Visuomotor learning and unlearning in children and adolescents with Tourette syndrome

Soyoung Kim[1,2], Stephen R. Jackson[2,3†], Maddie Groom[1,2] and Georgina M. Jackson[1,2†]

School of Medicine, University of Nottingham, UK[1]

Institute of Mental Health, University of Nottingham, UK[2]

School of Psychology, University of Nottingham, UK[3]

[†] Correspondence to:

Professor Georgina M. Jackson
Institute of Mental Health
School of Medicine
The University of Nottingham
Nottingham, NG7 2TU, UK
Email: georgina.jackson@nottingham.ac.uk

or

Professor Stephen R. Jackson
School of Psychology
The University of Nottingham
Nottingham, NG7 2RD, UK
Email: Stephen.jackson@nottingham.ac.uk

Abstract

Tourette syndrome (TS) is a childhood-onset neurological condition characterised by an evolving repertoire of chronic motor tics and one or more phonic tics. Tics, like habits, are inflexible and repetitive behaviours that are acquired over a period of time. It has been proposed that tics arise in TS as a result of increased habit learning: which may bias the child to acquire automatic behaviours (i.e. tics) more readily than is normal and make it harder to unlearn maladaptive habits once they have been acquired. Using a well-established visuomotor adaptation task, we investigated motor learning in a group of children and adolescents with a clinical diagnosis of TS relative to a group of age and gender matched typically developing individuals. In particular, we quantified differences in the strength and quality of motor learning and unlearning in TS, and the consolidation of motor learning over a 24 hour washout period. We demonstrated that there was a marginally significant decrease in learning rate in the individuals with TS relative to age and gender matched typically developing controls. However, this effect was not associated with tic severity and could be entirely accounted for by the severity of co-occurring ADHD symptoms. Thus, once ADHD symptoms had been accounted for, there were no between group differences in learning rate or the degree of learning observed. By contrast, and more importantly, we found that following learning the rate of forgetting (unlearning) was significantly negatively associated with motor tic severity, such that individuals with more severe tics took longer to unlearn previously learnt motor patterns of behavior. This finding is consistent with the proposal that TS is associated with alterations in the striatal habit learning system and with the view that TS may make it harder to unlearn maladaptive motor habits once they have been acquired.

Keywords: Tourette syndrome, habit learning, visuomotor adaptation, tics, ADHD

Introduction

Tourette syndrome (TS) is a childhood-onset neurological condition characterised by an evolving repertoire of chronic motor tics and one or more phonic tics (Leckman, 2002). Tics are involuntary, repetitive, stereotyped motor and vocal behaviours that occur in bouts, typically many times in a single day, and are the most common form of movement disorder in children. It has been proposed that tics arise in TS as a result of increased habit learning (Leckman & Riddle, 2000; Graybiel et al., 2008). This may bias the child to acquire automatic behaviours (i.e. tics) more readily than is normal and make it harder to unlearn maladaptive habits once acquired. However, few studies have yet explored habit learning in TS.

Habits can be defined as learned, repetitive, sequential, context-triggered behaviours (Graybiel, 2008). In the initial stages of habit learning, behaviours are goal-directed, but with repetitive training, behaviours become automatic. One of the main characteristics of habits is insensitivity to reward, which has repeatedly been shown in experimental settings using reward de-valuation paradigms in which animals or humans perform the same behaviour even when a reward is reduced or removed. Only a limited number of studies have investigated "habit learning" in individuals with TS, and most of these have focused on reward or reward de-valuation.

Treatments for TS currently focus on psychosocial education, behavioural therapies and medication (Roessner, Plessen, Rothenberger, et al., 2011). The lack of available, effective, and acceptable medication for tics has led to the development of non-pharmacological interventions (Piacentini, Woods, Scahill, et al., 2010) and two behavioural therapies have been shown to be efficacious in reducing tics (Piacentini, Woods, Scahill, et al., 2010; Verdellen, Keijsers, Cath, et

al., 2004). Both depend upon mechanisms of *learning* and *un-learning*, and require practice, particularly when tics are well established and associated with strong urges. One of these treatments, Habit Reversal Therapy (HRT), focuses on replacing tic movements with alternative, more acceptable, actions. The other, Exposure and Response Prevention (ERP), aims to develop and strengthen the ability to suppress tics. Despite the theoretical and practical importance of understanding habit learning in TS, remarkably few studies of learning in TS have been conducted to date, and to our knowledge, no quantification of habit formation, consolidation, and unlearning in TS has yet been published. Furthermore, the few learning studies that have been published have used behavioural tasks that were insensitive to differences in learning rate (i.e., the tasks were learnt too quickly) (e.g., Palminteri, Lebreton, Worbe, et al., 2011) or have involved very little or no motor learning (e.g., Keri, Szlobodnyik, Benedek, et al., 2002; Channon, Pratt, Robertson, 2003). We believe that this is an important omission as tics are motor phenomena and studying motor habit learning is likely to be closer to the mechanisms underpinning TS.

Marsh et al. (2004) used a probabilistic classification learning paradigm to study habit learning and found impaired habit learning in both children and adults with TS, and a negative correlation between the rate of learning and the severity of tic symptoms, such that impaired learning accompanied more severe tic symptoms. They interpreted this as indicating that impaired habit learning is in line with previous findings that individuals with TS have abnormalities within the striatum, which plays a critical role in habit learning. However, impaired habit learning in individuals with TS appears to contradict the clinical impression that individuals with TS appear to be more prone to the acquisition of repetitive motor behaviours like tics; and would therefore be expected to show enhanced habit learning. The contrasting results might be due to the fact that the task used in the Marsh et al. (2004) study involved very

little actual motor learning. By contrast, enhancement of habit learning in TS has been also reported. Palminteri et al. (2011) adopted a motor sequence learning task and found enhanced reinforcement learning in a TS group (unmedicated). However, their task was insensitive to differences in learning rate as their tasks were learnt too quickly. In a subsequent study, Delorme et al. (2015) used an instrumental learning task and showed that (unmedicated) individuals with TS exhibited a significant relationship between the degree of engagement in habitual responses and tic severity. However, this task again involved very little learning.

In summary, in spite of the fact that TS is chiefly characterised by motor symptoms (i.e. the occurrence of tics), surprisingly few of the previous studies of habit learning in TS have used habit learning tasks that involve learning dynamic movement and to our knowledge, no detailed quantification of habit formation and consolidation in TS has yet been reported.

In the current study, we adopted a visuomotor adaptation task that has been used extensively to investigate motor learning (Krakauer, 2009). In our visuomotor adaptation task, individuals were required to execute planar reaching movements to different target locations while learning to adapt to a visuomotor transformation (i.e., a systematic rotational bias was added to the visual feedback provided during the reaching movement). Following a period of adaptation to the visuomotor perturbation, there was a de-adaptation phase, in which no visual feedback was provided during reaching, that allowed us to test the retention of the motor memory acquired in the preceding (adaptation) phase. In order to test overnight memory consolidation, participants performed the same task again on the next day. Formal modelling analysis was conducted to precisely investigate and quantify the strength of automatic motor learning in children/adolescents with TS and age-matched typically developing controls. We recruited individuals with a confirmed clinical diagnosis of TS who presented without a

comorbid diagnosis of ADHD). However, as ADHD is highly co-occurring with TS, we measured ADHD symptoms using an appropriate clinical measure (see below).

Methods

Participants

25 participants with TS (mean age 13.21±1.94 years, all males) took part in the study. All TS participants had previously received a formal clinical diagnosis of TS from a clinician. The Yale Global Tic Severity Scale (YGTSS) was used to measure current tic severity. For the purpose of this study we recruited the only participants with a diagnosis of TS who presented without a co-occurring diagnosis of ADHD or ASD. Participants' characteristics are shown in Table 1. Also, none of the participants were on stimulant medication. One TS participant did not understand the instruction, so was excluded from entire data analyses. One TS participant did not complete the day 2 session due to technical problems, so only their day 1 session data were included in the analysis. 23 typically developing participants were recruited as a control group and were gender and age matched to the TS group (mean age 13.27±2.17, all males). Both the TS and control participants used a computer mouse with their right hand in daily life. The parents of all the participants gave written informed consent prior to the study. This study was approved by the ethics committee of School of Psychology, University of Nottingham, U.K..

Procedure

The participants visited the University of Nottingham on two consecutive days. Testing on day 1 and 2 was at least 20 hours apart. Participants performed the visuomotor adaptation task, which took approximately 30 minutes, on each day. In addition, on the first day IQ was

assessed using the Wechsler Abbreviated Scale of Intelligence (WASI, Vocabulary and Matrix Reasoning subscales, Wechsler, 1999) and current tic severity (Motor, Phonic and Global tic severity) was assessed in the TS group using the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989).

The parents/carers of both the TS and control group participants also completed clinical questionnaires on the day of testing or within one week of the session taking place. In all cases, ADHD symptoms were calculated from the 10 items of the Conners 3 – Parent (Conners, 2008) to assess severity of ADHD symptoms. The Social Communication Questionnaire (SCQ) lifetime version (Rutter et al., 2003) scores were used to measure levels of ASD symptoms. Although we excluded participants who met diagnostic criteria for ADHD or ASD, sub-threshold traits of these conditions may still influence habit-learning. We therefore checked for the influence of ADHD and ASD traits by modelling these questionnaires scores as covariates in all between-group analyses.

Task

Participants sat comfortably at a table facing a computer screen located at a distance of approximately 40 cm. The participants performed the task using a wireless computer mouse that was placed on a particularly large mouse pad (33 x 26 cm^2). The mouse pad was covered by a wooden cover (50 x 40 x 20 cm^3) to prevent participants viewing their hand during the task.

On every trial, an image of a car (1 x 2 cm^2) was presented in the centre and at the bottom of the computer screen (the start position). Participants were asked to place the mouse at the bottom edge of the mouse pad and to get ready. Once the mouse had been correctly positioned, an image of a chequered flag (1.23 x 1.23 cm^2) was presented either in the top-left or top right of

the screen (15.9 cm away from the start point at -45 or +45 degree) pseudo-randomly such that it did not appear on the same side more than three times in a row. Participants were asked to move the car toward the flag using the computer mouse (Figure 1). They were instructed not to stop at the target but to pass through it (i.e., a shooting-reaching movement) at a fast speed. If peak velocity was over 58.8 cm/s (this threshold was determined through pilot testing with children and young adults), a pleasant sound was played at the end of the trial as feedback. If peak velocity was below 58.8 cm/s, a low sound was played and an image of a snail (4.9 x 4.9 cm^2) was shown in the centre of the screen at the end of the trial to alert the participants that the speed on that trial was too slow. No explicit feedback about the spatial accuracy of the movement was provided, but the participants were instructed to move as straight as possible and to pass through the target.

FIGURE 1 about here

On day 1 participants performed 16 practice trials prior to the experimental task. After the practice trials, participants completed four blocks of the task: block 1 baseline (16 trials); block 1 and 2 adaptation (80 trials each); and block 4 de-adaptation (40 trials). In the baseline phase, veridical visual feedback was given of the mouse cursor. In the adaptation phase, there were two types of trials: perturbation trials (70 per block) where the mouse cursor was rotated by 30 degrees in a clock-wise direction and catch trials (10 per block) in which visual feedback was not shown (i.e., the mouse cursor disappeared as soon as the participants moved the computer mouse). Catch trials were inserted pseudo-randomly so that they occurred once in every eight trials. In the de-adaptation phase, no visual feedback was given. In order to keep the participants motivated until they finished the task, a smiley face image was shown with the message ‘you are

doing great' every 24 trials in the adaptation and de-adaptation phases. On day 2, participants completed the same identical four blocks again (i.e. baseline (washout), re-adaptation 1 and 2, and de-adaptation).

A 21.5 inch iMac computer (Apple Inc.) and a wireless mouse (M235, Logitech) were used to present stimuli and record responses. The task was programmed with Psychtoolbox (v 3.0.10) in Matlab (R2011a). The movement was recorded at a sampling rate of 60 Hz.

Data Analysis

Reach direction (RD) was calculated in angular degrees between a line from the start point to the target and a line from the start point to the location of the mouse cursor when the mouse was 15.9 cm away from the start point. Reaches in the same direction as the perturbation (i.e. clock-wise) were recorded as positive values and the reaches made in the opposite direction were recorded as negative values. Trials in which participants moved to the wrong target (i.e. RD > 60 or < -60 degree) or where participants did not reach the target level (i.e., 15.9 cm from the start point within 1 second) were excluded from the analysis. The alpha (significance) level was set at 0.05).

For each phase, trials were grouped into bins of trials and the median RD of the bin was calculated for each individual. In the baseline and de-adaptation phases, there were 8 trials in each bin. For the adaptation phase, 7 perturbation and 1 catch trial were included within each bin. A two-way mixed ANOVA (Group × Time) was conducted on binned data with Greenhouse-Geisser correction where appropriate.

Modelling analysis was applied to the binned data of day 1 to quantify the motor learning and the forgetting (unlearning) rates. An exponential decay function (shown below) was utilised

for this purpose based upon previous studies (Palminteri et al., 2011; Heathcote and Brown, 2000).

$$RD(n) = b \times exp^{-(a \times n)} + c$$

This exponential decay function models RD in bin n with three parameters: **a**, the motor learning rate; **b**, the magnitude of RD changes; and **c** the plateau to which the RD curve would converge after an infinite number of bins (n=∞, Palminteri et al., 2011). Parameters a and b were optimised to fit the data using least squares minimization within Matlab with bounds of $0<a<1$ for both the adaptation and de-adaptation phases, and $0<b<40$ for the adaptation phase and $-40<b<0$ for the de-adaptation phase. Parameter c was held constant at -30 for the adaptation phase which is the degree of RD adjustment required to compensate 30 degree of perturbation and hit the target without errors. Parameter c was held constant at 0 for the de-adaptation phase, which is the degree of RD that participant would show if they had completely forgotten what they had learnt within the adaptation phase. To model how the RD changed in the adaptation phase from the baseline, the RD of the last bin of baseline phase was entered to the model as bin 0 together with the RD of bins 1 to 20 of the adaptation phase. To model how RD changed in the de-adaptation phase from the level of the preceding adaptation phase, the predicted RD of the exponential fit of the adaptation phase at bin 20 was included as bin 0 together with the RD of bins 1 to 5 of the de-adaptation phase. While parameter b is a marker of asymptote, not all of the participants in the current study reached asymptote level within 20 bins of training. Therefore, the achieved level of performance at the end of the adaptation phase (bin 20) was estimated as the predicted RD of the modelled exponential fit. In the same way, the after-effects at the end of de-adaptation phase (bin 5) were estimated as the predicted RD of the modelled exponential fit.

Learning/forgetting rates (i.e. parameter a) and achieved level of performance were used as dependent variable for the following analysis. Grubb's test (Grubbs, 1969) was conducted to remove outliers prior to further analysis.

Figure 2 about here

Results

Day 1: Group comparison (TS vs. control group)

The binned results of day 1 for the TS and control group are shown in Figure 2. Inspection of this figure clearly illustrates that during the baseline phase, when veridical visual feedback was given of the cursor's position, there were no group differences in reaching accuracy (RDs for both groups are close to zero). This was confirmed by a repeated measures ANOVA which revealed no main effect of bin or group and no interaction effect (all $p>.05$). In the adaptation phase, Figure 2 shows that RDs progressively moved toward -30 degrees. A repeated measures ANOVA confirmed that there was a significant main effect of time (training) ($F(8.68, 390.38)=44.67$, $p<.001$, partial $\eta^2=.50$) and also a marginal main effect of group ($F(1,45)=3.685$, $p=.06$, partial $\eta^2=.08$), indicating that there was less adaptation in the TS group. However, since previous studies have reported that adolescents with ADHD have shown impaired learning on explicit (goal-directed) cognitive tasks (e.g., Shephard et al., 2016), we conducted an ANCOVA with individual ADHD scores entered as covariate to test if the marginally significant group differences in RD of the adaptation phase perturbation trials still approached statistical significance after having first controlled for ADHD scores. This analysis clearly showed that there was no significant difference in learning rate between TS and control groups once levels of ADHD were controlled for ($p>.05$) and that there was no significant interaction ($p>.05$).

Furthermore, ADHD score was a statistically significant predictor of individual learning rates (see below).

In the de-adaptation phase, participants exhibited clear aftereffects, especially at the beginning of the de-adaptation phase, and in the same direction as the perturbation, as they adjusted their RD back towards baseline. A repeated measures ANOVA confirmed that there was a significant main effect of time (training), ($F(2.79,125.46) = 26.75$, $p < .001$, partial $\eta^2 = .37$), but no main effect of group or time x group interaction effect ($p>.05$).

Learning/forgetting rates and the final level of performance (i.e. final bin RD) were quantified by modelling the RDs across bins as an exponential curve within each participant. Group means for each measure are shown in Table 2. Independent t tests were conducted for each measure. These analyses confirmed that there were no significant group differences for any of these measure (all $p > .05$, see Table 2).

Day1: Relationship between learning/forgetting rates and tic severity

We investigated the association between the learning/forgetting rates on day 1 and motor tic severity in TS group using a Pearson correlation analysis. Additionally, we carried out a stepwise linear regression analyses to examine if any other measures, or combination of measures, could explain the learning/forgetting rates of TS group. The following variables were included in the regression analysis: age (in months); motor tic severity (YGTSS); IQ estimates (WASI); ADHD score (Conners); and SCQ score. First, we examined relationships between these variables and learning rate. The correlation analysis demonstrated that there was no significant relationship between the learning rate (i.e. parameter a) of the adaptation phase and motor tic severity ($p>.05$). By contrast, the stepwise regression analysis revealed that ADHD index and IQ

estimates together could account for 29% of the learning rate in TS group. ADHD index was entered into the regression equation first and on its own significantly predicted 18% of the learning rate ($F(22,1) = 5.90$, $p = .024$, $R^2 = .21$, adj.$R^2 = .18$). IQ estimates were entered into the regression equation next and predicted a further 11% ($F(21,2) = 5.77$, $p = .01$, $R^2 = .36$, adj.$R^2 = .29$). None of the other variables significantly increase the predictive power of the model (all $p > .05$). In addition, there was no significant relationship between the final level of performance of the adaptation phase (i.e., last bin RD) and motor tic severity ($p>.05$) and stepwise regression analysis did not reveal any significant predictors (all $p>.05$).

Next, we examined relationships between these variables and forgetting rate. There was a significant correlation between the forgetting rate (i.e., parameter a) of the de-adaptation phase and motor tic severity ($r = -.43$, $p = .04$, See Figure 4a) such that the participants with more severe motor tic symptoms showed decreased forgetting rates (i.e., increased retention of learned information). Stepwise linear regression analysis also demonstrated that individual motor tic severity scores significantly predicted forgetting rates in the de-adaptation phase ($F(1,22) = 4.85$, $p = .04$, $R^2 = .18$, adj.$R^2 = .14$), but no other variables could significantly increase the predictive power of the model once motor tic severity was entered into the model (all $p > .05$). The analysis of the final level of performance of the de-adaptation phase (i.e. last bin RD) revealed a similar pattern of results. Specifically, there was a marginally significant correlation between the last bin RD and motor tic severity ($r = -.43$, $p = .05$, See Figure 4b) such that the participants with more severe tic symptoms showed more residual aftereffects at the end of the de-adaptation phase. Stepwise regression analysis revealed that age significantly predicted the last bin RD of the de-adaptation phase ($F(22,1) = 4.93$, $p = .04$, $R^2 = .18$, adj.$R^2 = .15$). After age was entered to the regression equation, motor tic severity did not account for any additional variance ($p > .05$),

however it is important to note that there was a significant negative correlation between age and motor tic severity ($r = -.56$, $p = .01$).

To further investigate how tic severity related to the rate of forgetting rate we binarized the TS group into a High tic severity and Low tic severity group (median split). This resulted in two sub-groups, each containing 12 TS participants. We then compared the forgetting rate (de-adaptation rate) for each sub-group against that for the control group. This analysis revealed that TS individuals with low tic severity scores had slightly higher forgetting rates than controls (means: CS group = 0.53 [±0.07], low tic severity group = 0.63 [±0.08]) but this difference was not statistically significant ($t(33) = -0.88$, $p = 0.19$). By contrast, individuals with high tic severity scores had significantly reduced forgetting rates compared to the control group (means: CS group = 0.53 [±0.07], low tic severity group = 0.33 [±0.08]; $t(33) = 1.78$, $p < 0.05$).

Day2: Group comparison (TS vs. control group)

The binned results of day 2 for TS and control group are shown in Figure 1. For the baseline washout phase, a repeated measures ANOVA revealed that there was a significant main effect of time (training) ($F(1,45) = 21.35$, $p < .001$, partial $\eta^2 = .322$). This indicated that participants still exhibited the aftereffects of the previous day's training, however it rapidly reduced once veridical visual feedback was provided. There was no significant main effect of group or a time x group interaction effect ($p > .05$).

In the adaptation phase, a repeated measures ANOVA revealed that there was a significant main effect of time (training) ($F(8.66,381.03) = 22.82$, $p < .01$, partial $\eta^2 = .34$). The pattern of results was similar to the those for the adaptation phase of day 1 insofar that

participants adjusted their RDs over bins again in day 2, but there was no significant main effect of group or a group x time interaction ($p > .05$).

In the de-adaptation phase, a repeated measure ANOVA revealed that there was a significant main effect of time (training) ($F(3.37,148.36) = 24.47$, $p < .01$, partial $\eta^2 = .36$) but no significant main effect of group or group x time interaction ($p > .05$).

Learning/forgetting rates and the magnitudes of learning/forgetting were quantified in the same manner as outlined above for day 1. The binned data for the adaptation/de-adaptation phases were modelled as exponential curves for each individual participant. For the adaptation phase, there were no group differences in the learning rate (i.e., parameter a) or the magnitude of the RD adjustment (i.e. parameter b) (both $p>.05$). In the de-adaptation phase, there was no group difference in the forgetting rates (i.e. parameter a) or the magnitude of decrease in aftereffects (i.e., parameter b) (both $p>.05$).

Previous studies have suggested that the amount of savings (consolidation) observed can be quantified by comparing performances at the beginning of the adaptation phase of each day (e.g., Krakauer et al., 2005). We therefore calculated the difference in RDs between the first bin of the Adaptation phase on Day 2 and the first bin of the Adaptation phase on Day 1. However, a between group comparison did not reveal significant difference in savings between the TS and control groups ($p > .05$).

Day2: Relationship between learning/forgetting rates, savings and tic severity

We investigated the degree of association between the learning/forgetting rates on day 2 and motor tic severity in TS group using Pearson correlation analysis. Additionally, we also carried out a stepwise linear regression analyses in the same manner as we reported for the day 1

data, with the following variables entered into the model: age (in months); motor tic severity (YGTSS); IQ estimates (WASI); ADHD score (Conners); and SCQ score. There was no statistically significant relationship between the any of the Day 2 measures and motor tic severity ($p > .05$). There was a trend toward a positive relationship between motor tic severity and the amounts of savings observed, such that the participants with severe motor tic symptoms showed increased savings in the adaptation phase of Day 2, but this did not reach conventional levels of statistical significance ($r = .36$, $p = .09$). We note however that this effect is consistent with the day 1 finding reported above that increased retention of learning (i.e., decreased forgetting rate) is associated with increased motor tic severity.

A stepwise regression analysis revealed that ADHD index was a significant predictor of the amount of saving observed during adaptation phase of day 2 ($F(21,1) = 5.46$, $p = .03$, $R^2 = .21$, adj.$R^2 = .17$). The stepwise regression revealed that none of the variables entered into the analysis could significantly predict: learning rates during adaptation; the last bin RD of adaptation phase; the forgetting rates during de-adaptation; or the last bin RD of de-adaptation phase of Day 2 (all $p > .05$).

Discussion

In the current study, we investigated motor learning using a visuomotor adaptation task in a group of children and young adults with TS, compared to a group of age and gender matched, typically developing, individuals. We quantified both motor learning and unlearning (forgetting) rates and investigated the retention/consolidation of motor learning over two consecutive days. We found that, once ADHD symptoms had been controlled for, there were no significant group differences between individuals with TS and control participants in motor learning or the retention of the acquired motor memory. However, we did find a significant correlation between

the severity of motor tic symptoms and the retention of motor memory (i.e., the rate at which previously learnt motor patterns are forgotten [unlearned]). More specifically we found that individuals with severe motor tic symptoms are significantly slower to unlearn (de-adapt) patterns of motor behaviour that have been acquired during the previous motor adaptation phase.

In our task, participants learnt to adapt to a visuomotor perturbation during the adaptation phase. One of the main hypotheses of our study was that, due to the proposed increase in striatal dopamine associated with TS (Buse et al., 2013), children/adolescents with TS may acquire automatic behaviours more rapidly than the matched typically developing controls. However, this hypothesis was not supported and, once ADHD scores were controlled for, there was no group difference in learning rates between TS and control participants and no relationship between learning rates and tic severity. In fact, there was a trend towards impaired learning in the TS group compared to CS group, however it was found to be uncorrelated with tic severity scores and entirely due to the presence of comorbid ADHD symptoms.

It is important to note that participants showed gradually increasing after-effects (i.e., reaching movements in a direction opposite to the perturbation) on the catch trials presented throughout the adaptation phase (recall that on catch trials visual feedback was not presented). If participants RD adjustments in the adaptation phase by using visual feedback to deliberately adjust their motor movements, they would show RD adjustment only on perturbation trials, not on catch trials, as online correction would not be possible without visual feedback. The presence of after-effects on catch trials therefore suggests that the motor learning occurred gradually and automatically insofar as it was largely independent of strategic processing such as online correction. The occurrence of after-effects on catch trials when no perturbation was applied therefore suggests that a visuomotor adaptation has occurred. The after-effects lasted a finite period of time during the de-adaptation

phase. The degree of after-effects has been suggested as a marker for the retention of acquired motor learning. Our main finding is that there was a statistically significant relationship between motor tic severity and the rate at which previously learnt motor patterns are unlearnt during the de-adaptation phase of the study. Specifically, TS individuals with severe motor tic symptoms showed slower rates in forgetting automatic behaviour obtained in the preceding phase and showed increased after-effects at the end of de-adaptation phase. This is a very important observation as it is consistent with anecdotal accounts of the acquisition of tics in TS which have proposed that motor habits may be readily acquired and once established are then particularly difficult to unlearn. For instance, a child's early tics might be associated with the onset of an infection such as a cold, and nose twitching, sniffing, and throat clearing may all relieve the uncomfortable sensations associated with the cold, and these behaviours may be reinforced by abnormal DA signalling in the child with TS (Buse et al., 2013). Once the infection is over, these newly acquired behaviours may remain, despite the original context for these actions having ceased, because the actions have become over-learnt. Our finding also supports the proposal that TS is associated with abnormalities in the striatum (Albin & Mink, 2006) and that tics arise as a result of abnormalities in the striatal habit learning system (Graybiel et al., 2008).

Previous studies have suggested that motor memory undergoes a process of consolidation that may take approximately 4-24 hours (Brashers-Krug, Shadmehr, & Bizzi, 1996; J. W. Krakauer, 2005; Shadmehr & Brashers-Krug, 1997). To test for consolidation of motor learning, participants performed the same task approximately 24 hours later (Day 2). Our results demonstrated that participants clearly showed more rapid learning when they were re-exposed to the same perturbation in the adaptation phase of day 2, which has been referred to as motor savings (Krakauer et al., 2005). There was a trend toward a positive correlation between the

amount of savings observed and motor tic severity in TS group. This finding should be interpreted with caution but is also consistent with the idea that tic severity in TS is associated with increased retention of learnt motor patterns. The lack of statistical significance might be due in part to the washout phase that preceded the adaptation phase on day 2. Importantly, not all of the participants in this study actually regained baseline levels during the washout phase on day 2. We suggest that further examination of motor consolidation in TS may be particularly worthy of investigation.

It is of interest that we tested child and adolescent participants in the current study, whereas most previous studies investigating learning in TS have tested adult participants (Palminteri et al., 2011; Delorme et al. 2015). The time course of tic symptoms is that it typically first presents during early childhood and often remits with increasing age in adolescents. As only a minority of individuals will continue to exhibit debilitating tics into adulthood (Cohena et al., 2013), the inclusion of adults with TS cannot be considered to be representative of the general TS population.

The underlying neurobiological mechanisms of TS are not yet fully understood, but there is broad agreement that TS is associated with impairment in the operation of cortical-striatal-thalamic-cortical (CSTC) brain circuits that are implicated in motor learning (particularly habit formation) and the selection of actions according to behavioural context (Albin & Mink, 2006; Graybiel et al. 2008). TS has been linked to dysfunctional signalling of neurotransmitters such as dopamine (Buse et al., 2013) and GABA (Lerner et al., 2012) that are strongly linked to reinforcement (Schultz et al., 1997) and motor learning (Reis et al., 2009). Our finding of the relationship between tic severity and habit learning is in line with the overlap between the

pathophysiology of TS and habit learning. However, the interpretation of our findings must be limited insofar as no neurobiological measures were obtained in the current study.

Co-occurring conditions or co-existing psychopathologies are highly prevalent in the TS population and ~90% of individuals with TS may have one or more co-occurring diagnoses or psychopathologies, most typically ADHD, OCB/OCD and/or ASD (Hollis et al., 2016). In our study we recruited individuals with a clinical diagnosis of TS who presented without a a co-occurring diagnosis of ASD or ADHD, as these comorbid conditions can have a differential role in motor learning. However, we note that our TS participants had significantly higher mean Conners (ADHD) and SCQ (ASD) scores than the age- and gender-matched control group. Furthermore, our data clearly demonstrate that the differences in learning rate between the TS group and controls that we observed on Day 1 could be entirely predicted by sub-clinical ADHD scores and not tic severity scores. As individuals presenting with TS but without co-occurring conditions may be somewhat unrepresentative to the typical clinical population, this suggests that further research is needed to further understand how habit learning mechanisms may be altered in individuals with TS.

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Tables

Table 1 Summary of demographic and clinical characteristics for TS and control groups. Group means are presented with SD in parentheses.

	TS (n=24)	Control (n=23)	t test
Age (years)	13.21 (1.94)	13.27 (2.17)	n.s.
Gender	all male	all male	
IQ	114.96 (13.09)	117.52 (8.91)	n.s.
Conners ADHD index	6.58 (6.39)	0.74 (1.14)	p<.001
SCQ scores	8.08 (6.97)	2.61 (2.59)	p=.001
YGTSS Motor	13.12 (4.26)	n/a	
YGTSS Phonic	9.48 (6.58)	n/a	
YGTSS Total	34.60 (15.62)	n/a	

Table 2 The results of modelling analysis of visuomotor adaptation/de-adaptation task in TS and control group

	TS		CS		t test		
	n	Mean (SD)	n	Mean (SD)	T	p	η^2
Day 1 Adaptation							
Learning rate	24	0.12 (0.08)	22	0.17 (0.12)	-1.61	.11	.06
Last bin RD	22	-26.58 (3.09)	23	-27.27 (3.30)	0.722	.47	.01
Day 1 De-adaptation							
Forgetting rate	24	0.48 (0.30)	23	0.53 (0.33)	-0.56	.59	.01
Last bin RD	24	-3.86 (3.49)	22	-3.64 (3.37)	-0.22	.83	.00
Day 2 Adaptation							
Learning rate	23	0.25 (0.29)	23	0.31 (0.33)	-0.60	.55	.01
Last bin RD	19	-28.79 (1.44)	20	-28.71 (1.59)	-0.17	.87	.00
Saving (Day 2 - Day 1)	23	6.51 (8.43)	23	7.15 (10.80)	-0.22	.83	.00
Day 2 De-adaptation							
Forgetting rate	23	0.32 (0.27)	23	0.43 (0.30)	-1.33	.19	.04
Last bin RD	23	-8.60 (7.22)	22	-5.59 (5.32)	-1.59	.12	.06

Figures

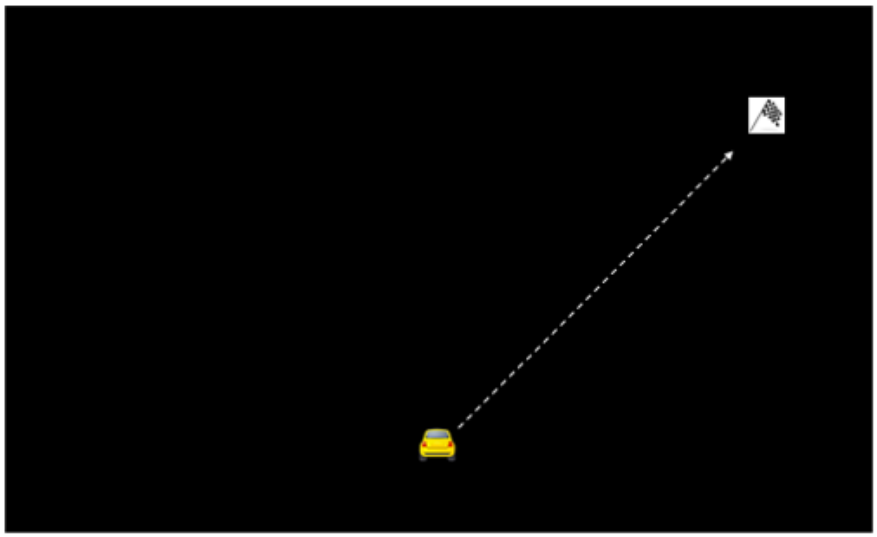

Figure 1: Illustration of the computer task. Participants are asked to move the cursor (car icon) as quickly as possible to pass over the chequered flag icon. The dotted white line represents a straight line path from the start location to the target location.

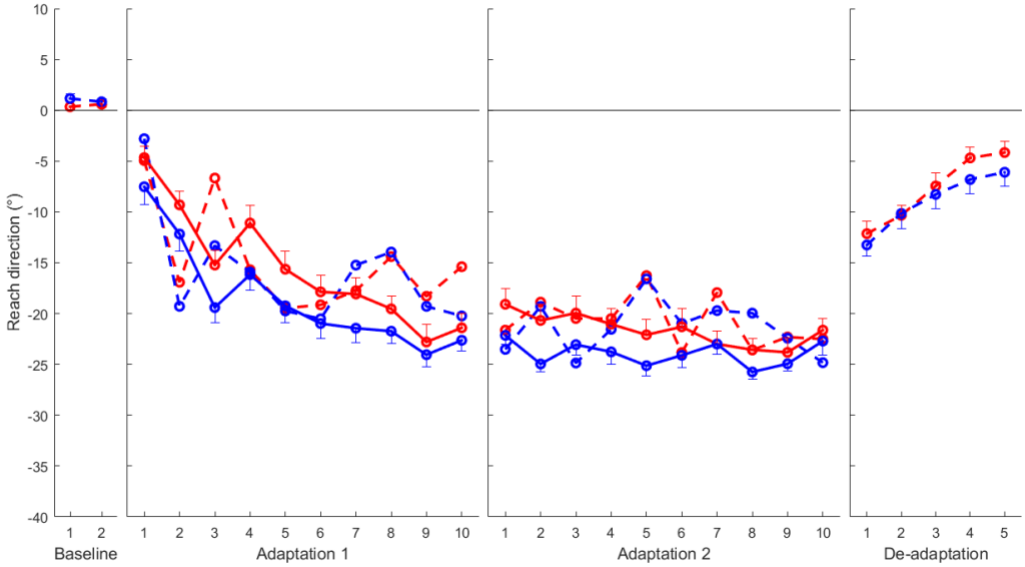

Figure 2: Binned results for the TS group (red) and control group for Day 1. Solid lines indicate the reach direction under the perturbation and the dashed lines indicate the reach direction when no perturbation was applied. Error bars indicate SEM. Error bars are not shown for catch trials of the adaptation phases for clarity.

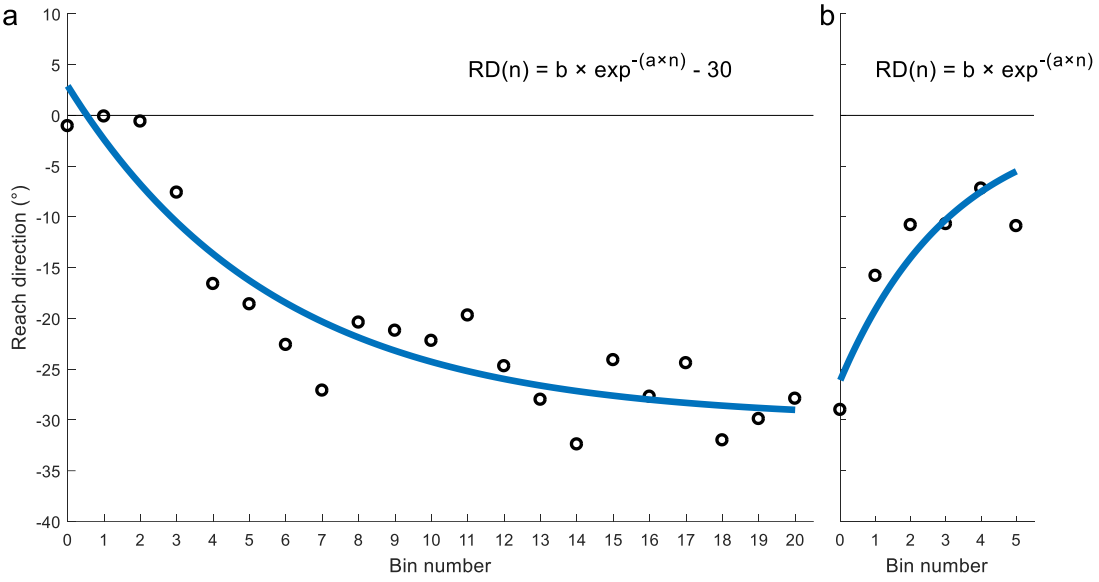

Figure3 The modelling analysis results for a single example participant. a. the adaptation phase and b. the de-adaptation phase for day 1. Parameter a was considered to reflect the learning rate during the adaptation phase (a) and the forgetting rates during the de-adaptation phase (b).

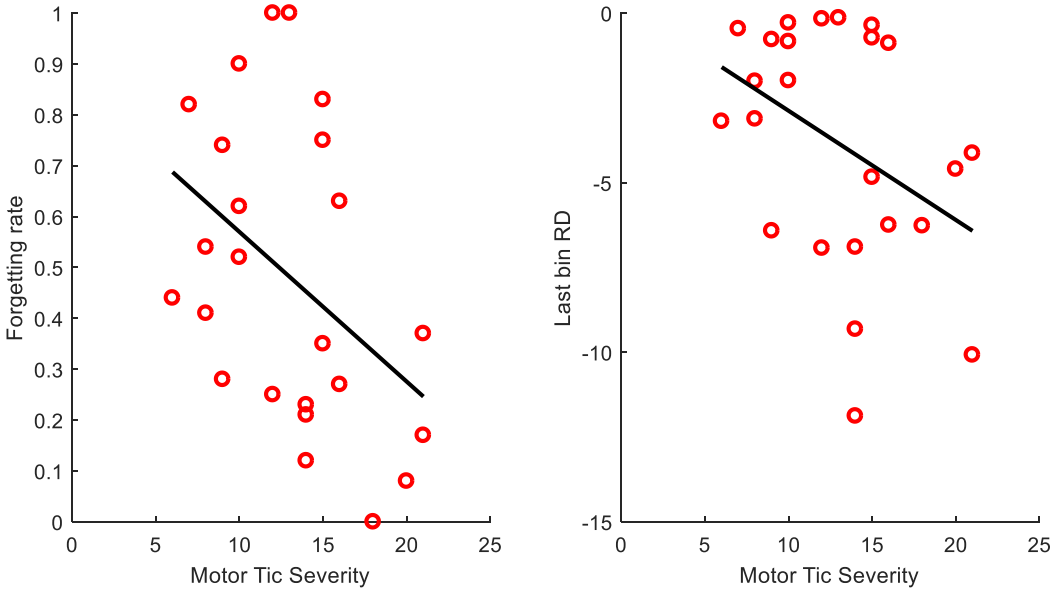

Figure 4 Illustrates the relationship between motor tic severity (YGTSS) and the day 1 forgetting rate [left panel]and the final level of performance (i.e. last bin RD) of day 1 de-adaptation [right panel].

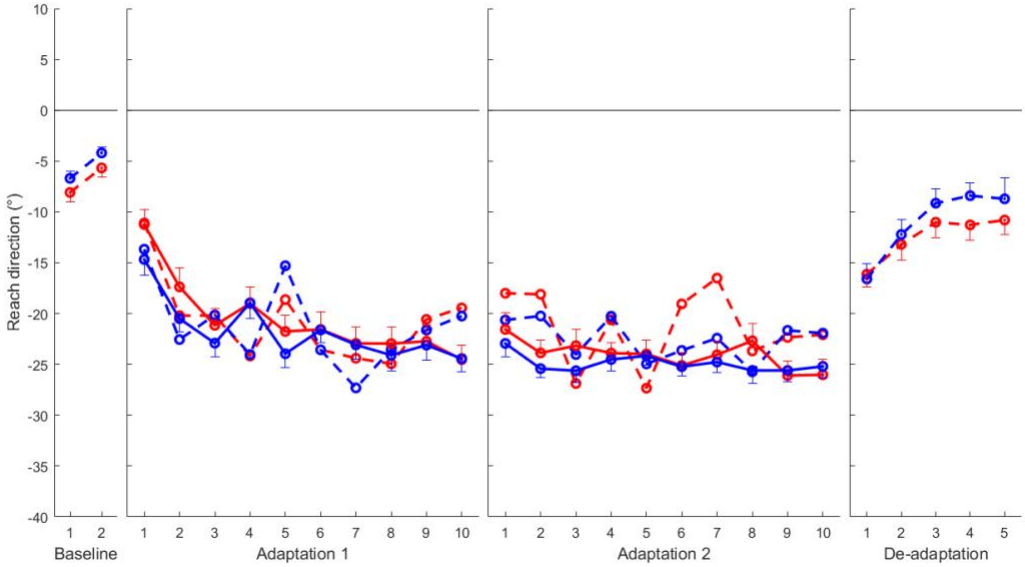

Figure 1 Illustrates binned results for the TS group (red) and the control group on Day 2. Solid lines indicate the reach direction under the perturbation and the dashed lines indicate the reach direction when no perturbation was applied. Error bars indicate SEM. Error bars are not shown for catch trials of the adaptation phases for clarity.