Implicit sequence learning in young people with Tourette syndrome with and without co-occurring attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Impaired habit-learning has been proposed to underlie the tic symptoms of Tourette syndrome (TS). However, accounts differ in terms of how habit-learning is altered in TS, with some authors proposing habit-formation is impaired due to a deficient “chunking” mechanism, and others proposing habit-learning is over-active and tics reflect hyper-learned behaviours. Attention-deficit/hyperactivity disorder (ADHD) frequently co-occurs with TS and is known to affect cognitive function in young people with co-occurring TS and ADHD (TS+ADHD). It is unclear, however, how co-occurring ADHD symptoms affect habit-learning in TS. In this study, we investigated whether young people with TS would show deficient or hyper-active habit-learning, and assessed the effects of co-occurring ADHD symptoms on habit-learning in TS. Participants aged 9-17 years with TS (n = 18), TS+ADHD (n = 17), ADHD (n = 13) and typical development (n = 20) completed a motor sequence-learning task to assess habit-learning. We used a 2 (TS-yes, TS-no) x 2 (ADHD-yes, ADHD-no) factorial analysis to test the effects of TS, ADHD, and their interaction on accuracy and reaction time indices of sequence-learning. TS was associated with intact sequence-learning, but a tendency for difficulty transitioning from sequenced to non-sequenced performance was suggestive of hyper-learning. ADHD was associated with significantly poorer accuracy during acquisition of the sequence, indicative of impaired habit-learning. There were no interactions between the TS and ADHD factors, indicating young people with TS+ADHD showed both TS- and ADHD-related atypicalities in habit-learning.

Keywords: habit-learning, Tourette syndrome, ADHD, sequence learning, tics, comorbidity
Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by chronic motor and phonic tics, i.e. involuntary and repetitive movements and sounds (American Psychiatric Association, 2013). The neural and cognitive mechanisms underlying tics are not fully understood, but increasing theoretical and empirical work suggests that abnormal habit-learning mechanisms may be involved. Habits are rigid, largely non-conscious and automatic behaviours that are performed regardless of motivation and outcome, for example, flipping a light switch despite knowing the light bulb has blown (Yin & Knowlton, 2006). Habit-learning is a gradual process subserved by dorsolateral regions of the striatum and sensorimotor cortical-striatal-thalamo-cortical (CSTC) circuitry (Seger & Spiering, 2011; Smith & Graybiel, 2013; Tricomi, Balleine, & O’Doherty, 2009). These regions are reportedly abnormal in individuals with TS (Kataoka et al., 2010; Worbe et al., 2012) and are involved in generating tic-like behaviours in non-human animals (e.g. Xu et al., 2015).

In line with the overlap between habit-learning and tic-related neural circuitry, several authors have proposed that tics are caused by specific functional abnormalities in the habit-learning system. One account hypothesises that excessive dopaminergic activity in the striatum leads to inappropriate hyper-learning of associations between sensory stimuli and motor responses, resulting in tic ‘habits’ that are ingrained and difficult to modify (Leckman & Riddle, 2000; Maia & Frank, 2011). In support, enhanced learning of rewarded motor response sequences (Palminteri et al., 2011) and enhanced habit-like responding to learned but devalued stimulus-outcome associations (Delorme et al., 2015) have been reported in unmedicated adults with TS (see also Palminteri et al., 2009). Further, enhanced learning performance was positively associated with tic severity and with connectivity in motor CSTC circuitry (Delorme et al., 2015; Palminteri et al., 2009; 2011). These effects were absent in adults with TS taking dopamine-blocking neuroleptic medication, supporting the view that
unregulated dopamine levels are involved in atypical habit-learning and tics in TS (Delorme et al., 2015; Palminteri et al., 2009; 2011). It should be noted, however, that adults with TS are atypical of the disorder since tics tend to remit by early adulthood (Bloch & Leckman, 2009; Leckman et al., 1998), and tics in adults are less fluctuating and may be more ingrained than in children (Leckman & Riddle, 2000). Thus, drawing conclusions about the role of habit-learning in tics from studies conducted exclusively with adults with TS is problematic.

In contrast to the hyper-learning account of tics, two studies have reported reduced learning of probabilistic cue-outcome associations in the Weather Prediction task in children and adults with TS (Kéri et al., 2002; Marsh et al., 2004). Further, correlations with tic severity showed that individuals with most severe tics had the poorest habit-learning performance (Kéri et al., 2002; Marsh et al., 2004). Marsh et al. (2004) explained this impairment in terms of an inability to concatenate or chunk individual actions into a complete habitual behaviour, a mechanism believed to be critical in habit-learning and dependent on changes in striatal dopaminergic firing (described by Graybiel, 1998). According to this view, the deficient chunking mechanism in TS results in the execution of fragmentary actions (tics) that would normally be part of sequenced, coherently executed habitual behaviours (Marsh et al., 2004). However, the Weather Prediction task involves learning only pairwise stimulus-outcome associations rather than sequences of actions. To fully test Marsh et al.’s (2004) account of tics, habit-learning tasks that more clearly require the to-be-learned actions to be concatenated, such as a motor sequence learning task, should be used.

One commonly used motor sequence-learning task is the serial reaction time (SRT) task (Nissen & Bullemer, 1987). In this task, participants respond to a stimulus that moves between different spatial locations with spatially corresponding buttons. Unknown to the participant, sometimes the stimulus samples the locations in a repeating sequence (sequence condition), while other times the stimulus samples the locations in a non-repeating manner.
(non-sequence condition). Despite not being informed of the repeating sequence, participants’ reaction times (RTs) decrease in the sequence condition (enhancement effect) and show a marked increase when the non-sequence condition is presented subsequently (disruption effect). Of relevance to TS, the structure of the repeating sequence can be manipulated to require more or less chunking. If the sequence is structurally “unbalanced” and some transitions between locations occur more frequently than others, simply learning the pairwise associations between the frequently transitioning locations may be sufficient to speed RTs (Cohen, 1990; Jackson & Jackson, 1992). For example, in the unbalanced sequence “A-B-C-D-B-C-A-B-D-C”, the transitions A-B and B-C occur more often than the other transitions (C-D and D-C). Rather than learning the entire sequence of locations, RT may speed up simply because a participant learns these two frequently occurring pairs of locations. In contrast, if the sequence is structurally “balanced” and the transitions between locations in the sequence are equally probable, knowledge of pairwise associations is not enough to support performance improvements; instead, knowledge of at least which location precedes a pair of locations is required to predict the following pair of locations (Cohen, 1990; Jackson & Jackson, 1992). For example, in the balanced sequence “B-C-D-B-A-D-A-C-A-B-D-C”, there are no pairwise associations between locations that occur more frequently than others and therefore a “chunk” of locations, such as D-B-A, must be consolidated in order to learn the sequence.

Two previous studies have used the SRT or a variant of this task to study sequence learning in children and adolescents with TS (Channon et al., 2003; Takács et al., 2017). Channon et al. (2003) compared sequence learning between children with TS and typically developing controls using a traditional SRT design. Participants first completed two blocks of trials in which the stimulus sampled on-screen locations in a pseudorandom manner, followed by four sequence blocks in which the stimulus sampled the screen locations in a 12-
item repeating sequence, one block of a “test sequence” in which a new repeating sequence of locations was presented, and finally another block of the original repeating sequence. Channon et al. (2003) found no group differences in the extent to which RTs speeded up over repetitions of the sequence or in the amount of disruption to RT performance when the repeating sequence was replaced by the test sequence, indicative of comparable sequence learning in children with TS and controls. Takács et al. (2017) used a variant of the SRT task, the Alternating Serial Reaction Time (ASRT) task, to assess sequence learning in young people with TS and typical development. Participants responded to a stimulus that moved in triplets of screen locations that occurred at high or low frequency across the task. Sequence learning was assessed by the extent to which RT decreased and accuracy increased for the high-frequency triplet compared to the low-frequency triplet across task blocks. Similar to Channon et al.’s (2003) findings, Takács et al. (2017) found no group differences in RT or accuracy changes for the high versus low frequency triplet, suggesting equivalent sequence learning performance between young people with TS and controls.

The comparable performance between TS and controls in these studies contradicts the majority of previous work reporting reduced (Kéri et al., 2002; Marsh et al., 2004) or enhanced (Delorme et al., 2015; Palminteri et al., 2009) habit-learning in TS, and particularly Palminteri et al.’s (2011) findings of enhanced motor sequence learning, and suggest that neither hyper-learning (Leckman & Riddle, 2000; Maia & Frank, 2011) nor impaired habit-formation (Marsh et al., 2004) are accurate accounts of the neurocognitive basis of tics. However, the sequence and non-sequence conditions in Channon et al.’s (2003) SRT design were not matched for structure, which can influence sequence-learning (Jackson et al., 1995), and Takács et al.’s (2017) task measuring learning of triplets of locations only may not have sufficiently pushed the chunking mechanism to elicit an impairment in TS. Further, neither study assessed explicit knowledge of the repeating sequence or controlled for such
knowledge in analyses of sequence-learning. Recognition and/or recall tasks after the SRT task can be used to assess and take account of the contribution of explicit sequence knowledge in facilitating performance. It is therefore possible that sequence-learning occurred in a more explicit, goal-directed manner rather than primarily via the habit-learning system. Consistent with this suggestion, a recent study demonstrated that young people with TS perform as well as controls in goal-directed learning (Shephard et al., 2016a).

Given the contrasting findings and methodological issues with previous research and the proposed overlap between tics and habits, further research on habit-learning in TS is warranted. Another key issue that should be addressed is how co-occurring conditions affect habit-learning in TS. Attention-deficit/hyperactivity disorder (ADHD), characterised by impairing symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013), is one of the most frequently co-occurring conditions in TS (Freeman, 2007) and its presence is associated with worse functional outcomes (Sukhodolsky, et al., 2003) and poor response to behavioural tic therapies (McGuire et al., 2014) but it is not clear why. Similar to TS, ADHD is associated with altered dopaminergic signalling and under-activation of fronto-striatal brain circuits (reviewed in Cubillo et al., 2012). This suggests there may be some overlap in the neural substrates underlying TS and ADHD, which may help explain their frequent co-occurrence. Despite this, there has been very little research comparing these populations, or investigating the basis of the overlap between them. Comparing TS with ADHD on cognitive functions linked to fronto-striatal dopaminergic systems, such as habit-learning, may help characterise the neural substrates that either contribute to the co-occurrence between these conditions, or that differentiate TS and ADHD from one another.

The literature on habit-learning in ADHD (without tics) is sparse. One model of ADHD (Sagvolden et al., 2005) proposed impaired dopamine-mediated learning in ADHD as
a consequence of hypo-dopaminergic activity in the nigro-striatal dopamine system. However, empirical work suggests that habit-learning, including motor sequence learning, is unimpaired (Karatekin et al., 2009; Vloet et al., 2010) or enhanced (Rosas et al., 2010) in ADHD relative to typically developing individuals. One study using the ASRT task reported a subtle alteration in sequence learning in children with ADHD compared with controls (Barnes et al., 2010). Nonetheless, the evidence overall suggests that this particular aspect of cognition is unimpaired in ADHD. Only one previous study has examined habit-learning in young people with TS, TS+ADHD, and ADHD (Takács et al., 2017) and found no differences in sequence learning between TS, TS+ADHD, and ADHD compared to typically developing controls. However, as noted above, explicit sequence knowledge was not controlled for in this study and triplet learning may not place sufficient demands on habit-learning to elicit sequence learning impairments in TS. Interestingly, these studies all reported general performance deficits in ADHD (longer RT, reduced accuracy across blocks), which may indicate more global motor preparation/attentional deficits, consistent with theories of ADHD as a deficit in arousal regulation (Sergeant, 2000). This suggests that ADHD may not contribute to altered habit-learning in TS but may produce additional impairments in general task performance.

The aim of the current study was to examine habit-learning in young people with TS, TS+ADHD, and ADHD compared to young people with typical development. We modelled TS and ADHD as separate between-subjects factors which enabled us to assess main effects of TS and ADHD as well as explore the additive effects of these conditions in TS+ADHD. We studied children and adolescents with these disorders to ensure habit-learning findings would be relevant to the typical presentation of TS rather than to adults with atypical non-remitting tics. We used a carefully designed SRT task to measure motor sequence-learning. In our task, repeating sequences were 12-items in length and fully balanced to push the
chunking mechanism proposed to be impaired in TS (Marsh et al., 2004). Further, we matched the structure of the non-sequence and sequence conditions, and measured explicit sequence knowledge and controlled for this in analysis. We hypothesised that young people with TS with or without co-occurring ADHD would show atypical motor sequence-learning and the degree of this atypicality would be associated with greater tic severity. If the hyper-learning hypothesis of tics (Leckman & Riddle, 2000; Maia & Frank, 2011) is correct, participants with TS and TS+ADHD would show greater sequence learning than participants without TS (ADHD and controls). If the impaired chunking hypothesis of tics (Marsh et al., 2004) is correct, participants with TS and TS+ADHD would show poorer sequence learning compared to ADHD and controls. If young people with TS rely on explicit learning processes during sequence-learning, which has not been assessed in previous studies, sequence-learning differences between participants with and without TS should be absent when controlling for explicit sequence knowledge, and these young people should show better explicit sequence knowledge than those without TS. We predicted young people with ADHD without tics would show comparable sequence-learning to controls, and ADHD symptoms would not be associated with sequence-learning. We further predicted effects of ADHD (with and without co-occurring tics) on global performance measures (longer RT and reduced accuracy across blocks).

Methods

Participants

Sixty-eight 9-17 year-olds with TS ($n = 18$), ADHD ($n = 13$), TS+ADHD ($n = 17$), or typical development ($n = 20$, Control group) took part in this study. A number of participants were excluded due to task non-completion or outlying task performance (detailed in the Testing procedure and participant exclusions section, below), leaving 17 young people with
TS, 13 with TS+ADHD, 11 with ADHD, and 20 typically developing controls for the current analysis. Participants had normal or corrected-to-normal vision and were free from neurological conditions such as epilepsy. Young people with TS, TS+ADHD and ADHD were recruited from Nottinghamshire and Lincolnshire Child and Adolescent Mental Health Services (CAMHS) and Tourette’s Action support groups. Control participants were recruited from Nottinghamshire primary and secondary schools. Ethical approval for the study was obtained from University and NHS Research Ethics Committees (NHS East Midlands REC 11/EM/0339) and Research and Development departments of Nottinghamshire and Lincolnshire NHS trusts. In accordance with the Declaration of Helsinki, parental written informed consent with child’s written assent was obtained for 9-15 year-olds; 16-17 year-olds provided written informed consent.

Consultant psychiatrists or paediatricians provided information on existing clinical diagnoses of TS, TS+ADHD and ADHD, and other co-occurring conditions. The Development and Well-Being Assessment (DAWBA, Goodman et al., 2000) was used to confirm diagnoses and obtain further information on clinical or sub-clinical co-occurring symptomatology. Tic severity (past week) was assessed using the Motor, Phonic, and Motor+Phonic scores from the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). ADHD symptom severity (past 6 months) was measured with the ADHD Index from the parent-rated Conners Rating Scale Revised (CPRS-R; Conners et al., 1998) and the Hyperactivity scale from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Participants were assigned to clinical groups based on clinical diagnoses and scores on these measures. Thirty-five participants had a clinical diagnosis of TS or chronic motor tic. Of these, 17 also held a diagnosis of ADHD and/or scored above-threshold for clinically significant symptoms on the ADHD rating scales (CPRS-R ADHD Index scores ≥ 60; SDQ Hyperactivity scores ≥ 7). These participants were assigned to the TS+ADHD group (n =
The remaining 18 participants with TS formed the TS group; these young people did not have a diagnosis of ADHD and their scores on ADHD rating scales were below clinical thresholds. Thirteen participants held a diagnosis of ADHD combined-type with no co-occurring tics and were assigned to the ADHD group. Typically developing control participants were screened for symptoms of neurodevelopmental disorders with the DAWBA and symptom rating scales. The groups were matched on age (+/- 8 months), gender, handedness, and socioeconomic status (SES) (+/- 1 classification on the Office of National Statistics Socio-Economic Classification system, Rose & Pevalin, 2003). The participant demographics and symptom profiles are shown in Table 1.

[Table 1]

The following co-occurring conditions were reported. TS: obsessive-compulsive disorder (OCD) (3), obsessive-compulsive behaviours (5), depression (3), anorexia (1), anxiety disorder (1); TS+ADHD: OCD (2), oppositional defiant disorder (ODD) (5), anxiety disorder (2), dyslexia (1); ADHD: ODD (5), conduct disorder (2), dyslexia (1), dyspraxia (1). Young people with actual or possible diagnoses of autism spectrum disorder (ASD) or intellectual disability, or with IQs less than 70 on the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999), were excluded from the study due to the likelihood that these conditions would interfere with implicit learning processes (Mostofsky et al., 2000) and/or the ability to follow task instructions. The following combinations of medications were being received. TS: Clonidine (2), Fluoxetine + Clonidine (1), Aripiprazole (2), Citalopram (1); TS+ADHD: Clonidine + methylphenidate (1), methylphenidate (1), Aripiprazole (2), Fluoxetine (1); ADHD: methylphenidate (8), Atomoxetine (1), methylphenidate + Atomoxetine (1). Methylphenidate was withdrawn 24 hours prior to testing. All other medications were continued, leaving 6 participants with TS, 4 participants with TS+ADHD, and 2 participants with ADHD on non-stimulant medication during testing.
The SRT task (Figure 1) was presented to participants as a game in which the aim was to stop a cartoon bomb character ‘Bob the bomb’ from exploding by pressing appropriate ‘extinguish buttons’. Every trial began with a display consisting of four white boxes (40x40mm) arranged in a horizontal line across the centre of a computer screen. The boxes were shown for 225ms after which Bob the bomb (a 33x33mm square colour image of a cartoon smiling bomb) appeared in one of the boxes. Participants used the index and middle fingers of each hand to press the ‘extinguish’ buttons on the laptop keyboard (keys 1, 2, 9, 0) corresponding to the box (far left, centre-left, centre-right, far right, respectively) Bob appeared in. To encourage accuracy and prompt responding, participants were instructed to press the correct extinguish buttons as quickly as possible to prevent Bob exploding. The stimulus screen terminated with the participant’s response or after 1500ms had elapsed, after which the trial ended.

Five blocks of 120 trials were completed. In blocks 2, 3 and 5 (sequence blocks) the stimulus sampled the boxes in a sequence of 12 locations that repeated ten times. In blocks 1 and 4 (non-sequence blocks) the stimulus sampled the boxes in ten different 12-item non-repeating sequences of locations. The non-repeating sequences matched the first order (number of times each location appeared) and second order (pairwise associations) structure of the repeating sequence. The non-repeating sequences were presented in a different order in blocks 1 and 4, so block 4 was not just a repeat of block 1, and none of the ten non-repeating sequences matched the repeating sequence used in sequence blocks. Repeating and non-repeating sequences were fully balanced in structure, such that the probability of the stimulus sampling one location after another location was equal for all items in the sequence and consequently, pairwise association learning would not be sufficient to support performance improvements. Two balanced sequences were created and administered in
alternating order across participants for counterbalancing: A: 0-1-9-2-1-0-9-0-2-9-1-2; B: 1-2-0-9-2-9-0-1-0-2-1-9. Following task instructions, participants completed four practice trials followed by the five blocks of experimental trials. The task was programmed using E-Prime version 1.2 (Psychology Software Tools Inc.) and performed on a Samsung P510 laptop (screen size 20x34cm, resolution 1280x800 pixels).

[Figure 1]

SRT Performance measures

Primary measures of SRT performance were reaction time indices. Following previous SRT methods (Thomas & Nelson, 2001), each participant’s median RT (ms) was computed for correct trials over 12-trial runs (one sequence repetition in sequence blocks or one non-repeating sequence in non-sequence blocks) in each block and averaged to obtain the mean-of-median RT for correct trials per block for each participant, which were used in analyses. The first trial from each block and trials on which incorrect responses were made were excluded from RT analysis. As is standard in research using the SRT task, a RT disruption index was calculated for each participant as RT in the disruption block (non-sequence block 2/task block 4) minus RT in the second sequence block (task block 3) to measure the extent to which performance was impaired (RT increased) by the removal of the learned repeating sequence. As an additional method of quantifying sequence learning, we computed each participant’s accuracy (% correct trials) in each SRT task block, as well as an accuracy disruption index (accuracy in the disruption block minus accuracy in the second sequence block) to quantify the extent to which performance was disrupted (accuracy decreased) by the removal of the repeating sequence. Participants with RT or accuracy measures 3SD outside of their group mean, or with insufficient correct trials for analysis (< 20% of trials per block), were considered outliers and were excluded from analyses (detailed below).
Generate task

Following the SRT task, participants completed a Generate task to probe for explicit knowledge of the repeating sequence. On each trial, one item of the repeating sequence was presented and participants were required to indicate, by pressing the appropriate location button on the keyboard, where they thought the stimulus would move next in the sequence. The sequence was presented twice (24 trials total). Generate performance was quantified by summing the number of correct trials i.e. trials on which the participants correctly identified the next location in the sequence (max score = 24, chance = 8).

Testing procedure and participant exclusions

The SRT task was administered in the afternoon of a one-day testing visit. In the morning of the visit, participants completed a 1-hour electro-encephalography (EEG) session in which they performed an explicit, goal-directed reinforcement learning task and a Go/Nogo cognitive control task (data published in Shephard et al., 2016a). After a 45-minute refreshment break, the SRT task was administered followed by the Generate task. Four participants with TS+ADHD and two participants with ADHD were unable to complete the SRT task due to fatigue/inattention. A further one participant with TS produced outlying RT scores (3 SD +/- group mean). These participants were excluded from analysis, leaving a final sample of 17 TS, 13 TS+ADHD, 11 ADHD, and 20 controls.

Statistical analysis

Statistical analyses were conducted in SPSS v22 (IBM Corp, 2012). Figures were created using SigmaPlot v.14 (SyStat Software, San Jose, CA). The hypothesis that TS but not ADHD would be associated with hyper-learning or impaired sequence learning was tested using 2 x 2 factorial ANOVAs. Each model included the between-groups factors TS with the levels TS-yes (TS and TS+ADHD group) and TS-no (ADHD and Control groups), and ADHD with the levels ADHD-yes (ADHD and TS+ADHD groups) and ADHD-no (TS and
Control groups). The factorial design allowed us to test for effects of TS and ADHD on performance measures, as well as for any interactive effects of TS and ADHD which would indicate that participants with TS+ADHD differ from those with TS or ADHD alone. To assess the effects of TS and ADHD and interactions between these factors on participants’ acquisition of the repeating sequence, mean-of-median RT and accuracy from the first (non-sequence) task block and the following two sequence task blocks were subjected to 3 (block) x 2 (TS) x 2 (ADHD) ANOVAs; separate models were used for RT and accuracy data. Significant main effects of block, TS, ADHD, and interactions between these factors were further investigated using planned contrasts between pairs of blocks and levels of each group factor with Sidak correction applied to control for multiple comparisons. Greenhouse-Geisser corrections for violations of sphericity were applied where appropriate. To assess the effects of TS and ADHD and interactions between these factors on the extent to which the sequence had been learned, the RT and accuracy disruption indices were subjected to 2 (TS) x 2 (ADHD) factorial ANOVAs; a separate model was used for each index. Significant TS*ADHD interactions were further investigated using Sidak-corrected planned contrasts between the levels of each factor.

To aid in interpreting the ANOVA results, we report the size (partial eta squared) and Bayes Factors for each effect. The Bayes Factors (BFs), described in Masson (2011) and Jarosz and Wiley (2014), complement the ANOVA F-test results and standard effect sizes by providing estimates of how likely the data are under the null hypothesis relative to the experimental hypothesis (termed ‘BF01’), and vice versa, i.e. how likely the data are under the experimental over null hypothesis (termed ‘BF10’). To compute these factors, the probability that the data support the null hypothesis (p(H0|D)) and the probability that the data support the experimental hypothesis (p(H1|D)) are first computed for each result using the sum of squares values for the experimental effect and associated error (see Jarosz &
Wiley, 2014 and Masson et al., 2011 for formulae). The BF01 is equivalent to dividing the p(H0|D) by the p(H1|D) and yields a value that indicates how many times more likely the data are under the null hypothesis rather than the experimental hypothesis. For example, a BF01 value of 2.5 would indicate the data are 2.5 times more likely to fit the null than experimental hypothesis. The BF10 is then calculated by dividing 1 by the BF01 value, which reverses the comparison of probabilities and yields a BF value that indicates how much more likely the data are to fit the experimental hypothesis than the null hypothesis. For example, if BF01 = 2.5, then BF10 = 1 / 2.5 = 0.4, indicating the data are 0.4 times more likely under experimental than null hypothesis. In this example, the BF01 and BF10 values suggest that the data are more likely to fit the null hypothesis.

The ANOVA analyses were repeated including Generate task performance (number of correct Generate items) as a covariate in the models to assess the extent to which explicit knowledge of the repeating sequence influenced learning performance and any TS- or ADHD-related differences in performance. In addition, a 2 x 2 ANOVA examined whether Generate task performance was better in young people with TS than those without TS. In addition, we repeated our analyses including the following covariates: 1) medication status (on or off medication during testing), since the longer-acting medications (e.g. clonidine, aripiprazole, atomoxetine) not withdrawn during testing may have directly or indirectly influenced neurotransmitters involved in sequence learning; 2) age, due to some previous findings that SRT performance can vary with age (e.g. Janacsek et al., 2012); 3) IQ, since the groups differed in IQ scores (see Table 1). Medication status, age and IQ were not significant covariates and did not alter effects of TS and ADHD on sequence learning and were therefore not retained in the models.

The hypothesised associations between tic and ADHD symptom severity and sequence-learning were examined by computing Pearson correlation coefficients between the
RT and accuracy disruption indices, YGTSS Motor+Phonic tic severity scores, and CPRS-R ADHD Index scores. We also calculated RT and accuracy enhancement indices (RT/accuracy in the second sequence block minus RT/accuracy in the first non-sequence block RT) to quantify performance improvements during sequence acquisition in a single measure, and computed Pearson correlations coefficients between these indices and tic and ADHD severity. All variables were z-transformed prior to computing correlation coefficients. Correlations between tic severity and sequence learning indices were computed only within the TS and TS+ADHD groups since participants with ADHD and control participants did not have tics. Correlations between ADHD severity and sequence learning were computed only within the TS+ADHD and ADHD groups since the TS and Control groups had low ADHD symptom scores.

Finally, we conducted a supplementary analysis to assess whether sequence learning performance was influenced by the severity of co-occurring clinical or subclinical OCD symptoms, since previous work has shown that sequence learning is impaired in OCD (Kathmann et al., 2005; Vloet et al., 2010). The Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Goodman et al., 1986) was used to measure symptoms of OCD and obsessive-compulsive behaviours (OCBs) in all participants. Only participants with OCD or OCB symptoms (n = 10) produced non-zero scores on this scale; the remaining participants uniformly scored zero. Analysis was therefore restricted to the sub-sample of participants with OCD/OCB symptoms, all of whom had TS or TS+ADHD. Within this sample, Pearson correlation coefficients were computed between z-transformed CY-BOCS Total (obsessions + compulsions) scores and the z-transformed SRT RT and accuracy enhancement and disruption indices.

Results

SRT performance
Overall RT and accuracy performance in each SRT task block is presented for the four groups in Figure 2. RT and accuracy performance is presented by TS and ADHD group factors during the acquisition phase in Figure 3 and during the disruption phase in Figure 4.

**Sequence acquisition**

The 3 x 2 x 2 ANOVA assessing the effects of task block, TS, ADHD, and their interaction on RT during the acquisition of the repeating sequence revealed a significant main effect of block ($F(2, 114) = 6.72, p = .002, \eta^2 = .105$). Across groups, RTs significantly decreased from the first non-sequence block to the first sequence block ($p = .006, d = .23$) and remained significantly faster in the second sequence block than in the first non-sequence block ($p = .01, d = .26$), but did not differ between the two sequence blocks ($p = .97, d = .02$) (Figures 2a and 3a&c). There were no significant main effects of TS or ADHD, and no significant interactions between these factors and block (all $F < 2.66, p > .11, \eta^2 < .045$) (Figure 3a&c). To assess the extent to which these null effects were likely to be genuine (rather than reflecting false negatives, for example), the BF01 and BF10 Bayes Factors were computed for each non-significant effect. All BF01 values were equal to or greater than 1.95, indicating the null effects were at least 1.95 times more likely to occur under the null than experimental hypothesis. Conversely, all BF10 values were equal to or less than 0.51, indicating the non-significant effects were only 0.5 times (or less) likely under the experimental hypothesis. When Generate performance was included as a covariate, the main effect of block was reduced to a trend ($F(2, 112) = 2.42, p = .09, \eta^2 = .041$); all other effects were unchanged.

The 3 x 2 x 2 ANOVA examining the effects of task block, TS, ADHD, and their interaction on accuracy during acquisition of the repeating sequence revealed significant main effects of block ($F(1.56, 88.85) = 6.22, p = .006, \eta^2 = .098$) and ADHD ($F(1, 57) = 6.81, p = .01, \eta^2 = .107$), and a significant ADHD*block interaction ($F(1.56, 88.85) = 3.91, p = .03,$
\( \eta^2 = .064 \). Participants without ADHD showed no changes in accuracy across the three task blocks (all \( p \geq .77, d \leq .11 \)), but participants with ADHD showed a significant decrease in accuracy in the second sequence block compared to the previous sequence and non-sequence blocks (both \( p \leq .004, d \geq .31 \)) (Figure 3d). Further, participants with ADHD had significantly lower accuracy than those without ADHD in the two sequence blocks (both \( p \leq .03, d \geq .56 \)) but did not differ in the non-sequence block (\( p = .18, d = .34 \)) (Figure 3d). To further characterise the effect of ADHD on accuracy, BF01 and BF10 Bayes Factors were computed for the main effect of ADHD to compare the probability of the data occurring under the null hypothesis versus the experimental hypothesis and vice versa. The BF01 was 0.25 and the BF10 was 4.01, indicating that the data were 4.01 times more likely under the experimental hypothesis and only 0.25 times more likely under the null. The effects of TS, TS*block interaction, and TS*ADHD interaction were non-significant (all \( F \leq 1.41, p \geq .25, \eta^2 \leq .024 \)) (Figure 3b). Bayes Factors computed for these null effects revealed BF01 values of \( \geq 28.97 \) and BF10 values of \( \leq 0.03 \), indicating the data were at least 28.97 times more likely under the null hypothesis and only 0.03 times more likely to fit the experimental hypothesis. When explicit knowledge of the repeating sequence was included as a covariate, the main effect of block became non-significant \( (F(1.55, 87.03) = 1.78, p = .18, \eta^2 = .031) \); all other effects were unchanged.

[Figures 2 & 3]

Disruption to sequence learning

The 2 x 2 ANOVA examining the effects of TS, ADHD, and their interaction on the RT disruption index revealed a marginal effect of TS \( (F(1, 57) = 3.73, p = .058, \eta^2 = .061) \), reflecting smaller disruptions to RT performance in participants with TS compared to those without TS (Figure 4a). This trend-level effect of TS was further investigated by computing BF01 and BF10 Bayes Factors to assess the fit of the data under the null hypothesis versus
the experimental hypothesis and vice versa. The BF01 was 1.13 and the BF10 was 0.89, indicating the data were slightly more likely under the null than experimental hypothesis.

The main effect of ADHD and TS*ADHD interactions were non-significant (both $F < 0.62$, $p \geq .43$, $\eta^2 \leq .011$). BF01 and BF10 values for these non-significant effects were $\geq 5.61$ and $\leq 0.19$ respectively, indicating the null effects were at least 5.61 times more likely under the null than experimental hypothesis, and less than 0.20 times more likely under the experimental hypothesis. The trend-level effect of TS remained when explicit sequence knowledge was included as a covariate ($F(1, 56) = 3.64$, $p = .06$, $\eta^2 = .061$), with a BF01 of 1.14 and BF10 of 0.88 suggesting similar support for the null hypothesis over the experimental hypothesis. The effect of ADHD and TS*ADHD interaction remained non-significant (both $F \leq 0.61$, $p \geq .44$, $\eta^2 \leq .011$).

The 2 x 2 ANOVA examining the effects of TS, ADHD, and their interaction on the accuracy disruption index revealed a trend-level effect of TS ($F(1, 57) = 3.37$, $p = .07$, $\eta^2 = .056$), which showed that participants with TS tended to show a larger decrease in accuracy during the disruption block than participants without TS (Figure 4b). BF01 and BF10 values for the trend-level effect of TS were 1.35 and 0.74, respectively, indicating the data were slightly more likely under the null than experimental hypothesis. There was also a trend-level effect of ADHD ($F(1, 57) = 3.35$, $p = .07$, $\eta^2 = .056$), showing that participants with ADHD tended to show an increase in accuracy performance during the disruption block while participants without ADHD did not (Figure 4b). BF01 and BF10 values for the trend-level effect of ADHD were 1.37 and 0.73, respectively, suggesting the data were slightly more likely under the null than experimental hypothesis. The TS*ADHD interaction was not significant ($F(1, 57) = .026$, $p = .87$, $\eta^2 < .001$). The BF01 and BF10 values for this null effect were 7.70 and 0.13, respectively, indicating the data were 7.7 times more likely under the null than the experimental hypothesis and only 0.13 times more likely under the
The trend-level effects of TS ($F(1, 56) = 2.99, p = .09, \eta^2 = .051$) and ADHD ($F(1, 56) = 2.89, p = .095, \eta^2 = .049$) on accuracy remained, although were somewhat reduced, when explicit sequence knowledge was included as a covariate; the TS*ADHD interaction remained non-significant ($F(1, 56) = 0.06, p = .81, \eta^2 = .001$). BF01 and BF10 values for the trend-level effects of TS and ADHD were similar when covarying explicit sequence knowledge (TS: BF01 = 1.60, BF10 = 0.63; ADHD: BF01 = 1.69, BF10 = 0.59), again indicating the data were slightly more likely under the null than experimental hypothesis. The BF01 and BF10 values for the non-significant TS*ADHD interaction remained similar when controlling for explicit knowledge (7.56 and 0.13 respectively) and indicated the data supported the null rather than experimental hypothesis.

[Figure 4]

**Generate task performance**

The mean number of correctly predicted Generate task items was similar across groups and close to chance performance: TS mean = 8.65 (SD = 3.61), ADHD mean = 7.73 (SD = 2.72), TS+ADHD mean = 8.00 (SD = 1.87), Control mean = 8.05 (SD = 2.96). A 2 (TS) x 2 (ADHD) ANOVA confirmed there were no significant effects of TS or ADHD and no interaction between these factors on Generate task performance (all $F < .395, p > .53, \eta^2 < .007$).

**Associations between implicit sequence learning, tic severity, and ADHD severity**

There were no significant associations between YGTSS Motor+Phonic tic severity scores and the RT and accuracy enhancement and disruption indices in the participants with TS and TS+ADHD (all $r < .165, p > .39$). There were no significant associations between ADHD Index scores and RT and accuracy enhancement and disruption indices in participants with ADHD and TS+ADHD (all $r < -.339, p > .13$).

**Associations between sequence learning and OCD symptom severity**
In the sample of young people with TS or TS+ADHD and co-occurring OCD/OCB symptoms, there were no significant associations between CY-BOCS scores and the RT and accuracy enhancement and disruption indices of sequence learning (all $r \leq -.361, p \geq .31$).

Discussion

This study used a motor sequence-learning task to investigate habit-learning in young people with TS, TS+ADHD, and ADHD compared to typically developing young people. We aimed to assess whether young people with tics would show enhanced or impaired sequence-learning to test previous authors’ hypotheses that tics are caused by hyper-learning or deficient habit-formation (Leckman & Riddle, 2000; Maia & Frank, 2011; Marsh et al., 2004). Further, we sought to determine the effects of co-occurring ADHD symptoms on habit-learning in young people with TS. We used a factorial approach to investigate the effects of TS, ADHD, and their interaction on sequence-learning. We found no evidence of altered sequence acquisition in TS, although there were trend-level TS-related differences in the extent to which performance was disrupted by removal of the repeating sequence. There was evidence of impaired sequence learning in ADHD, including poorer accuracy during sequence acquisition compared to young people without ADHD.

The main effects of TS on RT and accuracy performance during the acquisition phase of the task (blocks 1-3) were non-significant, indicating that TS was not associated with impaired learning of the repeating sequence. Further, the Bayes Factors for these non-significant effects indicated the data were more likely under the null rather than experimental hypothesis. These findings are consistent with the two previous studies examining sequence-learning in children and adolescents with TS (Channon et al., 2003; Takács et al., 2017). Our learned sequences were long (12-items) and fully balanced in structure, and therefore were likely to have placed considerable demands on the habit-learning chunking mechanism.
Taken together, our findings and those of the previous sequence-learning studies provide little support for the deficient habit-formation hypothesis of tics (Marsh et al., 2004).

However, we did find trend-level effects of TS on the RT and accuracy disruption indices, with participants with TS showing a tendency for smaller disruptions to RT and larger disruptions to accuracy when the repeating sequence was replaced by non-repeating sequences in the disruption block, although these effects were not associated with greater tic severity. While these differences did not reach conventional levels of significance, the effects were of medium size and thus warrant some discussion. The pattern of smaller RT disruption and larger accuracy disruption might indicate that young people with TS experienced difficulty in transitioning from sequenced to non-sequenced stimuli and because of this difficulty they “traded-off” accuracy for speed, i.e. they maintained RT at the expense of accuracy. These trend-level effects were largely unchanged when controlling for explicit knowledge of the repeating sequence, indicating that primarily habit-learning rather than goal-directed learning was involved. These findings may be in line with the hyper-learning hypothesis of tics (Leckman & Riddle, 2000; Maia & Frank, 2011) in that the disrupted performance could indicate that the sequence was over-learned and therefore difficult to stop executing when the repeating sequence was removed. This pattern of findings is somewhat similar to those of Delorme et al. (2015), who found increased habitual behaviour execution in TS when this was no longer appropriate. However, this interpretation must be considered with caution since the effects of TS on the disruption indices did not reach significance and did not correlate with tic severity, and the Bayes Factors indicated the trend-level effects were slightly more likely to under the null than experimental hypothesis. Also, these effects occurred in the context of typical acquisition of the sequence suggestive of typical learning and so it is not completely clear why typical learning might result in greater disruption. Further, our findings contrast with those of Channon et al. (2003), who reported no
differences between children with TS and controls in the extent to which RT performance was disrupted when their repeating sequence was replaced by a new sequence, although Channon et al. (2003) did not assess accuracy as well as RT and their repeating and test sequences were not matched for structure.

Considering our findings alongside those from other studies, habit-learning effects in TS appear to be heterogeneous, with some studies reporting clear enhancements (Delorme et al., 2015; Palminteri et al., 2009; 2011), others reporting clear impairments (Kéri et al., 2002; Marsh et al., 2004), and others (Channon et al., 2003; Takács et al., 2017) including our study reporting no or only subtle differences in habit-learning. It is unclear whether this heterogeneity reflects true individual differences in habit-learning ability or methodological differences across studies, for example in the different habit-learning paradigms used and the varying degree of control for comorbidity. Future work is needed to conduct more comprehensive assessments of habit-learning using a range of tasks in the same individuals, and in children and adults with TS with and without various co-occurring conditions.

In contrast to our hypotheses, ADHD was associated with impaired sequence learning. During the acquisition of the repeating sequence, young people with ADHD and TS+ADHD showed a significant decrease in accuracy rather than the expected increase or maintenance of accuracy performance as observed in the TS and control groups. Further, while accuracy did not differ between participants with and without ADHD in the first (non-sequence) task block, accuracy was significantly poorer in ADHD in the following two repeating sequence blocks. These findings indicate that the impairment in accuracy performance was related to sequence-learning and not to general performance difficulties in ADHD. There was no effect of ADHD on RT during the acquisition phase, indicating that young people with ADHD showed the same decrease in RT associated with sequence-learning as the young people without ADHD. This pattern of findings may indicate that
young people with ADHD and TS+ADHD traded-off accuracy for speed during the acquisition of the repeating sequence, perhaps because they had difficulty learning the sequence. When the repeating sequence was removed in the disruption block, participants with ADHD showed a tendency for increased accuracy (the opposite of the impaired accuracy performance that is expected with disruption) but comparable disruptions to RT performance (increases in RT) as young people without ADHD. Again, this pattern of findings may indicate that young people with ADHD traded accuracy for speed. Alternatively, it may have been easier for participants with ADHD to perform the task when the repeating sequence was not presented due to their sequence learning difficulties, and hence they showed no accuracy disruption effect. However, these trend-level effects of ADHD on performance during the disruption to sequence learning must be interpreted with caution since the Bayes Factors indicated the data were slightly more likely to fit the null hypothesis better than the experimental hypothesis. The effects of ADHD on sequence learning performance remained when controlling for explicit sequence knowledge, suggesting the atypical accuracy changes in these young people were not reflective of difficulties with goal-directed learning. These sequence learning difficulties were not correlated with ADHD symptoms, indicating the impairments did not vary with the severity of symptomatology.

Overall, the pattern of ADHD effects indicates that these young people had difficulties acquiring the repeating sequence and/or maintaining their accuracy performance while executing the sequence, in contrast to our hypothesis that habit-learning would be unimpaired in ADHD. Previous studies of habit-learning in ADHD, of which there are few, have reported comparable overall performance to controls on traditional sequence learning SRT tasks similar to our design (Karatekin et al., 2009; Vloet et al., 2010) and the triplet-learning ASRT task (Barnes et al., 2010; Takács et al., 2017), as well as superior performance compared to controls on an artificial grammar learning task (Rosas et al., 2010). However,
similar to our findings, one of these studies did find subtle alterations in motor sequence-learning: Barnes et al. (2010) found that children with ADHD showed inconsistent RT improvements in responding to repeating triplets of sequence locations, with comparable learning performance to controls at the beginning and end of the task but poorer learning performance in the middle of the task. Barnes et al. (2010) suggested their findings may have reflected difficulties with temporal processing in ADHD, rather than deficits in sequence learning. That is, participants with ADHD may have experienced difficulty in accurately predicting and preparing for the upcoming stimulus in the sequence, and this may have driven their inconsistent performance during triplet learning. Whether a temporal processing deficit could explain our findings in ADHD is unclear, since RT performance during the acquisition of the repeating sequence was not different from controls. Further, stimulus onset was similarly predictable in our task and the tasks used in Barnes et al. (2010) and in the other previous studies reporting no effects of ADHD on performance (Karatekin et al., 2009; Takács et al., 2017; Vloet et al., 2010). Future work using neuroimaging to examine neural circuitry involved in sequence-learning atypicalities in ADHD may help to clarify the nature of the difficulty and the reason for inconsistent findings across studies.

Importantly, we found no significant interactions between the TS and ADHD group factors on sequence-learning performance, indicating that the TS+ADHD group showed the same difficulties with acquisition of the sequence as the ADHD group, and the same difficulties with adjusting performance during the disruption block as the TS group. Thus, young people with both sets of symptoms were more impaired than young people with either condition alone. This finding is consistent with other research reporting that co-occurring ADHD symptoms introduce impairments in other cognitive functions in TS, including goal-directed learning (Shephard et al., 2016a) and cognitive control (Roessner et al., 2007; Shephard et al., 2016b), as well as impairing response to behavioural tic treatments and
general functioning (McGuire et al., 2014; Sukhodolsky et al., 2003). Together, these findings highlight the importance of treating both symptoms in young people with TS+ADHD and controlling for comorbid symptoms in research investigating neurocognitive mechanisms in either TS or ADHD. Indeed, given our findings of ADHD-related impairments in sequence-learning, it is possible that co-occurring ADHD symptoms may have contributed to previously reported findings of impaired habit-learning in TS (Kéri et al., 2002; Marsh et al., 2004).

There were limitations to the current study which should be considered. First, the modest sample sizes, particularly for the ADHD group, may have contributed to the trend-level effects and non-significant TS*ADHD interactions and future research investigating habit-learning with larger samples of young people with TS, ADHD, and TS+ADHD is required. Second, although stimulant medications were withdrawn prior to testing, it was not possible to withdraw other, longer-acting medications including aripiprazole, clonidine, and atomoxetine. This is important since these medications directly or indirectly affect dopamine levels, which may have influenced habit-learning performance. Our analysis covarying medication status (on or off longer-acting medications during testing) showed that these non-withdrawn medications did not associate with sequence learning performance and did not alter the effects of TS and ADHD on sequence learning. However, due to the small number of participants taking longer-acting medications during testing, we could not examine effects of different types of medications individually and this should be investigated in future research. In addition, a proportion of our sample of young people with TS and TS+ADHD had co-occurring OCD or OCB symptoms. This is to be expected since OCD, along with ADHD, is among the most common co-occurring conditions in TS (Freeman et al., 2007). The presence of co-occurring OCD in the current study is problematic since impaired habit-learning, including motor sequence learning, has been reported in children and adults with
OCD compared to typically developing controls (Kathmann et al., 2005; Vloet et al., 2010). Our supplementary analysis showed no association between OCD symptoms and sequence learning performance in the subsample of participants with TS and co-occurring OCD or OCB symptoms, indicating these co-occurring symptoms did not influence their sequence learning ability. Nevertheless, it will be important for future research to more thoroughly assess the effects of OCD on habit-learning in TS. Finally, the SRT task was completed following a morning of EEG tasks and IQ assessments, and it is possible that fatigue and inattention may have affected young people’s performance.
Acknowledgements

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* = significant at p < .05. SES = socioeconomic status assessed with the Office of National Statistics Socio-Economic Classification system. IQ = Wechsler Abbreviated Scale of Intelligence Full-Scale IQ. YGTSS = Yale Global Tic Severity Scale. CPRS = Conners Parent Rating Scale – Revised. SDQ Hyperactivity = Strengths and Difficulties Questionnaire Hyperactivity subscale. * Scores above 60 on the CPRS-R ADHD scale are considered to be clinically significant.
Figure 1 Diagram of the SRT task

A. Stimulus, screen set-up, and response buttons
The cartoon bomb stimulus sampled one of four box locations arranged horizontally across the screen. Participants responded to the stimulus using the keyboard keys 1, 2, 9, 0.

B. Trial structure
Every trial began with a screen displaying the four boxes for 225ms. Next, the cartoon bomb stimulus appeared in one of the four boxes and participants pressed the corresponding button on the keyboard. The trial ended when the participant pressed a button or after 1500ms had elapsed.

C. Task structure
Five blocks of 120 trials were completed. Block 1 was a non-sequence block, blocks 2 and 3 were sequence blocks, block 4 was the disruption (non-sequence) block, block 5 was a sequence block.
Figure 2 SRT task RT and accuracy performance plotted by task block and group

Plots show group averages for mean-of-median RT (ms) for correct trials in each task block (A), and accuracy (% correct trials) in each task block (B). N-S 1 = Task block 1 (first non-sequence block), S 1 = Task block 2 (first repeating sequence block), S 2 = Task block 3 (second repeating sequence block), N-S 2 = Task block 4 (disruption block / second non-sequence block), S 3 = Task block 5 (third repeating sequence block). Error bars represent the standard error of the group mean.
Figure 3 Performance in the acquisition phase by TS (TS-yes, TS-no) and ADHD (ADHD-yes, ADHD-no) group factors

Plots show RT (A and C) and accuracy (B and D) performance during the acquisition of the repeating sequence by TS (TS-yes, TS-no, plots A and B) and ADHD (ADHD-yes, ADHD-no, plots C and D) group factors. N-S 1 = Task block 1 (first non-sequence block), S 1 = Task block 2
(first repeating sequence block), $S_2 =$ Task block 2 (second repeating sequence block). Error bars represent the standard error of the group mean.
Figure 4 Accuracy and RT disruption indices plotted by TS (TS-yes, TS-no) and ADHD (ADHD-yes, ADHD-no) group factors.

A) Greater RT increase = greater disruption to performance

B) Greater accuracy decrease = greater disruption to performance

Plots show the RT and accuracy disruption indices reflecting the extent to performance was impaired by the removal of the repeating sequence in the disruption block. A) RT disruption index = increase in RT during the disruption block compared to the previous repeating sequence block. B) Accuracy disruption index = decrease in accuracy during the disruption block compared to the previous repeating sequence block. Greater disruption indices are indicative of greater learning of the repeating sequence. Error bars represent the standard error of the group mean.