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How do alterations of the basal ganglia affect procedural memory in Tourette syndrome?☆

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Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by repetitive movements and vocalizations called tics, which are linked to alterations in the cortico-basal ganglia-thalamo-cortical (CBGTC) circuits. CBGTC circuits also play a key role in procedural memory, which is a fundamental human ability that enables us to extract repeating patterns from the environment and underlies skill-based and habitual behavior. The present review summarizes findings on procedural memory in TS, with a focus on more recent studies probing the acquisition and consolidation of procedural knowledge in TS. The review reveals mixed findings; some aspects of procedural memory seem to be impaired in TS, whereas other aspects appear intact or even enhanced. We discuss these results in relation to alterations in the CBGTC circuits in TS, suggest reasons for potential inconsistencies across studies, and propose directions for future research.

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Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by recurrent, abrupt, semi-voluntary movements, and vocalizations, called tics [1,2]. Tics typically mimic some fragments of normal behavior, but they are misplaced in context and time. There is no generally accepted theoretical model for the development of tics in TS. A potential link between tics and habits has been suggested before [3], both on the behavioral and neural levels. On the behavioral level, tics — just as habits — are automatically executed, inflexible behavioral sequences that are hard to inhibit. On the neural level, TS is characterized by structural and functional alterations in the basal ganglia (BG) and, more broadly, in the related cortico-basal ganglia-thalamo-cortical (CBGTC) circuits. Structurally, studies have shown an increased volume of the putamen [4–6] and a decreased volume of the (anterior) caudate nucleus in TS [7,8], with a lower volume of the caudate in childhood predicting greater tic severity in early adulthood

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[9]. Functionally, studies suggest that tics are associated with an overactive/more strongly connected sensorimotor circuit [5,10–12] that involves the (mid/posterior) putamen [13,14] and an underactive associative circuit [10,11,15] that involves the (anterior/mid) caudate nucleus within the BG [13,14]. Importantly, convergent evidence suggests that these circuits are functionally related to the formation of skills and habits in procedural memory as well [16–18]. Overall, the similarities between tics and habits on the behavioral level and the involvement of the CBGTC circuits in both make the investigation of habits and related functions in TS highly relevant.

Habits as well as several motor and cognitive skills (e.g. language) are rooted in the BG-based procedural memory, which involves the acquisition of regularities of the environment [19,20]. Procedural knowledge is typically acquired gradually and implicitly via practice, leading to a rapid and reliable processing that is characteristic of automatized skills and habits [19,21,22]. Procedural memory is typically assessed using probabilistic classification and sequence learning tasks [19,23]. The present short review aims to summarize previous findings on the acquisition, consolidation, and processing of regularities using such procedural memory tasks in TS, discuss reasons for potential inconsistencies across studies, and propose future directions of research. Although there has been a recent increase in interest, studies on procedural memory in TS are relatively scarce. Therefore, beyond discussing the most recent findings on this topic, we decided to include earlier studies as well to provide a more comprehensive evaluation of procedural memory alterations in TS. This short review includes all research that has tested procedural memory in TS; however, to keep our review focused, we do not include studies that have examined related functions, such as motor learning or reinforcement learning.

Acquisition of regularities using probabilistic classification and related tasks in Tourette syndrome

Only a couple of studies have examined the acquisition of regularities using probabilistic classification or associative learning tasks in TS. A pioneering study by Keri et al. [24] used the Weather Prediction Task (WPT, [25]) to evaluate BG functions in TS. In the WPT, participants make binary predictions based on cues that are probabilistically associated with outcomes. The study by Keri et al. [24] examined TS children with high and low symptom severity and typically developing (TD) participants. The low-symptom TS group showed a slower but comparable learning to the TD group, whereas the high-symptom TS group was less accurate in the prediction of outcomes, and their score remained around chance level at the end of the task. Marsh et al. [26] also employed the WPT; however, the structure was more difficult, with subtler probabilistic associations. The study involved both children and adults with TS. Both groups showed lower predictive accuracy than the control groups, and impaired learning was accompanied by more severe symptoms, which is in line with the findings of Keri et al. [24].

Eördegh et al. [27] also probed the acquisition of associations, but these were deterministic (i.e. a certain cue or cue combination was always linked to the same outcome(s)). In the acquisition phase, participants were presented with a picture of a face and a pair of fish, and they had to learn the associative relations between them via trial and error. They received feedback after each trial. In the test phase, retrieval of the acquired pairs was probed without providing feedback. Moreover, the generalization of the acquired knowledge to new pairs was also tested. In this paradigm, performance in the acquisition phase is thought to rely on the BG, whereas retrieval and generalization are considered to be related to the medial temporal lobe [28]. Eördegh et al. [27] found that children with TS were slower to acquire the deterministic relations of cues and outcomes, but retrieval and generalization were comparable in the TS and control groups. Altogether, the learning of both probabilistic and deterministic associations seems to be impaired in TS at least as measured by the classification and associative learning tasks described above. These impairments might be related to the underactive associative circuit in TS, as probabilistic classification tasks seem to primarily rely on this circuit [18,23].

Acquisition of temporally distributed regularities using sequence learning tasks in Tourette syndrome

Another line of studies employed sequence learning tasks, namely, the serial reaction time (SRT) task [29] and its variants to test the acquisition of temporally distributed regularities in TS. During the SRT, participants make fast motor responses to cues. Unbeknownst to them, in certain blocks of the task, stimuli follow a predetermined sequence, and then, in later blocks, stimuli appear in a random order. Participants usually show slower reaction times (RT) and/or lower accuracy on the random blocks, suggesting that they acquired the predetermined sequence. In the classical version of the task, the stimuli appear following a deterministic sequence (e.g. 2-4-1-3-4-2-3-1, where the numbers correspond to locations on the screen), and the length of the sequence can vary between studies.

Two studies have employed the deterministic SRT task to investigate the acquisition of temporally distributed regularities in TS. Channon et al. [30] examined

children with 'pure' TS (i.e. without comorbidities), TS with comorbid attention deficit hyperactivity disorder (ADHD), TS with comorbid obsessive-compulsive disorder (OCD), and TD controls. There was no group difference in learning; all TS groups showed comparable learning to the control group. A recent study also used the deterministic SRT task in children and adolescents with TS, ADHD, or comorbid TS-ADHD, alongside neurotypical peers [31]. They employed a TS and an ADHD factor in their analyses, both with the level of yes and no; thus, the TS-yes factor corresponds to the individuals with TS and TS-ADHD, and the TS-no corresponds to participants with ADHD and control participants, whereas the ADHD-yes factor includes patients with ADHD and TS-ADHD, and the ADHD-no factor includes participants with TS and control participants. There was a trend-level effect of TS, indicating that TS is associated with difficulties in the transition from the sequence block to the random block. The authors suggested that participants with TS might have overlearned the sequence. In other words, this might indicate enhanced procedural functions (i.e. procedural hyperfunctioning) in TS. Interestingly, there was no interaction between the TS and the ADHD factors, suggesting that individuals with comorbid TS-ADHD do not differ from those with pure TS or ADHD but show the atypicalities of both disorders.

Enhanced learning has been found in a study employing an SRT variant that involves the acquisition of probabilistic regularities [32] as well. The alternating serial reaction time (ASRT) task [33], instead of employing separate sequence and random blocks as the classical SRT task, presents the predetermined sequence embedded between random elements (e.g. 1-r-2-r-4-r-3-r, where numbers indicate one of the four possible locations on the screen and 'r' indicates a random location out of the four possible ones). The alternating sequence makes three consecutive trials more probable than others, and participants usually become faster on the high-probability trials compared with low-probability ones. Using this task, Takács et al. [32] showed better learning at the end of the learning phase in children with TS. Similar findings emerged in a recent study by Tóth-Fáber et al. [34]. In a variation of the ASRT task, children with TS showed enhanced sensitivity to probabilistic regularities, but the acquisition of nonadjacent deterministic relations was impaired in TS. In contrast to these two studies, Takács et al. [35] did not find enhanced learning of probabilistic regularities in children with TS; performance was comparable in the clinical and control groups.

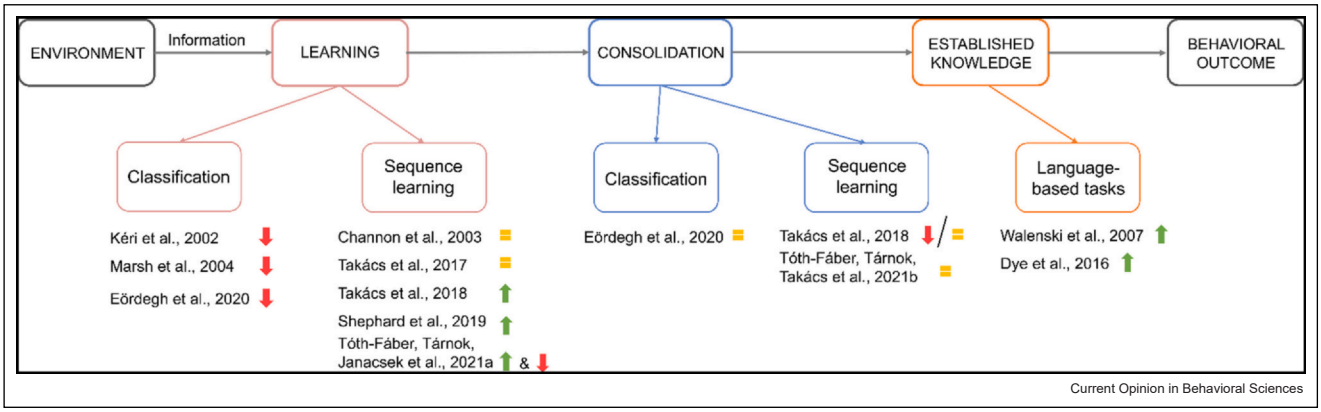
In conclusion, most sequence learning studies have found intact or enhanced learning in TS. It is important to note, however, that the studies showing intact learning (i.e. null findings; [30,35]) involved relatively few participants (less than 14 per group). Hence, these studies might have been underpowered, which can increase the chance of null findings. Enhanced learning on the sequence learning tasks might be explained at least partly by the overactive sensorimotor circuit in TS as these tasks often involve the sensorimotor circuit in addition to the associative circuit [17,18].

Consolidation of procedural knowledge in Tourette syndrome

In contrast to learning regularities in the procedural domain, the consolidation of such information in TS has received very little attention. Consolidation refers to the stabilization of the initially fragile encoded information, and it is essential to long-term memory performance [36,37]. In a laboratory setting, we can measure consolidation by contrasting memory performance at the end of a session and the beginning of the next one, following an offline period without practice. Retained knowledge (i.e. comparable performance between the sessions) or delayed gains of performance (i.e. better performance in the second session compared to the first, called offline learning) suggest successful consolidation [38]. The previously described results on the enhanced learning of some forms of regularities raise the question of whether procedural hyperfunctioning in TS is persistent over a longer period and affects consolidation as well.

Takács et al. [32] employed the ASRT task in two sessions with a 16-hour offline period to test the consolidation of probabilistic regularities in children with TS. As mentioned previously, learning was enhanced in TS. In contrast, the consolidation of the acquired knowledge seemed to be impaired; children with TS showed greater forgetting over the 16-hour offline period than TD controls. However, it is important to note that the group differences in learning could have confounded these results. Therefore, Takács et al. [32] compared the offline changes as a function of prior knowledge and found similar performance of retention in both groups. Altogether, as suggested by the authors, no strong conclusion can be inferred from this study regarding consolidation due to the initial group differences in learning [32]. Tóth-Fáber et al. [39] also investigated the consolidation of probabilistic and deterministic regularities in children with TS. Participants completed a variant of the ASRT task three times, with a 5-hour and 1-year offline delay. The TS group showed no significant learning of nonadjacent deterministic regularities; hence, the consolidation of such regularities could not be reliably tested. Retention of probabilistic knowledge was comparable between the groups both over the 5-hour and 1-year offline periods. Hence, the consolidation of such regularities was intact in TS.

Figure 1



Summary of the reviewed studies. The equal sign next to the citation indicates that the study found comparable performance between the clinical and control groups. The upward arrow indicates that the study showed enhanced performance in TS, whereas the downward arrow indicates impaired performance in TS. Tóth-Fáber et al. [34] investigated the acquisition of both probabilistic and deterministic regularities within the same task and found enhanced learning in the former and impaired learning in the latter, hence the two arrows for that study on the figure. Takács et al. [32] examined the consolidation of probabilistic regularities and initially found impaired performance in the TS group; however, after controlling for the learning differences between the TS and TD groups, retention was comparable between the groups, hence the downward arrow and the equal sign for that study.

To conclude, studies examining the consolidation of probabilistic or deterministic regularities, as tested in sequence learning tasks, so far suggest intact consolidation in TS. Nevertheless, future studies are warranted to test the consolidation of such regularities across a wider variety of tasks and various offline delays to better characterize the consolidation of procedural knowledge in this TS.

Processing and use of established procedural knowledge in Tourette syndrome — language tasks

To the best of our knowledge, no studies have probed the processing and use of well-established procedural knowledge using classification or sequence learning tasks. However, two studies have tested the aspects of language that are linked to BG-based procedural memory. Particularly, Walenski et al. [40] investigated the production of past tenses and the naming of manipulated or nonmanipulated objects in children with TS and TD peers. According to the procedural/declarative model of language [41], both the production of rule-governed past tenses (e.g. slip – slipped) and the naming of manipulated objects (e.g. hammer) are linked to the BG-based procedural memory. In contrast, the production of irregular past tenses (e.g. bring – brought) and the naming of nonmanipulated objects (e.g. elephant) are related to the medial temporal lobe-based declarative memory. Concerning the BG-based functions, Walenski et al. [40] found better performance in TS, whereas producing irregular past tenses and naming nonmanipulated objects were comparable between the groups. Relatedly, procedural hyperfunctioning in TS has been shown in the phonological domain of language as well. Dye et al. [42] employed a nonword repetition task; after hearing the nonwords, participants had to repeat them. This task involves the rule-governed (de) composition of the nonwords; hence, it is thought to be related to the BG-based procedural domain. Children with TS showed faster repetition of nonwords compared with TD controls, whereas accuracy was similar in the groups. To sum up, based on these studies, procedural hyperfunctioning in TS seems to be present not only in aspects of learning temporally distributed regularities in the procedural domain but also in accessing established procedural knowledge.

Conclusion and future directions

Altogether, the studies discussed above revealed mixed findings. Learning performance in classification tasks seems to be impaired in TS. In contrast, the acquisition of temporally distributed regularities seems to be at least intact, and in some cases, even enhanced, as measured by (A)SRT tasks, suggesting procedural hyperfunctioning in TS. Consolidation of procedural knowledge seems to be intact, whereas processing and using already established procedural knowledge (as measured in language tasks) appear to be enhanced in TS. An overview of these findings is presented in Figure 1.

The reason for the mixed findings is likely multifaceted. On the one hand, clinical samples are often heterogeneous and differ across studies regarding age, symptom severity, medication, and comorbid diagnoses, which hinders the comparability of different studies. This issue is further exacerbated by relatively low

Table 1

Main characteristics of the presented studies.

Study	Age range or mean age	Comorbidity	Sample size
Kéri et al., 2002 [24]	TS with high symptom severity: M = 12.9 years, SD = 3.7 years TS with less severe symptoms: M = 12.4 years, SD = 2.5 years controls: M = 12.3 years, SD = 2.2 years	TS with high symptom severity, TS with less severe symptoms, and controls	10, 10, and 20, respectively
Channon et al., 2003 [30][a]	9–18 years	TS, TS-ADHD, TS-OCD, and controls	14, 9, 6, and 21, respectively
Marsh et al., 2004 [26][b]	TS adults: M = 35.28 years, SD = 11.29 years TS children: M = 12.38 years, SD = 2.74 years controls adults: M = 31.68 years, SD = 12.10 years control children: M = 12.65 years, SD = 3.16 years	TS and controls	55 TS (32 children and 24 adults) and 67 controls (23 children and 44 adults)
Walenski et al., 2007 [40][c]	8–17 years	TS and controls	8 and 8
Dye et al., 2016 [42][d]	8–16 years	TS and controls	13 and 14
Takács et al., 2017 [35][e]	7–17 years	TS, ADHD, TS-ADHD, and controls	13, 22, 20, and 21, respectively
Takács et al., 2018 [32]	8–15 years	TS and controls	21 and 21
Shephard et al. 2019 [31]	9–17 years	TS, TS-ADHD, ADHD, and controls	18, 17, 13, and 20, respectively
Eördegh et al., 2020 [27][f]	8–17.5 years	TS, TS-ADHD, TS-OCD/ASD, and controls	21, 15, 10, and 46, respectively
Tóth-Fáber et al., 2021 [34][g]	10–15 years	TS and controls	21 and 21
Tóth-Fáber et al., 2021 [39][h]	10–15 years	TS and controls	19 and 19

Notes. The age ranges of the participants in the study of Kéri et al. (2002) [24] and Marsh et al. (2004) [26] are not available; hence, the samples' mean age and standard deviations are presented in the table. ADHD = attention decifit hyperactivity disorder; ASD = autism spectrum disorder; OCD = obsessive-compulsive disorder; TS = Tourette syndrome.

[a] There was no difference between the clinical groups.

[b] Within the TS children group, seven participants had OCD, seven participants had ADHD, six participants had OCD and ADHD, three participants had depressed mood, and eight participants had oppositional defiant disorder. Within the adult group, six participants had OCD, two had ADHD, and four had both OCD and ADHD. The exclusion of participants with comorbidities did not change the results.

[c] Only OCD and ADHD were allowed as comorbid diagnoses. One TS patient had ADHD, and one had both OCD and ADHD. Analyses were not conducted without these two participants, but the authors note that comorbidities possibly did not influence the results as only two patients had any.

[d] Only OCD and ADHD were allowed as comorbid diagnoses. Two patients had ADHD, three had OCD, and one child had both OCD and ADHD. Comorbidities were involved as a covariance factor in the analyses, but it did not have any significant effect.

[e] There was no difference between the clinical groups.

[f] There was no difference between the clinical groups either in learning or retrieval.

[g] Only OCD and ADHD were allowed as comorbid diagnoses. Three participants had ADHD, and one participant had OCD and ADHD. The exclusion of participants with comorbidities did not change the results.

[h] Only OCD and ADHD were allowed as comorbid diagnoses. Three participants had ADHD, and one participant had OCD and ADHD. The influence of comorbidities was not analyzed.

sample sizes in some studies, potentially affecting power and replicability. To provide an outline of these possible confounding factors, we present the sample size, age range, and included comorbidities of each study in Table 1. Given the available empirical evidence, it seems that comorbid ADHD does not influence procedural learning in TS, while more studies are needed on comorbid OCD. On the other hand, task characteristics may also contribute to the mixed findings and could shed light on the differential involvement of various BG and other circuits in TS. In Table 2, we summarized the main characteristics and differences of the classification and sequence learning tasks, which most previous procedural memory studies in TS focused on. Overall, studies suggest that the timing of feedback, speed of stimulus presentation, and length of training could all affect the involvement of various CBGTC circuits as well as other circuits in learning. For example, it has been shown in neurotypical populations that slower feedback and/or stimulus presentation promotes the

Table 2

Main characteristics and differences of the classification and sequence learning tasks.

	Classification tasks	Sequence learning tasks
What is being learned?	Acquisition of simultaneously presented cue-outcome associations, where the cue can be only one item or multiple items (e.g. different geometric patterns)	Acquisition of temporally distributed cue-outcome associations, which often involve multiple subsequent items (e.g. two, subsequently presented stimuli/cues predict the third stimulus/outcome)
Feedback	'Explicit' feedback that could be separate from the outcome itself (e.g. presenting the word 'Correct'), or repeated presentation of the outcome Learning with fast feedback involves the BG, while slow feedback involves the MTL [43]	'Implicit' feedback: the stimulus/cue stays on the screen until the correct response is made; after correct response, the next stimulus appears on the screen Slower stimulus presentation/feedback may promote more explicit/declarative knowledge about the regularities [45] and therefore greater MTL involvement
Stimulus-response (cue-outcome) mapping	Unclear, correct response/outcome is learned by trial and errors	Clear, predefined mapping: each stimulus/cue is associated with a predefined response button that participants know in advance, learning does not involve trial and error (guessing what the correct response is)
Learning measures	Typically accuracy	Typically reaction times
Length of training	On average, 50–90 trials of short, cue-outcome associations are presented [24,26] Automatization may not be involved due to the length of training Complex cue-outcome associations should be presented to avoid fast, MTL-based declarative learning [23]	Fast initial learning with further gradual improvement: typically 600–1600 trials are presented [31,32,34] Automatization with extended practice Longer sequences (more associations to be learned) should be used to minimize the involvement of MTL-based declarative learning
Neural substrates within the BG	The caudate nucleus may be more involved than the putamen [18,23]	Learning primarily relies on the (anterior) caudate nucleus, (anterior-to-mid) putamen, and globus pallidus [17,18]

emergence of explicit/declarative knowledge of regularities and a greater involvement of the medial temporal lobe (MTL) during probabilistic classification and sequence learning tasks [43,44]. Thus, simple task modifications can alter the involved neural circuits; hence, future studies could systematically test different task variants to shed further light on altered neural circuits in TS.

In terms of the CBGTC circuits, it has been suggested that classification tasks may rely primarily on the associative circuit, whereas the sequence learning tasks seem to involve multiple BG circuits, including both the associative and sensorimotor circuits. In TS, the involvement of the putamen and the caudate nucleus in tics is well-established, with an overactive sensorimotor circuit and an underactive associative circuit, both correlating with tic severity [10]. This pattern of neural alterations seems at least partially consistent with the behavioral pattern observed in the classification and sequence learning studies discussed above. Notably, alterations in neural circuits do not necessarily result in impairments but could also lead to improvements, such as enhanced learning in certain procedural memory tasks (referred to as procedural hyperfunctioning above).

Importantly, studies suggest great heterogeneity in patients with TS in terms of severity, comorbid diagnoses, and the extent of the affected neural circuits. Future studies therefore should focus on identifying subgroups within TS. Revealing the individual differences in behavioral and cognitive factors such as procedural learning and creating neuropsychological profiles within TS might pave the way for identifying such subgroups. For example, despite the enhanced statistical learning on the group level on the ASRT task, some TS individuals might show greater learning, whereas others might show only intact or even inferior learning compared with the neurotypical peers. Studies that systematically manipulate the factors summarized in Table 2 could help identify such TS subgroups and contribute to a detailed characterization of the alterations both at the behavioral and neural levels in those subgroups.

CRediT authorship contribution statement

ETF: Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition. **KJ:** Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition. **DN:** Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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