction was significant, suggesting that time-on-task had different effects in the two groups (1st epoch: TD: $M = 91.93\%$, $SD = 1\%$ vs. TS: $M = 90.93\%$, $SD = 1\%$; 8th epoch: TD: $M = 85.88\%$, $SD = 1.6\%$ vs. TS: $M = 79.52\%$, $SD = 1.6\%$). There was also a significant EPOCH*TRIPLET interaction. As indicated in Figure 1A, both groups showed an accuracy decrease for low-frequency but not high-frequency triplets (see Methods). A follow-up analysis on sequence knowledge accuracy scores revealed that, over both groups, sequence knowledge increased as the task progressed ($F(1, 40) = 121.1$, $p < .001$, $\eta_p^2 = .232$; 1st epoch: $M_{diff} = 1.48\%$, $SD = 3.7\%$ vs. 8th epoch: $M_{diff} = 8.67\%$, $SD = 5.8\%$). A marginally significant GROUP*TRIPLET interaction was qualified by a significant GROUP*EPOCH*TRIPLET interaction; see main text. *P*-values below .050 are **boldfaced.**

Discussion

Our goal was to comprehensively examine procedural learning in TS, from memory formation through overnight retention and further learning. We employed the Alternating Serial Reaction Time task, which probes the procedural learning of sequences. Children with TS and TD children were tested on the ASRT task twice, in two sessions given on subsequent days. We hypothesized that children with TS would show enhancements in learning and/or retention.

Indeed, the children with TS showed evidence of superior perceptual-motor sequence learning. This held in both sessions, despite a regression of sequence knowledge overnight to

the level of the TD children. The absence of correlations between sequence learning and learning in declarative memory suggests that learning did not take place in that system, underscoring the procedural nature of the task. To our knowledge, this is the first study that suggests aspects of enhanced procedural learning in TS.

The overnight regression of sequence knowledge seems at first blush surprising, given the observed learning advantages, including in the second session. One possibility is that, despite these advantages, children with TS have impairments at overnight consolidation. This is consistent with evidence suggesting that learning and consolidation processes are at least partially distinct in procedural memory (E. M. Robertson, 2009, 2012; Tunovic, Press, & Robertson, 2014). In line with consolidation alterations in TS, motor cortex excitability, which has been linked to procedural memory consolidation (E. M. Robertson & Takacs, 2017), has been found to be decreased in TS (Draper et al., 2014; Jung et al., 2013). Moreover, GABA levels, which are negatively associated with cortical excitability, appear to be elevated in motor cortex in TS (Draper et al., 2014). Additionally, it has been suggested that altered synaptic plasticity, as indicated by cortical excitability alterations, leads to worse skill consolidation in TS (Brandt et al., 2014). However, any links between the current results and such neural correlates is at this point tentative.

More importantly, the remarkable sequence knowledge advantage in the TS group at the end of Session 1 precludes the reliable examination of consolidation differences between the groups, since, as mentioned above, group comparisons of consolidation require equivalent performance prior to this process, since dissimilar performance between groups can in itself lead to group differences in overnight changes (Hauptmann et al., 2005; Wilhelm et al., 2012).

Indeed, consistent with group differences in performance leading to differences in subsequent changes, correlations between the level of sequence knowledge in epoch 4 (the

last epoch of session 1) and the amount of *change* in sequence knowledge overnight (between epochs 4 and 5) did not differ between the TS and TD groups ($z = -0.358$, $p = 0.720$), suggesting that the two groups showed equivalent overnight changes as a function of prior sequence knowledge. Moreover, both of these correlations were significant and negative (TS: $r = -.689$, $p = .001$; TD: $r = -.621$, $p = .003$), indicating the possibility that the greater the sequence knowledge, the greater the possible subsequent loss, for example in the next epoch. Interestingly, this negative relation was general rather than specific to the overnight delay, as it was found across the groups and epochs (as evidenced by significant negative regression effects of sequence knowledge on the amount of change to the next epoch, over both groups for all epochs after epoch 1, ps $< .001$). The same pattern has recently been observed in a large data set examining sequence learning in the ASRT task in children and adults (Janacsek, Juhasz, & Nemeth, 2016), suggesting it may be a general phenomenon. Future studies directly examining this phenomenon, and testing whether consolidation may also play a role, seem warranted.

Thus, overall, the TS group showed procedural learning advantages, as evidenced by their superior sequence learning advantages on both days, despite the overnight regression. Whether or not children with TS would continue to show sequence learning advantages would of course require the examination of learning for a longer period. Although the apparent convergence of sequence knowledge levels at the end of the second day could in part be due to the general pattern of loss following high levels of sequence knowledge, it could also be partly explained by both groups beginning to reach an asymptote of skill knowledge; see Figure 1B. Thus, any future examination of longer-term learning and retention effects could benefit from a task that probes the learning of more complex skills, which might not asymptote within the period of investigation, or at all.

Interestingly, the children with TS tended to make more errors on the low-frequency triplets as the task progressed, while performance on the high-frequency triplets remained stable, at a relatively high level. Thus, the children with TS showed better learning than the TD children by distinguishing between more predictable structured stimuli and less predictable ones. As has been argued (see Methods), this seems to be due to an increasing error rate on the low frequency triplets as the children increasingly learn to predict the last element of high-frequency triplets. Further research is needed to further elucidate the mechanisms underlying this pattern, and to examine whether the resulting TS advantage may be found especially in certain circumstances, such as in less structured contexts that are more demanding.

The learning advantages observed in this study, including on the second day, seem broadly consistent with the previously reported findings suggesting children with TS show enhanced processing of knowledge that was likely learned in procedural memory – that is, the enhanced processing both of grammar, including morphology and phonology, and of motor skill knowledge (Dye et al., 2016; Walenski et al., 2007). A clear link between the observed learning and processing advantages will require experimental approaches targeting this relation, such as testing whether learning advantages are directly associated with processing advantages. The data from the present study provide a critical foundation for such investigations by showing that children with TS are not only faster at processing knowledge which was likely learned in procedural memory, but also at the actual learning of procedural skills. This unique relationship between procedural memory and language skills provides an opportunity to investigate potentially enhanced motor-language coupling, which could elucidate research on embodied cognition (Cardona et al., 2014); future studies can investigate how simulation contributes to the altered cognition in TS. Overall, we suggest that

altered motor functions can lead not only to impaired but also to enhanced memory and language processes.

The present study was not designed to investigate the neural mechanisms underlying enhanced procedural learning. However, it has been suggested that the enhanced processing of procedural knowledge may due to the same frontal/basal-ganglia abnormalities that lead to tics (Dye et al., 2016). Additionally, as mentioned above, it has been suggested that alterations in procedural memory may underlie tics in TS (Goodman et al., 2014; Kéri et al., 2002; M. M. Robertson, 2015b). Future studies testing these hypotheses, and their links to enhanced procedural learning, seem highly warranted.

The study also suggests additional avenues of research, and has various implications. Further studies should probe whether or not the learning advantages are specific to sequence learning (see Hsu & Bishop, 2014; Krishnan et al., 2016). More generally, the findings seem to warrant further investigations of the neurocognitive and developmental mechanisms that can lead to improvements of procedural memory, which could potentially have broader implications. The results underscore the view that developmental disorders can be associated not only with disadvantages but also with potential advantages, as has also been suggested for aspects of cognitive control in TS (Draper et al., 2014; Jung et al., 2013). It is unclear how procedural memory advantages might be related to cognitive control advantages.

Note that, as we have seen above, in studies probing probabilistic categorization, a task that is (at least partly) dependent on procedural memory but does not involve visuomotor sequences, children with TS in fact showed worse performance than their TD counterparts (Kéri et al., 2002; Marsh et al., 2004). This contrast between procedural memory tasks in TS underscores the potential importance of motor-language coupling (Cardona et al., 2014). The different nature of these tasks also raises the possibility of different interconnections and

functional coupling between memory, motor and language processes in the two types of learning task. That is, motor actions in particular may be integrated with memory and language mechanisms, as suggested previously in research on embodied cognition (García & Ibáñez, 2016; Kiefer & Pulvermüller, 2012; Meteyard, Cuadrado, Bahrami, & Vigliocco, 2012). Indeed, the integration between motor action and language plays role even at the semantic level (García & Ibáñez, 2016; Kiefer & Pulvermüller, 2012; Meteyard et al., 2012)., Thus, it is possible that visuomotor sequences and sequential aspects of language both rely heavily on predictive simulations, as opposed to motor-independent probabilistic categorization.

The study has certain limitations. Participants in our study did not receive medications, and they possibly represent the lower end of the tic symptom severity dimension. Additionally, children with TS with various comorbidities were excluded, despite the fact that the presence of comorbidities in TS can contribute to the variability of procedural memory and symptom severity (M. M. Robertson, 2015a; Takács et al., 2017). Thus, it remains to be seen whether and how the findings here generalize to a more heterogeneous TS population. Investigations also seem warranted to examine whether the findings extend to other disorders, in particular those that have similar neurocognitive profiles as TS, such as OCD (M. M. Robertson, 2015a). Indeed, one study of OCD reported findings that the authors argued suggested procedural memory advantages (Roth et al., 2004). Although a highly intriguing result, the OCD group in this study already showed superior performance at baseline, making it difficult to argue convincingly for learning advantages. The present study also underscores the importance of examining not just initial learning, as many if not most studies of procedural (and declarative) memory focus on, but also retention and further learning.

Finally, our study has both educational and clinical implications. Enhanced procedural memory could potentially serve to benefit children with TS, especially for strong skill-based competencies such as reading, mathematics, and language, and perhaps even arts and sports (Evans & Ullman, 2016; Hedenius et al., 2013; James H. Howard et al., 2006; Kaufman et al., 2010). A targeted skill-based education program for children with TS leading to improvements could have downstream effects, including reducing labeling and social marginalization (M. M. Robertson, 2015a). In the clinical field, enhanced procedural memory, and its potential coupling with language skills, could serve as a basis of clinical training for impaired motor processes in TS. A potential candidate could be motor organization, including fine-motor skills (Avanzino et al., 2011; Bloch et al., 2006; Georgiou et al., 1997). Targeting motor skills could be essential in TS, since the level of motor skill impairment in childhood can predict symptom severity in adolescence (Bloch et al., 2006). Procedurally based training might be even more powerful by incorporating rewards. Indeed, it has been shown that children with TS respond well to reinforcement in associative learning (Palminteri et al., 2011). Applied research thus seems warranted to examine the effectiveness of procedural and reward-based training in TS, and to investigate its contribution to already established methods that may depend compensatorily on declarative memory, such as tic suppression training (Ullman & Pullman, 2015).

In sum, this study presented evidence that children with Tourette syndrome show procedural learning advantages, complementing previous findings of advantages at processing grammatical knowledge learned in this system. To our knowledge, this is the first demonstration of procedural learning advantages not only in TS, but in any disorder with frontal/basal ganglia abnormalities, or indeed any developmental or adult-onset disorder.

Acknowledgements

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