Lower-level associations in Gilles de la Tourette syndrome: Convergence between hyperbinding of stimulus and response features and procedural hyperfunctioning theories

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Abstract
Gilles de la Tourette syndrome (GTS) can be characterized by enhanced cognitive functions related to creating, modifying and maintaining connections between stimuli and responses (S-R links). Specifically, two areas, procedural sequence learning and, as a novel finding, also event file binding, show converging evidence of hyperfunctioning in GTS. In this review, we describe how these two enhanced functions can be considered as cognitive mechanisms behind habitual behaviour, such as tics in GTS. Moreover, the presence of both procedural sequence learning and event file binding hyperfunctioning in the same disorder can be treated as evidence for their functional connections, even beyond GTS. Importantly though, we argue that hyperfunctioning of event file binding and procedural learning are not interchangeable: they have different time scales, different sensitivities to potential impairment in action sequencing and distinguishable contributions to the cognitive profile of GTS. An integrated theoretical account of hyperbinding and hyperlearning in GTS allows to formulate predictions for the emergence, activation and long-term persistence of tics in GTS.

KEYWORDS
Gilles de la Tourette syndrome, habits, procedural memory, sequence learning, theory of event coding

Abbreviations: DA, dopemine; GTS, Gilles de la Tourette syndrome; MSNs, medium spiny neurons; S-R, stimulus–response; SRTT, serial reaction time task (SRTT); TD, typically developing; TEC, theory of event coding.

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1 | INTRODUCTION

Gilles de la Tourette syndrome (GTS) is a complex neuropsychiatric disorder with motor and vocal tics as the defining and cardinal features (American Psychiatric Association, 2013). Tics represent unintentional, repetitive and patterned actions (Robertson et al., 2017). Apart from tics as the core symptom, GTS is associated with a range of cognitive alterations, spanning from changes of inhibitory control to social perception, decision-making and communication (Albin, 2018; Hartmann & Worbe, 2018; Robertson, 2015). Thus, tics need to be conceptualized also in the context of their potential role within information processing. Additionally, it needs to be taken into account how they affect everyday cognition and behaviour. Particularly simple tics have been described as an automatic and encapsulated sequence of movements and vocalizations, and tics can be considered as habitual behaviour (Goodman et al., 2014; Maia & Conceição, 2017; Marsh et al., 2004). Habitual behaviour can be triggered by internal or external sensory cues and follows previously established stimulus–response (S-R) associations (Delorme et al., 2016; Graybiel & Grafton, 2015). It has been proposed that increased striatal dopaminergic activity in GTS leads to atypically strong links between sensory events (e.g., urges, irritating or stressful stimuli) and motor responses (i.e., tics) that are hard to modify (Beste & Münchau, 2018; Buse et al., 2016, 2013; Delorme et al., 2016; Goodman et al., 2014; Leckman & Riddle, 2000). Therefore, the processing of S-R connections has been one focus of GTS research (Beste & Münchau, 2018; Goodman et al., 2014; Kleimaker, Kleimaker, et al., 2020; Maia & Conceição, 2017; Shephard et al., 2019). However, the formation of S-R associations was suggested to be either facilitated (Beste & Münchau, 2018; Delorme et al., 2016; Dye et al., 2016; Kleimaker, Takacs, et al., 2020; Petruo et al., 2019; Shephard et al., 2019; Takács et al., 2018; Tóth-Fáber et al., 2021; Walenski et al., 2007) or impaired in GTS (Eördegh et al., 2020; Goodman et al., 2014; Kéri et al., 2002; Marsh et al., 2004). To solve this contradiction, a framework is needed that can create a bridge between different fields of GTS research.

In this review, we discuss the factors determining whether atypical S-R associations in GTS would lead to enhanced or attenuated performance in tasks investigating S-R mappings. Converging evidence of sensorimotor association/binding and learning functions do not only dovetail our knowledge of how habitual behaviours emerge in GTS but also provide a mechanistic link between the binding of S-R features and acquisition of long-term S-R contingencies (i.e., the probability or degree of an association). The attractiveness of such a theoretical connection lies in its potential of generalization: understanding atypical S-R associative functions both at a short-term (binding) and long-term (learning) time scale. As a result, complex forms of already established behavioural patterns could potentially be traced back to their origins at a level of individual S-R connections. Thus, we propose a unified framework of studying associative functions in GTS. Specifically, we emphasize two aspect with particular relevance for GTS: the procedural memory formation and event file coding.

2 | PROCEDURAL MEMORY FORMATION AND EVENT FILE CODING

Below, we briefly introduce the theoretical background relevant for procedural memory formation and event file coding as two important pillars of an overarching view on associative functions. There are a number of outstanding reviews on procedural learning and memory (Batterink et al., 2019; Conway, 2020; Frost et al., 2019; Squire, 2009; Ullman, 2004, 2016) and event file coding (Fring et al., 2020; Hommel, 2019; Hommel et al., 2001). Here, we focus on the most important aspects relevant for the goal of this conceptual contribution in the context of GTS.

2.1 | Procedural memory

Neuropsychological research on amnesic patients led to the recognition of separate declarative and procedural memories (Batterink et al., 2019; Cohen & Squire, 1980; Squire, 2004, 2009; Ullman, 2004). Learning and recalling facts and events in declarative memory relies predominantly on the medial temporal lobe, whereas the acquisition of skills and habits in procedural memory is most likely rooted in the basal ganglia (Batterink et al., 2019; Janacsek et al., 2019; Squire, 2004, 2009; Ullman, 2004, 2016), particularly in the striatum and its connections with the cerebellum and the neocortex (Janacsek et al., 2019). Procedural memories are established through repeated exposure to regularities in the environment creating persistent, long-term memory traces (Batterink et al., 2019; Conway, 2020; Kóbor et al., 2017). Unlike the declarative memory system, the stabilization of memories following procedural learning does not necessarily require sleep, and recalling the memories is a fast, automatic, effortless process (Conway, 2020; Csábi et al., 2016; Nemeth et al., 2010; Song et al., 2007; Wilson et al., 2012).

These characteristics support not only the idea of an independent, striatal procedural memory function in the human memory (Eberhardt et al., 2017; Haider et al., 2020; Squire, 2004, 2009; Ullman, 2004, 2016) but also
that procedural knowledge is encapsulated and operates through highly specialized dimensions of information, or so called modules (Eberhardt et al., 2017; Haider et al., 2020). These modules are the building blocks of procedural information acquisition and determine the limits of procedural learning capacities. One possibility is that these modules are specialized to either aspect of perceptual or response regularities, such as the distributional frequency or the relative order position of the required response (Conway, 2020). In contrast, other studies support the idea that these modules encode a single feature dimension (Eberhardt et al., 2017; Haider et al., 2020), irrespective of whether the feature is part of the response or the stimulus. Of note, any aspect of information can qualify as a feature, such as colour, angle, size of the stimulus, or force, direction, or effector of the response (Frings et al., 2020; Hommel, 1998).

Recent studies (Eberhardt et al., 2017; Haider et al., 2020) investigated the building blocks for coding procedural memories. In a series of experiments (Eberhardt et al., 2017), participants learnt sequences that could be coded as stimulus locations and sequences that could be coded as response locations. Both types of sequences could be learnt in parallel with an independent colour sequence if the sequence structures were uncorrelated. That is, if the sequences of stimulus location or response location did not overlap with the colour sequence. The follow-up experiment tested whether participants were able to learn the stimulus location sequence when it was presented either alone or together with a second sequence: the response location sequence, the uncorrelated colour sequence or a colour sequence that overlapped with the response location sequence (dual sequence). Importantly, the response location sequence and the dual sequence both interfered with learning the original stimulus location sequence. These results support the notion that the encapsulated modules are dedicated to abstract features, such as colour or location. However, because interference occurred between stimulus location sequences and response locations sequences, they are not specialized either for perceptual or motor information. Thus, learning the regularities in the external surroundings and related actions are intertwined in nature. Consequently, the building blocks of procedural memories likely use a shared code of stimulus and response features (see Figure 1).

In subsequent experiments (Haider et al., 2020), a stimulus-location sequence, which was only observed by the participants without a need to respond was transferred to a motor response-location sequence. This indicates that perceiving a stimulus feature activates the corresponding motor feature, providing further support of the idea that procedural learning operates via abstract feature codes (Haider et al., 2020). Procedural memory

![FIGURE 1](https://example.com/figure1.png)

Schematic illustration of interaction between event files and sequential regularities. The temporal coincidence between features (F) of the stimuli (S) and responses (R) create an event file (in blue). Features, such as the colour red or left side can occur in multiple unique S-R connections. ‘Event files’ are results of binding between S features and R features (Hommel, 1998), that is, an event file is a network of S-R associations (Hommel, 2011). The first event file is enlarged to illustrate the feature-based network (blue arrows) event files interact with each other through the mechanisms of partial repetition costs and response facilitation (Colzato et al., 2006; Hommel, 2004). These processes do not necessitate a systematic relationship between consecutive stimuli or responses. However, in case of a continuous regularity in the stimulus stream and/or in the response sequence, the predictability of the S-R connections may contribute to the binding mechanisms. If the probability between the already created event files is high (green arrows), the event file will be potentially reinforced. If the transitional probability is low (red arrows), the event file will be more susceptible to unbinding and reconfiguration. The presented probabilities are arbitrary.
relies on the predictability of the events that can lead to strengthening or weakening of the associations between feature codes in the specialized modules (Eberhardt et al., 2017; Haider et al., 2020). Based on these findings, the authors concluded that, in accordance with the theory of event coding (TEC) (Hommel et al., 2001) briefly reviewed in Section 2.2, procedural memory is a by-product of acting in an environment with limited stability.

When we learn a new habit, multiple features and sequences of S-R contingencies create integrated representations through striatal networks (Seger, 2018). Specifically, the formation of habits is rooted in the motor cortico–basal ganglia–thalamo–cortical loop, including sensorimotor cortices and the putamen (Goodman et al., 2014; Horga et al., 2015; Maia & Conceiç, 2017; Schroll et al., 2015). Within this network, the dorsolateral striatum is thought to have an ‘actor’ role and is, therefore, responsible for learning and implementing the habits (i.e., the S-R associations) (Maia & Conceiç, 2017). In contrast, the amygdala, the orbitofrontal cortex, and the ventral striatum are considered as ‘critics’: calculating the values of the individual’s current state, which can then be used for prediction errors (Maia & Conceiç, 2017). The ventral (limbic) striatum is particularly important: it is associated with reward expectations and projects as well as receives projections through the dopaminergic system. Importantly, as it comprises dopaminergic neurons projecting to other striatal areas, the ‘critic’ can update the ‘actor’ if the learning and implementation of S-R associations need to be modified. Thus, the ventral striatum as an ‘actor-critic’ plays a pivotal role in habit learning. Furthermore, medium spiny neurons (MSNs) in the striatum actively inhibit action requests that would cause disordered motor activations (Beste et al., 2014; Beste & Saft, 2015; Buxton et al., 2017; Tomkins et al., 2014). This selection process is highlighted in the chunking of action sequences, where the orchestration of subsequent actions is pivotal. Moreover, phasic dopamine (DA) bursts strengthen corticostratial synopsis to direct-pathway MSNs thus shifting information processing towards prediction errors and habitual behaviour (Maia, 2009; Maia & Conceiç, 2017; Schultz et al., 1997). Additionally, tonic DA lowers the threshold for action execution through no-go MSNs that promote the expression of habitual behaviour (Maia & Conceiç, 2017). These dopaminergic mechanisms require a large amount of external input: habits are acquired behaviourally, sequences that rely on experience-dependent plasticity (Graybiel, 2008). Habits are established through the procedural memory system as opposed to the declarative memory system that is responsible of learning facts and episodes (Graybiel, 2008; Seger, 2018). Of note, habits and procedural knowledge overlap but they are not the same. In both cases, the learning of sequential actions results in the ability to perform these actions without particular effort or attention (Graybiel, 2008). However, procedural learning also contributes to the acquisition of perceptual, motor, cognitive and social skills (Lieberman, 2000), such as learning a language, playing a musical instrument, dancing or recognizing social cues (Kaufman et al., 2010; Köbor et al., 2017; Ullman, 2004). In sum, procedural learning and memory have the necessary characteristics to provide a more cognition-driven understanding of habitual behaviour.

### 2.2 Event file coding

As outlined above, procedural memory relies on the predictability of the events that can lead to strengthening or weakening of associations between feature codes in the specialized modules (Eberhardt et al., 2017; Haider et al., 2020). Based on experimental findings (Eberhardt et al., 2017; Haider et al., 2020), procedural learning is a by-product of acting in an environment with limited stability, in accordance with the TEC (Hommel et al., 2001). Importantly, while procedural learning describes how habits develop as long-term memories, event file binding can explain habit formation at the level of individual S-R associations, irrespective of their longevity. Event file coding is proposed to be a general mechanism (Eberhardt et al., 2017; Hommel, 2004) and therefore largely independent from the competing declarative and procedural memory systems. More recently, it has been described how binding of event files can lead to changes in episodic memory traces, which provides a link between event file coding and declarative memories (Frings et al., 2020). A similar approach was taken in case of prospective memories, that is, when someone has to remember the intention to act in the future (Streeper & Bugg, 2020). While these accounts are paramount in understanding S-R associations as building blocks of declarative memories, it is important to consider that the most common task to investigate event file coding (Colzato et al., 2006) is one resembling procedural rather than declarative memory paradigms (Figure 2).

This is all the more important considering event file coding’s and the memory system’s potential contribution to habit formation and particularly habitual symptoms in GTS. Event files as universal representations of S-R connections have been proposed by the TEC (Hommel, 1998, 2004, 2019). The core statement of the TEC is that executing an action is not just determined by perception but also creates new perceptual information; thus, the bidirectional nature between perception/stimulus (S) and action/response (R) requires shared representations:
the event files. Event files have two main components: the object file (Treisman, 1996; Treisman & Kahneman, 1984) and the action file (Stoet & Hommel, 1999). Object files represent stimulus feature codes (e.g., location, colour and luminance), whereas action files contain feature codes of the corresponding responses (e.g., direction, force and angle). Importantly, stimulus and response features are closely integrated via the mechanism of event file binding (Hommel, 1998, 2004, 2019). As a consequence, feature-based S-R integration facilitates network architecture (Hommel, 2011; Takacs, Zink, et al., 2020). Within this network, activation of a feature either through perception or action spreads through the connections (Hommel, 2011). Therefore, responses can be triggered automatically, based on their previous feature associations. This encapsulated mode of activation closely resembles habitual behaviour. Thus, event file binding provides a process-level explanation of how S-R associations behind habits come to existence (Beste & Münchau, 2018; Kleimaker, Kleimaker, et al., 2020), whereas procedural memory likely builds upon the event files to promote the long-term persistence of habits (Eberhardt et al., 2017; Haider et al., 2020). Therefore, both should be considered to play an important part of the cognitive neurophysiology of GTS. This is all the more relevant considering that event file processing depends on functional neuroanatomical structures and neurobiological system altered in GTS. Several studies suggest that event file coding is modulated at a striatal level. There are strong links between the updating of mental sets and different dopamine-modulating genotypes that significantly influence the amount of striatal dopamine (Colzato et al., 2016) or striatal dopamine receptor density (Persson et al., 2015). Striatal dopamine levels modulate the flexible management of S-R associations (Colzato et al., 2013). It has also been demonstrated that L-dopa medication in Parkinson’s disease patients modulates event file processing, with increased (striatal) dopamine concentrations in patients on medication leading to increased event file binding (Colzato et al., 2012). Therefore, because several lines of evidence in GTS suggest that the basal ganglia play a key role in this disorder (Bronfeld et al., 2011; Kataoka et al., 2010) and given robust evidence for alterations of dopaminergic transmission in GST (Buse et al., 2013), event file coding is expected to have a central role in GTS. Using functional brain imaging and noninvasive brain stimulation, it has been shown that event file coding is mediated via a widely distributed network including the inferior parietal cortex, SMA, the dorsolateral prefrontal cortex, fusiform gyrus, hippocampus and parahippocampal gyrus (Chmielewski & Beste, 2019; Dobbins

FIGURE 2 Task designs to study stimulus–response (S-R) associations in Gilles de la Tourette syndrome (GTS). The type of stimuli, the expected responses and (if applicable) explicit outcomes (O) are pictured. High probability S-R connections are shown with green arrows; low probability connections are shown with red arrows. Random (technically low probability) connections are shown in orange. In a probabilistic categorization task (left panel), such as weather prediction, participants learn the associations between geometric shapes and binary outcomes (sunny or rainy weather). Responses are followed by visual feedback. In a sequence learning task (central panel), participants usually follow a moving target on the screen with four possible locations. As quickly as possible, a button corresponding to the position of the target has to be pressed. Unknown to the participants, the presentation of the target follows a sequential structure that can be deterministic, random, continuous probabilistic or probabilistic interleaved with random elements. Responses are not followed by (explicit) feedback; however, in some versions of the task, erroneous trials are repeated once. In an event file binding or S-R task (right panel), cues are followed by a pair of stimuli. An arbitrary response triggered by the cue has to be executed when the first stimulus (S1) is presented, which creates an S1-R1 binding. The second stimulus (S2) requires a response based on one of the stimulus’ features. The overlap between features of S1-R1 and S2-R2 either facilitates the second response (e.g., same response and high feature overlap) or interferes with it (e.g., different response, high feature overlap or same response, and low/no feature overlap)
et al., 2004; Elsner et al., 2002; Kühn et al., 2011; Petruo et al., 2016; Takacs, Zink, et al., 2020; Zmigrod et al., 2014), suggesting that perceptual and/or attentional mechanisms as well as response selection and memory encoding are relevant.

Accumulated evidence implicates the motor cortico–basal ganglia–thalamo–cortical loop in the development of tics in GTS (Goodman et al., 2014; Maia & Conceição, 2017; Worbe et al., 2010). Indeed, tic-related activation has been found in every element of this circle: supplementary motor area (Bohlhalter et al., 2006; Neuner et al., 2014; Tübing et al., 2018; Wang et al., 2011; Worbe et al., 2015), premotor cortex (Bohlhalter et al., 2006; Stern et al., 2000; Wang et al., 2011), sensorimotor cortex (Bohlhalter et al., 2006; Stern et al., 2000; Wang et al., 2011; Worbe et al., 2015), putamen (Bohlhalter et al., 2006; Stern et al., 2000; Wang et al., 2011), globus pallidus (Bohlhalter et al., 2006; Wang et al., 2011), and thalamus (Bohlhalter et al., 2006; Kakusa et al., 2021; Wang et al., 2011; Worbe et al., 2015).

Given the implication of similar neuronal networks both in event file coding and the pathophysiology of GTS alterations of event file processing is to be expected in GTS. In fact, recent data provide evidence that altered event file coding is relevant in GTS (Brandt et al., 2016; Kleimaker, Takacs, et al., 2020; Petruo et al., 2019; Weissbach et al., 2020) (see Section 4 for details). The finding that patients with GTS have a tendency to create stronger S-R associations compared with healthy controls (Kleimaker, Takacs, et al., 2020) is in keeping with previous work showing that they also have an increased tendency to form habits (Delorme et al., 2016). Notably, it was shown that alterations in event file coding can be brought into connection with the cardinal feature of GTS—tics (Kleimaker, Takacs, et al., 2020; Weissbach et al., 2020).

Based on this evidence, striatal functions, such as event file binding (Beste & Münchau, 2018; Kleimaker, Kleimaker, et al., 2020; Kleimaker, Takacs, et al., 2020) and procedural learning (Goodman et al., 2014; Marsh et al., 2004; Shephard et al., 2019; Takács et al., 2018), became a candidate to explain the formation of habits and tics in GTS.

3 PROCEDURAL MEMORY IN GTS

Procedural learning and memory functions have been investigated in GTS by using tasks designed to tap into different parts of the procedural system. For instance, some required learning of transient S-R connections, whereas others also tested nonadjacent transitional probabilities. In some of the experiments, participants had to perform discrete decisions based on their previous experience, whereas in others the accumulated knowledge of S-R contingencies was tested by continuous performance measures. Participants either received feedback on their performance or their performance remained hidden during learning. Furthermore, the tasks also differed on how much they relied on chunking mechanisms, and if they did, the sequential regularities were deterministic or probabilistic. In the next part, we introduce the diverse studies of procedural memory in GTS in terms of how they relate to these factors outlined above.

3.1 Procedural memory in GTS: Probabilistic categorization

Early evidence suggested that procedural learning is impaired in GTS (Kéri et al., 2002; Marsh et al., 2004). The first studies to investigate procedural memory functions in GTS showed impaired performance in a task that requires probabilistic category learning (Kéri et al., 2002; Marsh et al., 2004). In the probabilistic categorization or weather prediction task (Knowlton et al., 1994), participants are asked to guess, whether the geometric shapes (cues) on the screen predict sunny or cloudy weather (outcome). The guess is then corrected with immediate feedback. Because the cues are associated with the two possible outcomes with different frequencies, the task is considered to be probabilistic. In the first weather prediction study of GTS (Kéri et al., 2002), children and adolescents with high and low symptom severity were compared with typically developing (TD) participants. The high severity GTS group was less accurate in predicting the outcome than the low severity and TD groups. Moreover, the performance of the low severity GTS group was below the level of TD. Interestingly, the TD and high severity GTS groups gained a similar level of explicit knowledge of contingencies in the task, which was negatively correlated with the weather prediction performance. This raises the possibility that the low and high severity groups followed different learning strategies: GTS participants with low severity were likely able to employ implicit procedural learning mechanisms to perform better in the task than their high severity GTS peers. However, the weather prediction task performance does not necessarily reflect procedural functions, as participants can also rely on their declarative memory to solve the task (Newell et al., 2007). This could also explain the difference between the two severity groups: the more implicit performance in patients with mild GTS was achieved via procedural memory, whereas the more explicit results of the high severity GTS group could reflect declarative memory. However, the original study
could not differentiate between these alternative explanations (Kéri et al., 2002). To overcome the methodological challenge of possible declarative involvement, another study lessened the difference between the frequent and rare associations to evoke more procedural learning (Marsh et al., 2004). Declarative strategies cannot be effectively employed to solve the task because of the more subtle differences between probable and less probable outcomes. Prediction accuracy was lower in GTS both for children and adults than in the control groups. Moreover, in both GTS groups, the performance on the weather prediction task was correlated with symptom severity. Thus, learning of probabilistic categories, one of the striatal procedural functions (Poldrack et al., 2001), seems to be impaired in GTS and also related to the main, habitual symptoms (Marsh et al., 2004, 2005).

3.2 | Procedural memory in GTS: The role of feedback

Interestingly, children with GTS showed impaired performance in another S-R learning task that has similarities with the weather prediction paradigm (Eördegh et al., 2020). The task consists of two phases: acquisition and test. In the acquisition part, participants learnt the association between items of two categories (fish and faces) in a trial-and-error way. Each time, visual feedback was given to the participants. Thereafter in the test phase, retrieval of the original pairs and generalization to new ones was tested without feedback. The first part of the task is considered to rely on basal ganglia, whereas the second half is related to activity changes in the medial temporal lobe (Myers et al., 2003). Children with GTS needed more trials to learn the S-R contingencies in the acquisition phase; however, their subsequent retrieval and generalization performance did not differ from the TD children (Eördegh et al., 2020). Importantly, in this task, the S-R associations were completely deterministic; thus, the results cannot be explained by impaired probabilistic categorization. This raises the possibility that in the weather prediction studies (Kéri et al., 2002; Marsh et al., 2004), children with GTS showed attenuated performance not as a result of procedural learning dysfunction but due to the method how procedural memory was measured. From a TEC point of view, the weather prediction task consists of stimulus (cue)–response (guess)–effect (weather) or S-R-E associations, similarly to the task used by Eördegh et al. (2020). Immediate feedback is known to have a facilitatory effect on S-R binding (Tanaka et al., 2020). However, this benefit from feedback might not arise in GTS. Whereas positive feedback can promote learning in GTS, negative feedback could cause the opposite effect (Maia & Conceição, 2017).

Importantly, as the studies did not differentiate between positive and negative feedback when assessing the learning performance (Eördegh et al., 2020; Kéri et al., 2002; Marsh et al., 2004), the alterations in GTS could have been caused by the negative feedback effect (Maia & Conceição, 2017). Therefore, further studies are warranted to compare discrete decisions on S-R pairings between positive and negative feedback effects and between probabilistic and deterministic associations.

Nevertheless, it is important to note that given the multifaceted nature of procedural functions, the attenuated weather prediction performance in GTS was originally interpreted as an indicator of impaired probabilistic category learning (Marsh et al., 2004, 2005). However, later it was referred to as a marker of general impairment of procedural memory (Goodman et al., 2014). Importantly, subsequent studies which tested other aspects of procedural functions painted a different picture (Delorme et al., 2016; Dye et al., 2016; Shephard et al., 2019; Takács et al., 2018; Walenski et al., 2007). The most important similarity among these studies is the sequential nature of the stimulus stream. Next, we introduce the importance of testing sequences instead of discrete associations and their contribution to the cognitive profile of GTS.

3.3 | Procedural memory in GTS: Sequence learning

Importantly, the impairment in probabilistic category learning in GTS was explained as an inability to concatenate events (‘chunking’), which would lead to less efficient habitual behaviour (Marsh et al., 2004). According to this explanation, action sequences would remain fragmented and therefore, potentially, be subject to activations outside of their original context, similar to tics (Goodman et al., 2014; Marsh et al., 2004, 2005). However, neither the weather prediction task (Kéri et al., 2002; Marsh et al., 2004) nor associative learning (Eördegh et al., 2020) requires extensive chunking: S-R contingencies are based on pairwise associations, and subsequent decisions of the participants are largely independent of the previous ones. Tasks with longer, sequential regularities and interdependencies across larger series of trials are better suited to study chunking mechanisms (Batterink et al., 2019; Howard & Howard, 1997; Nemeth et al., 2013). The most widely used task with such a pattern of stimuli is the serial reaction time task (SRTT) and its variants (Howard & Howard, 1997; Nemeth et al., 2013; Robertson, 2007). In this paradigm, participants have to follow a stimulus on a screen, which can appear in four possible locations. Unbeknown to
them, the stimulus presentation follows a sequential pattern, in which adjacent and nonadjacent probabilities can be learnt to predict the upcoming stimuli. Thus, chunking of the sequence has the advantage of using not only the adjacent but also the nonadjacent probability information in the task, therefore making more precise predictions. The first exploratory study of sequence learning in GTS (Channon et al., 2003) reported no evidence for altered performance in children and adolescents with GTS compared with TD participants. In another exploratory study (Takács et al., 2017), children with GTS, children with attention deficit hyperactivity disorder (ADHD), comorbid GTS and ADHD and TD children were compared on a sequence learning task. Similar to the previous report (Channon et al., 2003), there were no group difference in learning performance (Takács et al., 2017). However, in both studies (Channon et al., 2003; Takács et al., 2017), sample sizes were relatively small (less than 14 per group), raising the possibility that these studies were underpowered. Furthermore, the first study did not exclude participants who became aware of the sequence structure (Channon et al., 2003). Similar to the weather prediction task, explicit awareness of the regularities in the presented sequential stimuli can shift the learning from procedural to declarative (Howard & Howard, 1997; Nemeth et al., 2013).

Statistical power was larger and solutions for task awareness provided in two subsequent studies (Shephard et al., 2019; Takács et al., 2018). Crucially, these studies showed enhanced sequence learning in children with GTS. In the first study, a modified version of the SRTT, the alternating SRTT (Howard & Howard, 1997), where sequential stimuli are interleaved with random stimuli, was tested (Takács et al., 2018). In this ‘noisy’ presentation of the targets, explicit awareness of the sequence does not emerge; however, participants can learn the sequence implicitly (Howard & Howard, 1997; Kóbor et al., 2017; Nemeth et al., 2013; Song et al., 2007). Children with GTS and TD children participated in two sessions (Takács et al., 2018), where they learnt a visuomotor sequence in the first one, and retained this knowledge on the following day during the second session. Importantly, learning of the sequence and retention of this procedural knowledge was achieved in both groups; however, children with GTS made more prediction errors during learning than their TD peers. As a result, accuracy gradually decreased for less-predictable items compared with predictable ones. This learning pattern was shown in both groups, but the difference between predictable and less-predictable events was larger in the GTS than in the TD group. Thus, children with GTS were characterized by enhanced sensitivity to the presented probabilities within the sequence.

A recent follow-up study confirmed the enhanced learning function in GTS with a cued version of the alternating SRTT (Tóth-Fáber et al., 2021). In this task, participants receive explicit instructions to pay attention and learn the pattern of the sequential stimuli (dogs appearing in the four possible locations). In contrast, the alternating random elements (penguins in the four possible locations) are learnt incidentally as part of the triplet structures (Nemeth et al., 2013; Tóth-Fáber et al., 2021). Interestingly, children with GTS (10–15 years of age) showed better learning of triplet probabilities (statistical learning) than TD children. However, the opposite was true for the intentional learning of the sequence (rule-based learning): TD children performed better than children with GTS.

This picture of enhanced probabilistic sequence learning in GTS was further supported by the second study (Shephard et al., 2019). Here, participants learnt a visuomotor sequence implicitly, were then exposed unknowingly to a second (interference) sequence and, finally, were retested on the original sequence. In this blockwise design, higher performance in blocks where the old sequential regularity returns can either indicate better learning or less susceptibility to interference. Curiously, children with GTS showed larger disruptions in performance during the interference block than TD participants as measured in accuracy, but a larger disruption effect measured in RTs. Thus, the GTS group was sensitive to changes of the sequence as shown by their altered response strategies. In contrast, when the original sequence was reintroduced, the GTS group’s behaviour returned to the preinterference level, and it did not differ from that in the TD group. It was suggested (Shephard et al., 2019) that the altered performance by the interference sequence in the GTS group was caused by hyperlearning at the beginning of the task. Notably, learning performance before the interference sequence did not differ between groups casting some doubt on the notion of hyperlearning. However, the introduction of the original sequence was brief with only two data points to compare. The blockwise design and the length of the exposure were, therefore, less appropriate to describe the dynamics of sequence learning. As a consequence, direct evidence for hyperlearning could not be gained in this study design. Interestingly, normalization of task performance in GTS at the end of the task came with a higher price than for the controls, given that the interference block had altered their responses to a larger extent. Thus, the results of Shephard et al. (2019) indirectly suggest enhanced procedural memory functions in GTS.

In sum, the two sequence learning studies complement each other (Shephard et al., 2019; Takács et al., 2018): online (i.e., trial by trial) learning measures showed enhanced learning in GTS via increasing...
prediction errors in the former (Takács et al., 2018), whereas sequence knowledge was robust against disruption in the latter (Shephard et al., 2019). Thus, enhanced procedural sequence learning in GTS (Takács et al., 2018) can lead to more stable procedural memories (Shephard et al., 2019). This shows that children with GTS are not only hypersensitive to S-R contingencies but also more resistant to modifications bearing resemblance to habitual behaviour (Delorme et al., 2016; Maia & Conceição, 2017).

Other sequence learning studies demonstrated the role of reinforcement in GTS (Delorme et al., 2016; Palminteri et al., 2011). Palminteri et al. (2011) found that adults with TS showed enhanced learning of rewarded as compared with nonrewarded motor response sequences. Furthermore, Delorme et al. (2016) found a higher rate of responses to previously learnt but devalued stimulus–response–outcome associations in patients with GTS as compared with healthy controls, which also suggest enhanced procedural functions. However, as it has been pointed out earlier (Shephard et al., 2019), these studies examined adults with GTS. GTS that is stable over the lifetime and persists in adulthood is not representative of the GTS population as a whole (Robertson, 2015).

3.4 Procedural memory in GTS: Interim summary and remaining questions

In sum, sequence learning seems to be intact (Channon et al., 2003; Takács et al., 2017) or even enhanced (Shephard et al., 2019; Takács et al., 2018) in children and adolescents with GTS. Importantly, larger statistical power and more careful design in terms of awareness of the sequence tip the balance towards enhancement (Shephard et al., 2019; Takács et al., 2018). Furthermore, it has been suggested that processes within sequence learning can dissociate in GTS: while (implicit) statistical learning is enhanced, (explicit) learning of sequential rules can be impaired (Tóth-Fáber et al., 2021). Thus, the type of information (statistical vs. sequence rule) and the explicitness of the learning process (incidental vs. intentional) can influence the results, as well, with more implicit, probability-based sequence learning being enhanced in GTS. Moreover, adults with GTS also seem to be characterized by procedural hyperfunctioning, at least when learning was reinforced by rewards (Delorme et al., 2016; Palminteri et al., 2011).

Against this background there are several open questions:

1. Does reinforcement increase the existing difference between children with GTS and TD children in procedural sequence learning?

Given patients with GTS sensitivity to feedback (Maia & Conceição, 2017), this appears likely. Prediction errors produced by positive reinforcement promote phasic DA responses (Schultz et al., 1997). If phasic DA is enhanced in GTS during childhood and adolescence, then similar sensitivity to reinforced S-R contingencies should be similar to adult patients with GTS (Delorme et al., 2016; Palminteri et al., 2011). However, the detrimental effect of negative feedback should be considered as well (Maia & Conceição, 2017). It is conceivable that the type of feedback would modulate the acquisition of sequential regularities in GTS in both ways: whereas positive feedback would further enhance this cognitive function, negative feedback would result in impaired learning, similar to the decreased performance in the weather prediction and associative learning tasks (Eördegh et al., 2020; Kéri et al., 2002; Marsh et al., 2004). In addition, the interaction between positive and negative reinforcement should be considered. Weather prediction tasks are dominated by negative feedback at the outset followed by a tendency for positive feedback as the learning progresses. Thus, early negative reinforcement might have a lasting detrimental effect in GTS, which might not be overturned by rewards. This behavioural pattern would also be in line with the habitual nature of tics: robust S-R associations requiring long reversal trainings to be weakened and decreased in frequency (Petruo et al., 2020). In sum, an ideal study in children would combine the effects of positive and negative reinforcement on sequence learning. Moreover, if probabilistic categorization could be studied at the same time using a within-subject design, it would have the potential to clarify the issue of impaired (Eördegh et al., 2020; Kéri et al., 2002; Marsh et al., 2004) versus enhanced (Shephard et al., 2018; Takács et al., 2018) procedural memory in GTS.

Other questions relate to the connection between learning and consolidation in GTS, an area with potentially important clinical implications albeit with very little evidence so far.

2. Do the results of Shephard et al. (2019) imply hyperlearning as in Takács et al. (2018) or overstable consolidation of sequential knowledge? How stable are overlearnt sequences over longer periods? Finally, what is the potential connection between too stable procedural memories and tics?

Retention of procedural memories and underlying consolidation mechanisms are central for the understanding of procedural functions (Conway, 2020; Köbor et al., 2017). The results of Shephard et al. (2019) suggest that knowledge accumulated during procedural sequence
learning is more resistant to interference in GTS than in TD children. That is, learning in GTS might lead to overstable associations. However, this result alone does not provide evidence for retention, which would require testing performance on the original and the interference sequences after an offline period (Kóbor et al., 2017; Nemeth & Janacsek, 2011). This contrast has been included in the study of Takács et al. (2018). Surprisingly, the evidence of hyperlearning prevented the analysis of retention effects for the following reason. To investigate consolidation-related differences between groups, performance levels before the offline period should be similar. Takács et al. (2018) reported enhanced performance in GTS at the end of the first session; that is, there was a performance difference between groups before the offline testing, which might have influences any potential retention effect. A follow-up study could solve this methodological issue in two ways: first, by ensuring that participants reach an optimal level of sequence knowledge as an end-goal of the first session without limiting the length of learning at an individual level; second, by recruiting a large sample of TD participants comprising enough children from the upper end of the performance spectrum, so that children with GTS and TD children could be matched based on their performance before the offline period. Again, the developmental aspect is crucial: as Adams et al. (2018) suggested, the transfer from learning to long-term representations gradually develops with age. This implies that overstable procedural memories in children with GTS may resemble consolidated representations of older TD children. Understanding the consolidation of procedural memories in GTS would pave the way to better connect symptoms and cognitive mechanisms. If tics are expressions of already established S-R connections, then tic severity should not be related to the degree of learning but the stability of consolidation after the initial learning. Despite the lack of conclusive evidence from memory research, language studies indirectly suggest that consolidation in the procedural memory system is also hyperfunctioning in GTS (Dye et al., 2016; Walenski et al., 2007). Specifically, children with GTS showed faster performance in mental grammar (Dye et al., 2016; Walenski et al., 2007) and speeded access to the procedural part of the mental lexicon (Walenski et al., 2007). Both indicate that already established procedural knowledge was more accessible, that is, represented mentally more efficiently in GTS than in TD. These findings should further motivate the study of memory consolidation in GTS, preferably in the contexts of development and symptom severity. Furthermore, future studies should include neurophysiological correlates of procedural memory functions to get a grip on the underlying neural mechanisms of hyperlearning and possible hyperconsolidation. Furthermore, the investigation of already consolidated knowledge requires analyses at the representation-level, such as multivariate pattern analysis (MVPA) (Fahrenfort et al., 2018; King & Dehaene, 2014; Takacs, Mükcschel, et al., 2020). Overall, without careful study design and innovative neurophysiological solutions, consolidation mechanisms in GTS cannot be clarified.

Importantly, all sequence learning studies in GTS used visuomotor sequences (Channon et al., 2003; Delorme et al., 2016; Kéri et al., 2002; Palminteri et al., 2011; Shephard et al., 2018; Takács et al., 2017, 2018), despite evidence of modality-specificity results in other forms of atypical development, such as developmental dyslexia or specific language disorder (Conway, 2020). In GTS, multimodal or bimodal sequential information might further increase hyperfunctioning (Beste et al., 2016).

Taken together, despite the growing evidence of enhanced procedural sequence learning in GTS, the exact functional relevance and underlying mechanisms of this cognitive advantage remain unclear. However, the proposed ideas above could bring us closer to relating atypical learning (and consolidation) of sequential regularities to clinical phenomenology and neurophysiology of GTS. Moreover, these insights could be further refined by considering how S-R mappings are constituted and how they develop in GTS. Therefore, in the next part, we introduce the latest evidence on binding processes in GTS.

4 | EVENT-FILE BINDING IN GTS

Hyperlearning of sequential regularities in GTS reviewed above might originate from alterations in a more elemental function: enhanced event file binding (Beste & Münchau, 2018; Brandt et al., 2016; Kleimaker, Kleimaker, et al., 2020; Kleimaker, Takacs, et al., 2020; Petruo et al., 2020, 2019; Weissbach et al., 2020). The possibility of hyperbinding was raised by an action-interference study in adult patients with GTS and healthy controls (Brandt et al., 2016). Participants had to follow acoustic cues to perform facial movements. Only in patients with GTS, some of these facial movements could be part of the tic repertoire. Simultaneously, video clips of facial movements were shown that were either compatible or incompatible with the acoustically instructed actions. From a TEC perspective, the auditory cues and the respective actions were bound together as event files. The video clips represented object files that could interfere with these event files. Consequently, when the object files were incompatible with the non-tic-like actions, both groups showed slower response times than in the
compatible condition. However, this interference effect did not occur in the GTS group when the to-be-performed movement was part of the individual tic repertoire. Thus, tic-like action files were resistant to interference by the new (visual) object files, which implies that the original binding between the previous (acoustic) object file and the tic-like action was too strong to be modified (Brandt et al., 2016). This is in line with the notion that tics are overlearnt actions, and once triggered, their execution is less susceptible to interference (Beste & Münchau, 2018; Kleimaker, Kleimaker, et al., 2020). Importantly, non-tic related associations between cues and actions in GTS showed a sensitivity to disruption that was comparable with controls (Brandt et al., 2016). Thus, it is likely not interference control that is altered in GTS but the formation of too strong S-R connections. Accordingly, adults with GTS may have advantages when creating event files. On the other hand, this could come at a price when switching between events is needed and the original event file needs to be reconfigured. The result of altered tic-related action-interference opened the path to study potential hyperbinding in GTS (Beste & Münchau, 2018; Brandt et al., 2016).

However, as mentioned above, because symptoms persist into adulthood, only in a small proportion of patients with GTS results from the subpopulation of adult patients with GTS are not representative for the group of patients with GTS as a whole. Crucially, altered binding functions during interference were confirmed by another study of children and adolescents with GTS (Petruo et al., 2019). In this study, a bimodal version of the go/no-go inhibitory paradigm was used. The go (perform the action) or no-go signals (withhold the action) were given either unimodally (visual only) or bimodally (both auditory and visual signals). Interestingly, children with GTS and TD children differed only in the unimodal no-go condition: the false alarm rate was higher in GTS than in TD. In contrast, when stimuli were presented bimodally, children with GTS showed comparable performance with TD children, including trials where the two modalities were incompatible. Thus, the difference between the groups did not arise due to inhibitory impairment in GTS but rather as a result of updating the response selection mechanisms when less information was available compared with multimodal presentation. The behavioural alterations were reflected by the decomposed neurophysiological data: a temporally decomposed EEG-cluster related to S-R translational processes (C-cluster) showed differences between groups. In the unimodal no-go condition, a negative deflection emerged in the time window corresponding to the classical N2 component. The negativity in the C-cluster was larger (more negative) in TD than in GTS. This effect was related to activation modulations in the right inferior parietal cortex (BA40). The implication of a parietal area suggests that altered behavioural performance in GTS was related to updating processes. Based on these results, it was suggested that children with GTS might have difficulties with binding in unimodal conditions: too stable event files are harder to reconfigure, that is, to unbound and rebound. Consequently, stronger representations of S-R mappings attenuate inhibitory performance. Thus, the proposed enhanced binding in an inhibitory situation (Brandt et al., 2016) was confirmed also in a sample of children with GTS (Petruo et al., 2019). This extension to the larger group of children/adolescents with GTS suggests that stronger S-R binding is a general cognitive characteristic of GTS, and a potential mechanism behind the emergence of tics (Beste & Münchau, 2018; Kleimaker, Kleimaker, et al., 2020).

However, the two studies did not investigate event file binding mechanisms directly in GTS (Brandt et al., 2016; Petruo et al., 2019). To examine event file processes irrespective of inhibitory functions in GTS, another study (Kleimaker, Takacs, et al., 2020) employed a specific S-R, or event file coding task (Colzato et al., 2006). In this task, first, a cue representing left- or right-hand responses was shown to the participants. Importantly, the response had to be withheld until the next stimulus (S1) was presented. Despite the lack of functional connection between the visual features of S1 and the required response to the cue, the temporal coincidence between these two created an association between stimulus and response features: an event file. Next, a second stimulus (S2) appeared with visual features overlapping with S1 either, completely, partially or not at all. Participants had to respond to one of these features with either the left or the right hand, that is, either repeating or alternating the previous response. In line with the predictions of TEC (Hommel, 1998, 2004), feature overlap between consecutive stimuli in case of response repetition facilitated response selection, whereas response alternation led to slower reaction times and lower accuracy (Kleimaker, Takacs, et al., 2020). This effect, the so-called partial repetition cost (Colzato et al., 2006; Hommel, 1998), reflects the extra time and effort needed to reconfigure the original S1-R binding. Importantly, this cost was higher in the GTS than in the control group along with larger response facilitation in the repetition condition (Kleimaker, Takacs, et al., 2020). Thus, adults with GTS showed enhanced event file binding. Crucially, the magnitude of the binding effect correlated positively with motor tic frequency, suggesting that increased binding is related to the expression of tics in GTS. Furthermore, neurophysiological results corroborated the behavioural findings in the temporally decomposed C-cluster. In the control
group, a positive deflection corresponding to the P3 component was smaller in complete feature overlap than in no overlap when responses had to be alternated, possibly reflecting the effortful aspect of rebinding. However, the GTS group did not show such modulation suggesting less optimal effort allocation for event file reconfiguration. The modulation of the C-cluster mean amplitude was localized in the left inferior parietal cortex (BA40). Because this study comprised adults with GTS, developmental aspects of event file processing in GTS still have to be addressed. This notwithstanding, it represents a milestone as it connects enhanced event file binding to behavioural, neurophysiological and clinical alterations at the same time and also provides a potential neural source (BA40). Moreover, the neurophysiological pattern shows remarkable similarities with the study of children with GTS by Petruo et al. (2019). Both studies (Kleimaker, Takacs, et al., 2020; Petruo et al., 2019) emphasized the role of parietal areas albeit with different laterality. Furthermore, they both found event file binding-related group differences in the C-cluster. This suggests that altered event file coding is not a result of strictly perceptual or motor problems but related to S-R translational processes. Interestingly, object file coding, that is, binding of perceptual features, is shown to be attenuated in GTS, however, unrelated to symptom severity (Beste et al., 2016). Thus, GTS represents a unique dissociation between object file coding and event file processing with the latter being related to the emergence of tics (Kleimaker, Kleimaker, et al., 2020; Kleimaker, Takacs, et al., 2020).

As outlined above, procedural memory and event file binding both seem to play a role in GTS. It is plausible that abnormal striatal networks in GTS affect cognitive functions influenced by striatal activity including procedural memory and event file binding. However, rather than considering these alterations as independent consequences of striatal abnormalities, we propose that the presence of hyperfunctioning of both binding and procedural learning in GTS can be explained by their interrelated functional relevance, that is, that hyperbinding enhances the chance to form stronger S-R connections in GTS. The procedural system then organizes the event files into sequential structures, based on the perceived probabilities in the environment (Figure 3).

Because event files are building blocks of procedural (sequential) memories (Eberhardt et al., 2017; Haider et al., 2020), atypical binding would inevitably lead to atypical procedural memory in GTS. Specifically, hyper-binding in GTS creates overly stable S-R connections, which makes the reconfiguration of event files, that is, unbinding and rebinding suboptimal. Consequently, rigid associations reduce the chance to successfully update response plans according to contextual changes. This fits the concept of tics being encapsulated, habitual behavioural programmes removed from their original context. If associations in the early phase of the task create rigid

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**FIGURE 3** Conceptual links between event file binding and procedural sequence learning and memory functions in Gilles de la Tourette syndrome (GTS). Enhanced binding of event files forms stronger S-R connections in GTS. Chunking in the procedural memory then organizes the event files into sequential structures, based on the perceived probabilities in the S-R stream. Stronger representations of S-R connections likely contribute to better learning performance in GTS than in typically developing (TD) controls. Similarly, better learning of sequential regularities would lead to stronger interference when probabilities in the environment change (i.e., another sequence is presented). Finally, hyperlearning may lead to atypically stable procedural memories that persist long after their original significance.
procedural memories, new sequential regularities or a lack of them would impede the responses as presented by Shephard et al. (2018). Similarly, event files reinforced by external rewards (Delorme et al., 2016; Palminteri et al., 2011) or by being more frequently required in the task (Takács et al., 2018) would give rise to more prediction errors. This leads to the question: Is enhanced procedural processing a direct consequence of hyperbinding in GTS?

Although this explanation seems plausible, there are three aspects of procedural sequence learning that cannot readily be explained by the hyperbinding account: (1) the different temporal dimensions of event file binding and procedural learning (Figure 3); (2) the difference in the need of chunking and sequencing; and (3) the specificity of enhancement within the memory systems. Thus, the main measures of event file binding, partial repetition costs/benefits last for seconds only (Colzato et al., 2006; Hommel, 2004; Pastötter et al., 2020), whereas sequential regularities form long-term memories that can persist even for months or years (Köbor et al., 2017). Therefore, hyperlearning is also needed over and above hyperbinding to explain the relative persistence of habitual behaviour (Delorme et al., 2016; Maia & Conceição, 2017). Of note, the difference of temporal dimensions between binding and procedural learning can be a matter of task design (Moeller & Frings, 2019a), and experiments could potentially be designed to study the long-term effects of event file binding. Apart from previous work on sequence learning in the context of TEC (Eberhardt et al., 2017; Haider et al., 2020), other studies analysed possible interaction between S-R binding and learning in event file coding tasks (Colzato et al., 2006; Moeller & Frings, 2017, 2019a, 2019b). For instance, Colzato et al. (2006) conducted a series of experiments, in which they identified how learning might influence the speed and strength of binding. Specifically, the first experiment showed that binding was not modulated by previously experienced frequency of S-R connections. That is, event file coding occurred without the influence of memories that encode the same features. However, task-relevance contributed to this relation: in infrequent conjunctions, bindings that were not task-relevant disappeared in the second session but not in frequent conjunctions. Replication of this effect in subsequent experiments further strengthened the view that binding is an automatic process that is largely independent from long-term memory representations (Colzato et al., 2006). At the same time, learning and memory processes may influence the content of the binding, that is, which features will be integrated. Another study (Herwig & Waszak, 2012) corroborated these findings by showing that long-term associations are only modulated if they followed intentional but not incidental actions. Furthermore, to differentiate between binding and learning factors, stimulus grouping effect was observed on binding but not on incidental learning (Moeller & Frings, 2017). Moreover, binding effect occurred when response–stimulus interval was short (500 ms) but not when it was long (2000 ms), whereas the opposite effect emerged for learning. Thus, binding is not equivalent of single trial learning (Moeller & Frings, 2017), and therefore, dissociations between binding and learning effects are expected (Colzato et al., 2006; Herwig & Waszak, 2012; Moeller & Frings, 2017).

However, the above-mentioned studies investigated the learning of independent S-R associations and not in the context of sequential regularities. Crucially, GTS studies reviewed in the current paper support the idea that binding and (procedural) learning are interrelated. Nevertheless, this interaction might not be present at the level of separate event files but only when they have functional significance in larger perceptual and/or action sequences. This is also supported by the finding that binding is independent of the representation of order information (Moeller & Frings, 2019a) even for contiguous response series (Moeller & Frings, 2019b). Sequence learning, however, largely relies on processing and storing the order of S-R contingencies (Conway, 2020; Dehaene et al., 2015). Thus, the relationship between binding and sequence learning processes are likely complex (Eberhardt et al., 2017; Haider et al., 2020) and not always evident in neurotypical population due to testing methods (Moeller & Frings, 2019a). However, current findings in GTS suggest that the connections between individual bindings and bindings in sequential regularities need to be studied in more details.

Event file binding and procedural learning in GTS might be two sides of the same coin: hyperbinding explains the formation of overly strong S-R connections, whereas hyperlearning represents the retention of the event files in a larger time frame (see also Figures 1 and 3). Still, even longer time perspectives are needed to make better predictions of the course of GTS symptoms over the lifetime and through clinical interventions. For instance, it has been suggested (Ullman & Pullman, 2015) that the imbalance between procedural and declarative memory systems can be used to design adapted behavioural therapies, for instance, by relying more on typically functioning declarative learning, for example, as in habit reversal therapy or related interventions. In line with this, comprehensive behavioural intervention therapy comprising habit reversal elements has been shown to be related to the normalization of event file binding in an inhibitory task (Petruo et al., 2020).
Further studies are needed to tie the evidence of hyper-binding and hyperlearning to clinical outcomes.

Moreover, tics represent action elements that are part of sequences in everyday behaviour (Goodman et al., 2014; Marsh et al., 2005). However, event file binding is usually studied in the context of two consecutive events (Colzato et al., 2006) and not in longer action sequences. As shown in the weather prediction task (Kéri et al., 2002; Marsh et al., 2004), learning of simple adjacent probabilities as a procedural memory function might not be enhanced in GTS or even impaired. The difference of chunking possibilities between event file binding and sequence learning also suggests that the latter is needed to explain the pathophysiology of tics. That is, procedural memories may represent event files bracketed together based on their interdependence in the stimulus stream. Therefore, even if procedural learning is a by-product of binding in a probabilistic environment (Eberhardt et al., 2017), it appears to have a unique contribution to the neurocognitive profile of GTS over and above the consequences of hyperbinding.

Intriguingly, only procedural memory functions but not declarative seem to be altered in GTS (Goodman et al., 2014; Marsh et al., 2005; Ullman & Pullman, 2015). However, event file binding mechanisms were proposed to contribute to the development of declarative memories, as well (Frings et al., 2020). If binding as a universal mechanism would explain the alterations in procedural memory in GTS, what are the compensatory mechanisms that potentially normalize the declarative system? Alternatively, GTS may be an example of a disorder characterized by a unique dissociation between the role of event file binding in procedural and declarative memories.

6 | CONCLUSIONS

In sum, both procedural sequence learning and event file binding are enhanced in GTS and can be considered as cognitive mechanisms behind habitual symptoms, such as tics (Beste & Münchau, 2018; Delorme et al., 2016; Kleimaker, Kleimaker, et al., 2020; Kleimaker, Takacs, et al., 2020; Petruo et al., 2019; Shephard et al., 2018; Takács et al., 2018). Converging evidence of enhanced functions in GTS are probably not coincidental, and they have consequences for cognitive theories in addition to understanding of GTS. Despite their similarities, event file binding and procedural sequence learning have different time scales, different sensitivities to potential impairment in action sequencing, but both contribute to the overall cognitive profile of GTS. To provide a complete cognitive account of how tics emerge and persist in GTS, it would be important to study binding and procedural learning simultaneously during development. On the other hand, the double enhancement in GTS represents a unique opportunity to understand the mechanistic link between event file binding and the procedural system.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

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