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Procedural learning in Tourette syndrome, ADHD, and comorbid Tourette-ADHD: Evidence from a probabilistic sequence learning task

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ABSTRACT

Procedural memory, which is rooted in the basal ganglia, plays an important role in the implicit learning of motor and cognitive skills. Few studies have examined procedural learning in either Tourette syndrome (TS) or Attention Deficit Hyperactivity Disorder (ADHD), despite basal ganglia abnormalities in both of these neurodevelopmental disorders. We aimed to assess procedural learning in children with TS (n = 13), ADHD (n = 22), and comorbid TS-ADHD (n = 20), as well as in typically developing children (n = 21). Procedural learning was measured with a well-studied implicit probabilistic sequence learning task, the alternating serial reaction time task. All four groups showed evidence of sequence learning, and moreover did not differ from each other in sequence learning. This result, from the first study to examine procedural memory across TS, ADHD and comorbid TS-ADHD, is consistent with previous findings of intact procedural learning of sequences in both TS and ADHD. In contrast, some studies have found impaired procedural learning of non-sequential probabilistic categories in TS. This suggests that sequence learning may be spared in TS and ADHD, while at least some other forms of learning in procedural memory are impaired, at least in TS. Our findings indicate that disorders associated with basal ganglia abnormalities do not necessarily show procedural learning deficits, and provide a possible path for more effective diagnostic tools, and educational and training programs.

1. Introduction

Tourette syndrome (TS) and Attention Deficit Hyperactivity Disorder (ADHD) are both neurodevelopmental disorders associated with frontal and basal ganglia abnormalities (Arnsten & Rubia, 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Robertson, 2015b). These disorders, which are often comorbid with each other (Denckla, 2006; Robertson, 2015a), are characterized by behavioral symptoms such as compulsions, tics, and impulsive actions (Robertson, 2015a). It has been suggested that the frontal/basal-ganglia abnormalities may lead to procedural memory abnormalities in both disorders (Goodman, Marsh, Peterson, & Packard, 2014; Kéri, Szlobodnyik, Benedek, Janka, & Gádoros, 2002).

Despite these links between procedural memory and both disorders, few studies have examined procedural learning in either TS or ADHD. Moreover, these have yielded mixed results (Channon, Pratt, & Robertson, 2003; Kéri et al., 2002; Marsh et al., 2004). There has been even less work examining procedural learning (or other cognitive functions) in comorbid TS-ADHD – despite the fact that 60% of children with TS also have ADHD (Denckla, 2006). Here we attempt to address these gaps and inconsistencies by testing four groups of age- and sex-matched children – with TS, ADHD, TS-ADHD, and typically

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developing children – on the same well-studied implicit probabilistic sequence learning task.

1.1. The disorders

TS is a developmental disorder characterized by multiple motor tics and at least one vocal tic, which are not explained by medications or another medical condition (American Psychiatric Association, 2013). The prevalence of the disorder appears to be in the range of 0.85–1% (American Psychiatric Association, 2013; Robertson, 2015a). TS is associated with both structural and functional abnormalities of the basal ganglia and frontal cortex, and their connecting circuits (Goodman et al., 2014; Müller-Vahl et al., 2009; Tremblay, Worbe, Thobois, Sgambato-Faure, & Féger, 2015). The tics appear to be caused by disturbances of the basal ganglia and closely connected regions of cortex, especially motor and cognitive regions of frontal cortex (Albin & Mink, 2006; Müller-Vahl et al., 2014). In particular, they may be caused by enhanced excitability in the direct relative to the indirect striatal pathway (Maia & Frank, 2011). It has been suggested, that basal ganglia hyperactivity in TS is associated not only with tics and impulsivity, but also with alterations of the related cognitive systems, such as procedural memory (Goodman et al., 2014; Kéri et al., 2002).

ADHD is a developmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity, with a prevalence of about 5–10% in school-age children (American Psychiatric Association, 2013; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Similarly to TS, fronto-striatal networks are compromised in ADHD (Arnsten & Rubia, 2012), including the basal ganglia and inferior prefrontal cortex, as well as its connections to striatal as well as cerebellar and parietal regions. The heterogeneous neural alterations in ADHD have been linked to impairments in a wide range of cognitive functions, from perception to learning (Arnsten & Rubia, 2012; Kóbor et al., 2015; Sjöwall, Roth, Lindqvist, & Thorell, 2013).

The majority of children with TS (88%) have comorbidities, which can affect cognitive, social, and academic outcomes of TS (Robertson, 2015a). ADHD is perhaps the most frequent comorbid disorder, occurring in about 60% of individuals with TS (Denckla, 2006). There are significant anatomical and neurobehavioral differences between children with TS-ADHD and those with just TS or just ADHD. For example, the basal ganglia, right prefrontal cortex, and rostral corpus callosum appear to be smaller in children with comorbid TS-ADHD than in children with TS only (Denckla, 2006; Robertson, 2015a). We are not aware of studies that directly compare anatomical differences in TS-ADHD and ADHD.

1.2. Procedural memory in TS and ADHD

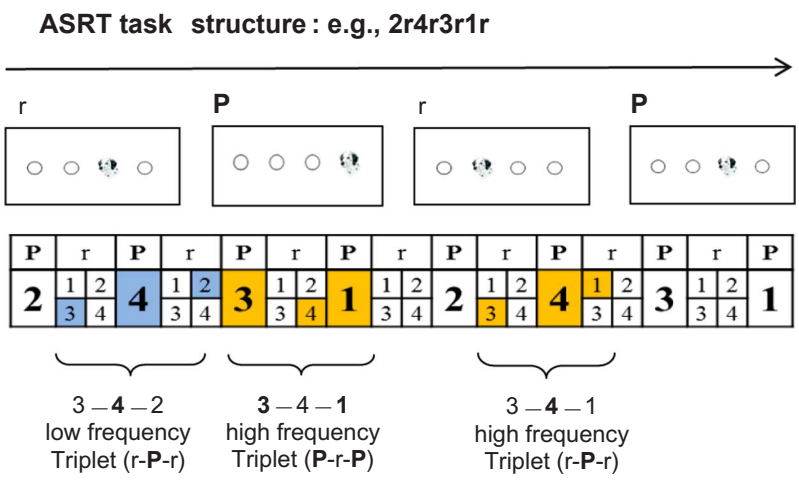
This implicit memory system involves a network of interconnected brain structures rooted in frontal/basal-ganglia circuits (Cleeremans, Destrebecqz, & Boyer, 1998; Doyon et al., 2009; Eichenbaum, 2012; Song, Howard, & Howard, 2007a; Ullman, 2004, 2016). We use the term procedural memory to refer to a particular brain system that underlies implicit memory, rather than implicit memory more generally, which is subserved by other systems as well (Squire, 2004; Ullman, 2004). The procedural system underlies the implicit learning and processing of a wide range of perceptual-motor and cognitive skills, including navigation, sequences, rules, and categories. The basal ganglia play a critical role in the learning and consolidation of these new skills, whereas frontal regions (in particular premotor and related regions) may be more important for processing skills after they have been automatized (Sefcsik et al., 2011; Stillman et al., 2013). The system may be specialized for learning to predict, perhaps especially probabilistic outcomes – for example the next item in a sequence or the output of a rule. Learning in the system requires practice, which seems to eventually result in rapid and automatic processing of skills and knowledge. For a more computational approach, which emphasizes implicit learning processes rather than the above described brain system, please see the review of Reber (2013). In the current paper, our focus is on procedural memory, and not implicit learning more generally.

Few studies have examined procedural memory in TS. We are aware of three published studies probing learning in this system, two of which found impairments. Kéri et al. (2002) reported impaired learning in children with TS in a study employing the weather prediction task. Moreover, this impairment in learning was positively associated with TS symptom severity. In the weather prediction task participants learn probabilistic associations between simple visual stimuli and their outcomes (good or bad weather). The task has been shown to depend on procedural memory brain structures (Knowlton, Ramus, & Squire, 1992; Poldrack & Foerde, 2008), though declarative memory also appears to play a role, especially in earlier stages of learning (Newell, Lagnado, & Shanks, 2007; Speekenbrink, Channon, & Shanks, 2008). Another study examining learning with the weather prediction task also found impaired learning, both in children and adults with TS (Marsh et al., 2004).

In contrast, Channon et al. (2003) observed intact sequence learning in children with TS on the serial reaction time (SRT) task, which depends on procedural memory (Janacsek, Shattuck, Lum, Tagliatelli, & Ullman, in preparation; Lum, Conti-Ramsden, Morgan, & Ullman, 2014; Lum, Ullman, & Conti-Ramsden, 2013; Nissen & Bullemer, 1987). It has been suggested that sequence learning may be a distinct procedural memory function (Hsu & Bishop, 2014; Krishnan, Watkins, & Bishop, 2016), since sequence learning might dissociate from other types of procedural learning in other developmental disorders (Hsu & Bishop, 2014; Kemény & Lukács, 2010; Krishnan et al., 2016). Thus, sequence learning may warrant further investigation in TS.

We are also aware of two studies examining the processing of knowledge that has previously been learned in procedural memory, that is, of already established knowledge. One study found that children with TS were faster (but not more accurate) than TD children at producing past tense forms that are posited to be combined (walk + -ed, rick + -ed) by the mental grammar, but not those that appear to be retrieved from (*dug*) or processed in (*splung*) associative lexical memory (Walenski, Mostofsky, & Ullman, 2007). Since independent evidence suggests that rule-governed combinatorial aspects of grammar, across syntax, morphology and phonology, are learned and processed in procedural memory (Ullman, 2004, 2016), it was suggested that the observed pattern reflects speeded processing of knowledge learned in procedural memory more generally, that is, of both linguistic and non-linguistic knowledge. Indeed, the same participants were faster (but not more accurate) than controls at naming manipulated objects such as *hammer* (which involve learned motor skill knowledge), but not non-manipulated objects such as *elephant* (Walenski et al., 2007). A second study found evidence for speeded combination in children with TS in phonology, in a non-word repetition task, and also attributed it to fast processing in procedural memory (Dye, Walenski, Mostofsky, & Ullman, 2016). These findings are also consistent with the possibility that sequence-based knowledge in procedural memory in both language and non-language domains (Krishnan et al., 2016) may remain unimpaired in TS.

The literature examining procedural memory in ADHD is sparser. We are aware of two studies examining procedural learning in ADHD in children or adolescents (Barnes, Howard, Howard, Kenealy, & Vaidya, 2010; Karatekin, White, & Bingham, 2009) and two in adults (Adi-Japha, Fox, & Karni, 2011; Pedersen & Ohrmann, 2012). One study, which examined sequence learning with the SRT task, found evidence of intact procedural learning in adolescents with ADHD (Karatekin et al., 2009). Another study found that children with ADHD showed similar performance at early and later stages of sequence learning in the ASRT task, but altered performance at a middle stage (Barnes et al., 2010). In adults with ADHD, one study of sequence learning with the SRT task found intact learning (Pedersen & Ohrmann, 2012). Another study, of finger sequence learning in women with ADHD, found normal initial learning, but



	Structure: 3 – r – 1	Structure: r – 4 – r
High frequency triplets (62.5 % of all trials)	3 – 4 – 1 (50%)	3 – 4 – 1 (12.5%)
Low frequency triplets (37.5 % of all trials)	never occurring (always high)	3 – 4 – 2 (12.5%) 3 – 4 – 3 (12.5%) 3 – 4 – 4 (12.5%)

Fig. 1. Design of the ASRT task, showing pattern (P) and random elements (r), and high- and low-frequency Triplets. High frequency Triplets are expected with 62.5% probability, while low frequency Triplets have a 37.5% probability of occurring.

impairments one day and two weeks later, suggesting consolidation deficits (Adi-Japha et al., 2011).

Thus, the literature is also somewhat mixed regarding ADHD. In sum, one study of procedural learning in children with ADHD found normal performance, while the other found mixed results. Similarly, one study of adults with the disorder found normal performance, while the other found impairments suggesting consolidation difficulties. We are not aware of any studies designed to examine the processing of knowledge previously learned in procedural memory.

Finally, we are aware of very few studies examining procedural memory in comorbid TS-ADHD. One study found that children with comorbid TS-ADHD showed similar performance in an SRT task to children with TS only, and also to their TD peers (Channon et al., 2003). Kéri et al. (2002) also broached the topic, suggesting that the impaired procedural learning in TS that they observed in the weather prediction task (see above) could not be explained by the co-occurring ADHD, since, in their study, the learning difference between TS and TD children in the weather prediction task remained significant even after removing children with comorbid ADHD from the analysis. We are not aware of any studies directly comparing procedural learning across TS, ADHD and comorbid TS and ADHD.

1.3. The present study: motivation and summary

The present study addresses the still-sparse literature examining procedural memory in TS and ADHD. In particular, it examines a well-studied procedural learning paradigm, the Alternating Serial Reaction Time Task, or ASRT (Howard & Howard, 1997), in four groups of children: those with TS, ADHD, comorbid TS and ADHD, and typically developing children. This allows us to directly compare each of the three groups to each other and to TD controls with the exact same paradigm, providing for more reliable comparisons across the groups than in previous studies. Given the mixed literature, which has reported both impaired and intact procedural learning in both TS and ADHD, we did not have any strong predictions regarding the outcomes.

2. Methods

2.1. Participants

Seventy-six children between 7 and 17 years of age participated in the study: children with TS only, that is, without comorbid ADHD (n = 13; 2 girls); children with ADHD, but not TS (n = 20; 4 girls); children with comorbid ADHD and TS (TS-ADHD; n = 22; 5 girls), and typically developing children (TD; n = 21; 8 girls). The groups did not differ in their sex ratio ($\chi^2(3) = 5.122$, $p = 0.163$), or in age (in years: $M_{ADHD} = 12.7$, $SD_{ADHD} = 1.8$, $M_{TD} = 13.6$, $SD_{TD} = 3.1$, $M_{TS} = 13.5$, $SD_{TS} = 3.1$, $M_{TS\text{-}ADHD} = 12.3$, $SD_{TS\text{-}ADHD} = 2.7$; $F(3, 71) = 0.994$, $p = 0.401$, $\eta_p^2 = 0.042$). All children were native Hebrew speakers. Children with TS were recruited through the Tourette Syndrome multidisciplinary clinic at Shaare Zedek Medical Center, Jerusalem, Israel. Children with ADHD were recruited from the pediatric neurology unit of the same center. TD children were recruited through the hospital staff (i.e., non-referred relatives of patients), and were evaluated by a pediatric neurologist to rule out TS, ADHD, or one of the exclusionary criteria (see below). In the clinic, children and their parents received information about the goals of the study and the general procedure. If they agreed to participate, parents or legal guardians signed an informed consent. The study was approved by the local ethical committee for medical research, based on the criteria laid down in the Declaration of Helsinki. Diagnosis of TS and ADHD conditions were made on the basis of DSM-IV criteria (DSM-IV-TR; American Psychiatric Association, 2000) by experienced child and adolescent psychiatrists or pediatric neurologists. TS was diagnosed in according to the Tourette Syndrome Association Medical Advisory Board: Practice Committee guidelines (Scahill et al., 2006). ADHD was diagnosed according to American Academy of Pediatrics guidelines (American Academy of Pediatrics, 2011). All children were screened for relevant diagnoses and exclusion criteria during an interview with one of the aforementioned experts. Exclusionary criteria included major psychiatric or neurological conditions, including mood disorders, psychosis, and autism spectrum

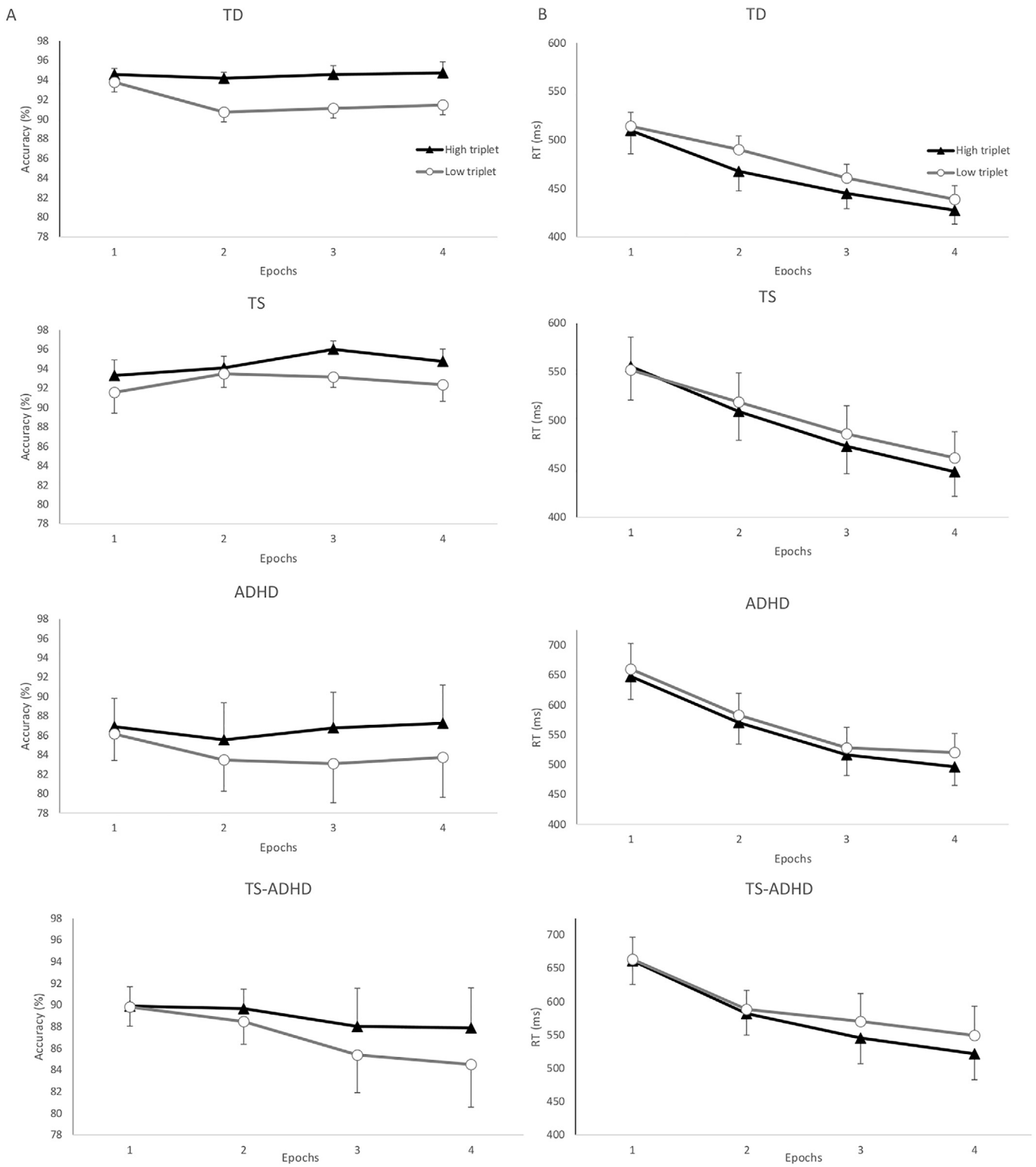


Fig. 2. Accuracy (A) and RT for correct responses (B) as a function of Epoch (1–4) and trial type (high- vs. low frequency Triplets). TD: Typically developing; TS: Tourette syndrome; ADHD: Attention Deficit Hyperactivity Disorder; TS-ADHD: comorbid TS and ADHD. Error bars denote standard error of means. For interested readers, see Supplementary Material for analyses corresponding to these eight panels, that is, separate analyses for each group on accuracy and RTs.

disorder, but not obsessive-compulsive disorder or oppositional defiance disorder, since these are common in children with TS or ADHD. One child in the ADHD group had a diagnosis of oppositional defiance disorder, while four children in the TS-ADHD group were diagnosed with obsessive compulsive disorder. The children with TS did not have any other known psychiatric or neurologic conditions. All participants had normal or corrected vision and normal hearing.

2.2. Task

Probabilistic sequence learning was examined with the ASRT task (Howard & Howard, 1997). In the version of the task used here (Nemeth et al., 2010), participants were instructed to press keys corresponding to four equally spaced circles on the computer screen (see Fig. 1). On each trial, a target stimulus (a dog's head) appeared in one of four

possible locations, and remained until the participant pressed any of the four keys. Following any response, and a subsequent delay of 120 ms, the next target appeared. The basic trial sequence consisted of eight elements, in which random trials alternated with pattern trials (e.g., 1r2r3r4r, where 1–4 indicate circle positions from left to right, and r indicates a randomly selected position), with this trial sequence being repeated 10 times in each block. Six patterns were counterbalanced across participants in each participant group: 1r2r3r4r, 1r2r4r3r, 1r3r2r4r, 1r3r4r2r, 1r4r2r3r, and 1r4r3r2r. This structure results in some of the three consecutive elements (henceforth referred to as Triplets) occurring more frequently than others. In accordance with this structure, each item was categorized as the third element of either a high- or low-probability Triplet, and the accuracy and reaction time (RT) of the response to this item were compared between them (Howard & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010). In the ASRT task, learning is operationalized as increasing differences in response times or accuracy between high and low frequency Triplets over the course of the task (Howard & Howard, 1997; Song et al., 2007a). The task had 20 blocks, each of which consisted of 85 trials, that is, presentations of the dog's head with a corresponding key press. In each block, the first 5 trials were randomly positioned, and were for practice purposes only (not analyzed further), after which the 8-element alternating sequence was repeated 10 times. Participants were allowed to take a brief break between each block. The procedure did not include a test for explicit knowledge, since no previous ASRT studies probing for explicit knowledge have found evidence for such knowledge, either in adults (e.g., Howard & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010; Nemeth et al., 2010; Romano, Howard, & Howard, 2010; Song, Howard, & Howard, 2007b), or children (Barnes et al., 2010; Janacsek, Fiser, & Nemeth, 2012; Nemeth, Janacsek, & Fiser, 2013; Nemeth et al., 2010).

2.3. Statistical analysis

Statistical analyses were based on previous studies (e.g., Howard & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010; Nemeth et al., 2010; Romano et al., 2010; Song et al., 2007b). The entire ASRT task was collapsed into four Epochs of five blocks each. Mean accuracy (percentage of correct responses) and the median of RT data (for correct responses) were calculated for each participant and each Epoch, separately for high- and low-frequency Triplets. To investigate the difference in probabilistic sequence learning between groups, we conducted ANOVAs. We used LSD (Least Significant Difference) tests for post hoc pair-wise comparisons. The Greenhouse-Geisser epsilon correction was applied when necessary. Here we report the η_p^2 effect size index for ANOVA main effects and interactions.

3. Results

3.1. Accuracy analyses

We conducted a mixed design ANOVA on accuracy, with Triplet (2: high vs. low frequency) and Epoch (1–4) as within-subjects factors, and Group (TS, ADHD, TS-ADHD, TD) as a between-subjects factor. Accuracy data as a function of Epoch (1–4) and trial type (high- vs. low frequency Triplets) for each group are presented in Fig. 2A. The main effect of Group (that is, over all Epochs and over both low- and high-frequency Triplets) was marginally significant ($F(3, 68) = 2.494$, $p = 0.067$, $\eta_p^2 = 0.099$). The main effect of Triplet was significant ($F(1, 68) = 73.481$, $p < 0.001$, $\eta_p^2 = 0.519$), indicating that participants (over all four groups) were significantly less accurate on the low- than high-frequency Triplets ($M_{low} = 88.9\%$, $SD_{low} = 1.3\%$; $M_{high} = 91.1\%$, $SD_{high} = 1.3\%$), consistent with sequence-specific learning (Nemeth et al., 2011). The Triplet ∗ Group interaction was not significant ($F(3, 68) = 0.777$, $p = 0.511$ $\eta_p^2 = 0.033$), suggesting similar level of sequence-specific learning in all groups. The main effect of Epoch was also not significant ($F(3, 204) = 0.589$, $p = 0.623$ $\eta_p^2 = 0.009$), suggesting that overall accuracy (that is, over both the high- and low-frequency Triplets, over all groups) did not change during the task. In contrast, there was a significant Triplet ∗ Epoch interaction, over all groups ($F(3, 204) = 6.611$, $p < 0.001$, $\eta_p^2 = 0.089$). Following up on this interaction, post hoc analyses revealed that, over all four groups, the difference between low- and high-frequency Triplets increased from the 1st Epoch ($M_{low} = 90.3\%$, $SD_{low} = 1.1\%$; $M_{high} = 91.2\%$, $SD_{high} = 1.1\%$) both to the 3rd ($M_{low} = 88.2\%$, $SD_{low} = 1.6\%$; $M_{high} = 91.3\%$, $SD_{high} = 1.5\%$; $p < 0.001$) and the 4th ($M_{low} = 88.0\%$, $SD_{low} = 1.8\%$; $M_{high} = 91.2\%$, $SD_{high} = 1.7\%$; $p < 0.001$), and from the 2nd ($M_{low} = 89.90\%$, $SD_{low} = 1.2\%$; $M_{high} = 90.9\%$, $SD_{high} = 1.3\%$) to the 4th ($p = 0.024$), confirming probabilistic sequence learning across the four groups (none of the other Epoch comparisons were significant; $ps > 0.08$). The Epoch ∗ Group and the Triplet ∗ Epoch ∗ Group interactions were not significant ($F(5, 204) = 0.79$, $p = 0.625$, $\eta_p^2 = 0.034$; $F(3, 213) = 1.07$, $p = 0.362$, $\eta_p^2 = 0.015$, respectively), suggesting that the time course of learning was similar across groups.

3.2. Reaction time analyses

Similarly to the analysis on accuracy, to examine response times we conducted a mixed design ANOVA, with Triplet (2: high vs. low frequency) and Epoch (1–4) as within-subjects factors, and Group (TS, ADHD, TS-ADHD, TD) as a between-subjects factor. RT data as a function of Epoch (1–4) and trial type (high- vs. low frequency Triplets) for each group are presented in Fig. 2B. The main effect of Group was significant ($F(3, 68) = 3.284$, $p = 0.026$, $\eta_p^2 = 0.127$), revealing differences among groups in general response times. Post-hoc analyses revealed that the children with ADHD ($M = 565.28$ ms, $SD = 28.76$ ms) were overall slower than the TD children ($M = 469.22$ ms, $SD = 31.19$ ms; $p = 0.027$). Similarly, the children with TS-ADHD were slower than the TD children ($M = 585.29$ ms, $SD = 27.42$ ms; $p = 0.007$). All other comparisons were not significant ($ps > 0.05$). The main effect of Triplet ($M_{low} = 536.55$ ms, $SD_{low} = 15.64$ ms; $M_{high} = 523.50$ ms, $SD_{high} = 15.31$ ms) was significant ($F(3, 68) = 42.562$, $p < 0.001$, $\eta_p^2 = 0.385$), consistent with sequence-specific learning across all groups. The Triplet ∗ Group interaction was not significant ($F(3, 68) = 0.569$, $p = 0.638$, $\eta_p^2 = 0.024$), consistent with a lack of group differences in sequence-specific learning. A significant main effect of Epoch (1st epoch: $M = 595.51$ ms, $SD = 17.74$ ms; 2nd epoch: $M = 538.71$ ms, $SD = 15.76$ ms; 3rd epoch: $M = 503.12$ ms, $SD = 17.22$ ms; 4th epoch: $M = 482.75$ ms, $SD = 16.80$ ms; $F(3, 68) = 39.319$, $p < 0.001$, $\eta_p^2 = 0.366$) indicates that, over all groups, participants became faster with practice, over both low- and high-frequency triplets. A significant Triplet ∗ Epoch interaction ($F(3, 204) = 2.909$, $p = 0.036$, $\eta_p^2 = 0.041$) indicates that, over all four groups, participants responded increasingly faster on high- than on low-frequency Triplets over the course of practice, suggesting sequence-specific learning. Post hoc analyses revealed that the difference between Triplet types (over all groups) increased from the 1st Epoch ($M_{low} = 597.45$ ms, $SD_{low} = 17.98$ ms; $M_{high} = 593.56$ ms, $SD_{high} = 17.80$ ms) to both the 3rd ($M_{low} = 511.28$ ms, $SD_{low} = 17.69$ ms; $M_{high} = 494.96$ ms, $SD_{high} = 16.93$ ms; $p = 0.04$) and the 4th ($M_{low} = 492.38$ ms, $SD_{low} = 17.55$ ms; $M_{high} = 473.38$ ms, $SD_{high} = 16.18$ ms; $p = 0.012$); none of the other Epoch comparisons, including with the 2nd ($M_{low} = 545.08$ ms, $SD_{low} = 15.69$ ms; $M_{high} = 532.33$ ms, $SD_{high} = 16.11$ ms), were significant; $ps > 0.1$. The Epoch ∗ Group interaction was not significant ($F(5, 112) = 0.974$, $p = 0.463$, $\eta_p^2 = 0.041$), and neither was the Triplet ∗ Epoch ∗ Group interaction ($F(9, 204) = 0.88$, $p = 0.544$, $\eta_p^2 = 0.037$) suggesting that the time course of learning was similar across groups.

4. Discussion

Our goal was to investigate procedural learning with an implicit probabilistic sequence learning task, the alternating serial reaction time (ASRT) task, in children with TS, ADHD, or comorbid TS-ADHD, as well as in typically developing children. To our knowledge, this is the first study to examine this fundamental learning system across both TS and ADHD, let alone also in comorbid TS-ADHD.

Analyses suggested intact procedural learning in all four groups. First of all, in both the accuracy and RT analyses performed across all four groups (TD, TS, ADHD, TS-ADHD), both the Triplet main effect and the Triplet by Epoch interaction were significant, while neither the Triplet by Group nor the Triplet by Epoch by Group interactions were significant. This suggests that all four groups showed sequence learning, with no significant differences between them in this learning. Overall, the results suggest intact procedural learning in all four groups: not only in TD children, but also children with TS, ADHD, or comorbid TS and ADHD.

Together with previous results, the findings presented here suggest an intriguing possibility: perhaps in both TS and ADHD, as well as in comorbid TS-ADHD, learning *sequences* in procedural memory may remain intact, while certain other forms of learning (e.g., non-sequential categorization) in this system may be impaired. Together with the present study, two out of two studies of sequence learning in TS have found normal acquisition (the present study and Channon et al., 2003). Similarly, all four studies of sequence learning in ADHD, including two with children, reported normal learning, other than one time point in the acquisition process in Barnes et al. (2010). In contrast, both studies of learning in the weather prediction task reported impairments in TS (Kéri et al., 2002; Marsh et al., 2004). Thus it is possible that whereas sequence learning in procedural memory remains intact in these disorders, other forms of learning in this system are impaired, or at least those forms measured by the weather prediction task. Future studies may elucidate the mechanisms underlying this difference. The current study corroborates the hypothesis that sequence learning can dissociate from other forms of procedural learning in atypical development (Hsu & Bishop, 2014; Krishnan et al., 2016).

Even if sequence learning in procedural memory remains intact in TS and ADHD, the role of this memory system in other aspects of sequences may be abnormal in these disorders. First, at least some evidence suggests that consolidation of learned sequences may be impaired, at least in ADHD (Adi-Japha et al., 2011). However, these results should be treated with caution, since only females were tested, and moreover only adults with ADHD, which evidence suggests differs from ADHD in children (Rubia, Alegria, & Brinson, 2014). Second, the processing of previously learned (established) sequences seems to be not just spared, but enhanced in TS, at least in processing speed (Dye et al., 2016; Walenski et al., 2007). It remains to be seen whether future studies of TS might find such enhancements in learning as well. Note that these observations are not in fact contradictory, since the consolidation impairments were found in ADHD, while speeded processing was observed in TS.

The present findings suggest paths for future research. This should not only further examine implicit sequence learning in TS and ADHD (and related disorders), but also non-sequence learning, not just in the weather prediction task, but in other tasks as well. Note that it is possible that the observed dissociations between the weather prediction task and sequence learning tasks in TS may be due to factors other than a sequence/non-sequence distinction. For example, as mentioned in the Introduction, learning in the weather prediction task may depend in part on declarative memory. Future studies could examine learning in TS with different procedural and declarative memory loads. It is possible that children with TS show intact learning in relatively pure procedural learning tasks (e.g., in the present study and Channon et al., 2003) and declarative learning tasks (Robertson, 2015b; Ullman & Pullman, 2015), but their performance deteriorates when they need to rely on both systems interactively.

Additionally, both consolidation and the processing of previously learned knowledge in procedural memory should be further examined, for both sequence and non-sequence learning, in both TS and ADHD, as well as comorbid TS-ADHD. The finding that sequence learning may be intact in TS and ADHD, in which the basal ganglia are abnormal, suggests that, unlike other disorders with basal ganglia abnormalities, such as specific language impairment and Parkinson's disease (Hsu & Bishop, 2014; Krishnan et al., 2016; Lum et al., 2014), abnormalities of these structures do not necessarily lead to procedural learning deficits. Further studies seem warranted to deconstruct the structure and function of the basal ganglia regarding these differences, as well as the differences between sequence and non-sequence implicit learning.

The current study is not without limitations. Since children from a wide age range were recruited, developmental trends could contribute to the variability of the data, which may have masked potential group differences. Additionally, the diagnostic assessments in the study were clinical only, so linking the procedural memory findings to neuropsychological or symptom severity measures was not possible. It has been suggested that habit-like symptoms, such as impulsivity and tics arise from abnormalities in the frontostriatal system (Goodman et al., 2014; Kéri et al., 2002). Namely, abnormalities in the structure and function of the striatum can lead to atypical learning of skills and habits. Therefore, individual differences in procedural memory in TS can be associated with severity of habit-like symptoms. Future studies with more specific samples can clarify these questions.

In sum, we found intact implicit sequence learning in TS, ADHD, and comorbid TS-ADHD. Together with previous studies, the findings suggest the possibility of intact procedural learning of sequences in TS and ADHD, even while other forms of learning in procedural memory, as probed by the weather prediction and perhaps other tasks, appear to be impaired, at least in TS. The sparing of implicit sequence learning in TS and ADHD may provide insights for more effective diagnostic tools, as well as educational and training programs, for example, by emphasizing sequence vs. non-sequence learning in these disorders. Thus, the present study may open new avenues of both basic and clinical research.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandc.2017.06.009.

References

Adi-Japha, E., Fox, O., & Karni, A. (2011). Atypical acquisition and atypical expression of memory consolidation gains in a motor skill in young female adults with ADHD. *Research in Developmental Disabilities*, *32*(3), 1011–1020. http://dx.doi.org/10.1016/j.ridd.2011.01.048.

Albin, R. L., & Mink, J. W. (2006). Recent advances in Tourette syndrome research. *Trends in Neurosciences*, *29*(3), 175–182. http://dx.doi.org/10.1016/j.tins.2006.01.001.

American Academy of Pediatrics (2011). ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*, *128*(5), 1007–1022. http://dx.doi.org/10.1542/peds.2011-2654.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* (Vol. 1). Arlington, VA: American Psychiatric Association. http://dx.doi.org/10.1176/appi.books.9780890423349.

American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental

Disorders, 5th Edition. In *Diagnostic and Statistical Manual of Mental Disorders, 5th ed*. American Psychiatric Publishing, Inc. http://dx.doi.org/10.1176/appi.books.9780890425596.744053.

Arnsten, A. F. T., & Rubia, K. (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: Disruptions in neurodevelopmental psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. http://dx.doi.org/10.1016/j.jaac.2012.01.008.

Barnes, K. A., Howard, J. H., Howard, D. V., Kenealy, L., & Vaidya, C. J. (2010). Two forms of implicit learning in childhood ADHD. *Developmental Neuropsychology*, *35*(5), 494–505. http://dx.doi.org/10.1080/87565641.2010.494750.

Channon, S., Pratt, P., & Robertson, M. M. (2003). Executive function, memory, and learning in Tourette's syndrome. *Neuropsychology*, *17*(2), 247–254. http://dx.doi.org/10.1037/0894-4105.17.2.247.

Cleeremans, A., Destrebecqz, A., & Boyer, M. (1998). Implicit learning: News from the front. *Trends in Cognitive Sciences*, *2*(10), 406–416. http://dx.doi.org/10.1016/S1364-6613(98)01232-7.

Cubillo, A., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *48*(2), 194–215. http://dx.doi.org/10.1016/j.cortex.2011.04.007.

Denckla, M. (2006). Attention-Deficit Hyperactivity Disorder (ADHD) Comorbidity: A Case for"Pure"Tourette Syndrome? *Journal of Child Neurology*. http://dx.doi.org/10.2310/7010.2006.00164.

Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., ... Benali, H. (2009). Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behavioural Brain Research*, *199*(1), 61–75. http://dx.doi.org/10.1016/j.bbr.2008.11.012.

Dye, C. D., Walenski, M., Mostofsky, S. H., & Ullman, M. T. (2016). A verbal strength in children with Tourette syndrome? Evidence from a non-word repetition task. *Brain and Language*, *160*, 61–70. http://dx.doi.org/10.1016/j.bandl.2016.07.005.

Eichenbaum, H. (2012). *The Cognitive Neuroscience of Memory: An Introduction. The Cognitive Neuroscience of Memory: An Introduction*. http://dx.doi.org/10.1093/acprof:oso/9780199778614.001.0001.

Goodman, J., Marsh, R., Peterson, B. S., & Packard, M. G. (2014). Annual research review: The neurobehavioral development of multiple memory systems - Implications for childhood and adolescent psychiatric disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *55*(6), 582–610. http://dx.doi.org/10.1111/jcpp.12169.

Howard, J. H., & Howard, D. V. (1997). Age differences in implicit learning of higher order dependencies in serial patterns. *Psychology and Aging*, *12*(4), 634–656. http://dx.doi.org/10.1037/0882-7974.12.4.634.

Hsu, H. J., & Bishop, D. V. M. (2014). Sequence-specific procedural learning deficits in children with specific language impairment. *Developmental Science*, *17*(3), 352–365. http://dx.doi.org/10.1111/desc.12125.

Janacsek, K., Shattuck, K., Lum, J. A. G., Tagliatelli, K., & Ullman, M. T. (in preparation). *Partially distinct neural correlates are associated with the acquisition of sequential information and its changes over time: A coordinate-based ALE functional neuroimaging meta-analysis of brain activations during sequence learning*.

Janacsek, K., Fiser, J., & Nemeth, D. (2012). The best time to acquire new skills: Age-related differences in implicit sequence learning across the human lifespan. *Developmental Science*, *15*(4), 496–505. http://dx.doi.org/10.1111/j.1467-7687.2012.01150.x.

Karatekin, C., White, T., & Bingham, C. (2009). Incidental and intentional sequence learning in youth-onset psychosis and Attention-Deficit/Hyperactivity Disorder (ADHD). *Neuropsychology*, *23*(4), 445–459. http://dx.doi.org/10.1037/a0015562.

Kemény, F., & Lukács, Á. (2010). Impaired procedural learning in language impairment: Results from probabilistic categorization. *Journal of Clinical and Experimental Neuropsychology*, *32*(3), 249–258. http://dx.doi.org/10.1080/13803390902971131.

Kéri, S., Szlobodnyik, C., Benedek, G., Janka, Z., & Gádoros, J. (2002). Probabilistic classification learning in Tourette syndrome. *Neuropsychologia*, *40*(8), 1356–1362. http://dx.doi.org/10.1016/S0028-3932(01)00210-X.

Knowlton, B. J., Ramus, S. J., & Squire, L. R. (1992). Intact artificial grammar learning in amnesia: Dissociation of classification learning and explicit memory for specific instances. *Psychological Science*, *3*(3), 172–179. http://dx.doi.org/10.1111/j.1467-9280.1992.tb00021.x.

Kóbor, A., Takács, Á., Bryce, D., Szűcs, D., Honbolygó, F., Nagy, P., & Csépe, V. (2015). Children with ADHD show impairments in multiple stages of information processing in a stroop task: An ERP study. *Developmental Neuropsychology*, 1–19. http://dx.doi.org/10.1080/87565641.2015.1086770.

Krishnan, S., Watkins, K. E., & Bishop, D. V. M. (2016). Neurobiological basis of language learning difficulties. *Trends in Cognitive Sciences*, *20*(9), 701–714. http://dx.doi.org/10.1016/j.tics.2016.06.012.

Lum, J. A. G., Conti-Ramsden, G., Morgan, A. T., & Ullman, M. T. (2014). Procedural learning deficits in specific language impairment (SLI): A meta-analysis of serial reaction time task performance. *Cortex*, *51*, 1–10. http://dx.doi.org/10.1016/j.cortex.2013.10.011.

Lum, J. A. G., Ullman, M. T., & Conti-Ramsden, G. (2013). Procedural learning is impaired in dyslexia: Evidence from a meta-analysis of serial reaction time studies. *Research in Developmental Disabilities*, *34*(10), 3460–3476. http://dx.doi.org/10.1016/j.ridd.2013.07.017.

Maia, T. V., & Frank, M. J. (2011). From reinforcement learning models to psychiatric and neurological disorders. *Nature Neuroscience*, *14*(2), 154–162. http://dx.doi.org/10.1038/nn.2723.

Marsh, R., Alexander, G. M., Packard, M. G., Zhu, H., Wingard, J. C., Quackenbush, G., & Peterson, B. S. (2004). Habit learning in Tourette syndrome. *Archives of General Psychiatry*, *61*, 1259–1268.

Müller-Vahl, K. R., Grosskreutz, J., Prell, T., Kaufmann, J., Bodammer, N., & Peschel, T. (2014). Tics are caused by alterations in prefrontal areas, thalamus and putamen, while changes in the cingulate gyrus reflect secondary compensatory mechanisms. *BMC Neuroscience*, *15*(1), 6. http://dx.doi.org/10.1186/1471-2202-15-6.

Müller-Vahl, K. R., Kaufmann, J., Grosskreutz, J., Dengler, R., Emrich, H. M., & Peschel, T. (2009). Prefrontal and anterior cingulate cortex abnormalities in Tourette syndrome: Evidence from voxel-based morphometry and magnetization transfer imaging. *BMC Neuroscience*, *10*, 47. http://dx.doi.org/10.1186/1471-2202-10-47.

Nemeth, D., Janacsek, K., Balogh, V., Londe, Z., Mingesz, R., Fazekas, M., ... Vetro, A. (2010). Learning in autism: Implicitly superb. *PLoS ONE*, *5*(7), http://dx.doi.org/10.1371/journal.pone.0011731.

Nemeth, D., Janacsek, K., Csifcsak, G., Szvoboda, G., Howard, J. H., & Howard, D. V. (2011). Interference between sentence processing and probabilistic implicit sequence learning. *PLoS ONE*, *6*(3), 6–11. http://dx.doi.org/10.1371/journal.pone.0017577.

Nemeth, D., Janacsek, K., & Fiser, J. (2013). Age-dependent and coordinated shift in performance between implicit and explicit skill learning. *Frontiers in Computational Neuroscience*, *7*(October), 147. http://dx.doi.org/10.3389/fncom.2013.00147.

Nemeth, D., Janacsek, K., Londe, Z., Ullman, M. T., Howard, D. V., & Howard, J. H. (2010). Sleep has no critical role in implicit motor sequence learning in young and old adults. *Experimental Brain Research*, *201*(2), 351–358. http://dx.doi.org/10.1007/s00221-009-2024-x.

Newell, B. R., Lagnado, D. A., & Shanks, D. R. (2007). Challenging the role of implicit processes in probabilistic category learning. *Psychonomic Bulletin and Review*, *14*(3), 505–511. http://dx.doi.org/10.3758/BF03194098.

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology*, *19*(1), 1–32. http://dx.doi.org/10.1016/0010-0285(87)90002-8.

Pedersen, A., & Ohrmann, P. (2012). Impaired behavioral inhibition in implicit sequence learning in adult ADHD. *Journal of Attention Disorders*. http://dx.doi.org/10.1177/1087054712464392.

Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *International Journal of Epidemiology*, *43*(2), 434–442. http://dx.doi.org/10.1093/ije/dyt261.

Poldrack, R. A., & Foerde, K. (2008). Category learning and the memory systems debate. *Neuroscience & Biobehavioral Reviews*, *32*(2), 197–205. http://dx.doi.org/10.1016/j.neubiorev.2007.07.007.

Reber, P. J. (2013). The neural basis of implicit learning and memory: A review of neuropsychological and neuroimaging research. *Neuropsychologia*, *51*(10), 2026–2042. http://dx.doi.org/10.1016/j.neuropsychologia.2013.06.019.

Robertson, M. M. (2015a). A personal 35 year perspective on Gilles de la Tourette syndrome: Prevalence, phenomenology, comorbidities, and coexistent psychopathologies. *Lancet Psychiatry*, *2*, 68–87. http://dx.doi.org/10.1016/S2215-0366(14)00132-1.

Robertson, M. M. (2015b). A personal 35 year perspective on Gilles de la Tourette syndrome: Assessment, investigations, and management. *The Lancet Psychiatry*, *2*(1), 88–104. http://dx.doi.org/10.1016/S2215-0366(14)00133-3.

Romano, J. C., Howard, J. H., & Howard, D. V. (2010). One-year retention of general and sequence-specific skills in a probabilistic, serial reaction time task. *Memory (Hove, England)*, *18*(4), pp. 427–441. http://dx.doi.org/10.1080/09658211003742680.

Rubia, K., Alegria, A., & Brinson, H. (2014). Imaging the ADHD brain: Disorder-specificity, medication effects and clinical translation. *Expert Review of Neurotherapeutics*, *14*(5), 519–538. http://dx.doi.org/10.1586/14737175.2014.907526.

Scahill, L., Erenberg, G., Berlin, C. M., Budman, C., Coffey, B. J., Jankovic, J., ... Walkup, J. (2006). Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRX*, *3*(2), 192–206. http://dx.doi.org/10.1016/j.nurx.2006.01.009.

Sefcsik, T., Nemeth, D., Janacsek, K., Hoffmann, I., Scialabba, J., Klivenyi, P., ... Vecsei, L. (2011). The role of the putamen in cognitive functions—A case study. *Learning & Perception*, *1*(2), 215–227. http://dx.doi.org/10.1556/LP.1.2009.2.4.

Sjöwall, D., Roth, L., Lindqvist, S., & Thorell, L. B. (2013). Multiple deficits in ADHD: Executive dysfunction, delay aversion, reaction time variability, and emotional deficits. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *54*(2010), 619–627. http://dx.doi.org/10.1111/jcpp.12006.

Song, S., Howard, J. H., & Howard, D. V. (2007a). Implicit probabilistic sequence learning is independent of explicit awareness. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *14*(3), pp. 167–176. http://dx.doi.org/10.1101/lm.437407.

Song, S., Howard, J. H., & Howard, D. V. (2007b). Sleep does not benefit probabilistic motor sequence learning. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *27*(46), 12475–12483. http://dx.doi.org/10.1523/JNEUROSCI.2062-07.2007.

Speekenbrink, M., Channon, S., & Shanks, D. R. (2008). Learning strategies in amnesia. *Neuroscience and Biobehavioral Reviews*, *32*(2), 292–310. http://dx.doi.org/10.1016/j.neubiorev.2007.07.005.

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory*, *82*(3), 171–177. http://dx.doi.org/10.1016/j.nlm.2004.06.005.

Stillman, C. M., Gordon, E. M., Simon, J. R., Vaidya, C. J., Howard, D. V., & Howard, J. H. (2013). Caudate resting connectivity predicts implicit probabilistic sequence learning. *Brain Connectivity*, *3*(6), 601–610. http://dx.doi.org/10.1089/brain.2013.0169.

Tremblay, L., Worbe, Y., Thobois, S., Sgambato-Faure, V., & Féger, J. (2015). Selective dysfunction of basal ganglia subterritories: From movement to behavioral disorders. *Movement Disorders*, *0*(0), n/a-n/a. http://dx.doi.org/10.1002/mds.26199.

Ullman, M. T. (2004). Contributions of memory circuits to language: The declarative/

procedural model. *Cognition*, *92*(1–2), 231–270. http://dx.doi.org/10.1016/j.cognition.2003.10.008.

Ullman, M. T. (2016). The Declarative/Procedural Model : A Neurobiological Model of Language. In *Neurobiology of Language* (pp. 953–968). http://dx.doi.org/10.1016/B978-0-12-407794-2.00076-6.

Ullman, M. T., & Pullman, M. Y. (2015). A compensatory role for declarative memory in neurodevelopmental disorders. *Neuroscience & Biobehavioral Reviews*, *51*, 205–222. http://dx.doi.org/10.1016/j.neubiorev.2015.01.008.

Walenski, M., Mostofsky, S. H., & Ullman, M. T. (2007). Speeded processing of grammar and tool knowledge in Tourette's syndrome. *Neuropsychologia*, *45*(11), 2447–2460. http://dx.doi.org/10.1016/j.neuropsychologia.2007.04.001.