Impaired forward model updating in young adults with Tourette syndrome

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

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
Division of Psychiatry and Applied Psychology
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

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Abbreviations

CS = Control Subjects; WASI = Wechsler Abbreviated Scale of Intelligence; YGTSS = Yale global tic severity scale

Abstract

Current theories of motor control emphasise how the brain may use internal models of the body to ensure accurate planning and control of movements. One such internal model - a forward model - is thought to generate an estimate of the next motor state and/or the sensory consequences of an upcoming movement, thereby allowing movement errors to be monitored. In addition, forward models may provide a means by which to determine a sense of agency, i.e., the (conscious) sense of authorship and control over our actions. Tourette syndrome is a developmental neurological condition characterised by the occurrence of motor and phonic tics. The involuntary (or voluntary) nature of tics has been the subject of considerable debate, and it was recently argued that the presence of tics in Tourette syndrome could result in a blurring of any subjective boundary between voluntary and involuntary movements. In particular, it was proposed that the level of sensorimotor noise that accompanies tics may be particularly high in Tourette syndrome, and this may contribute to less efficient forward models used to determine agency. We investigated whether the internal monitoring of movements is impaired in individuals with Tourette syndrome, relative to a matched group of typically-developing individuals, using a task that involved executing double-step aiming movements using a hand-held robot manipulandum. Participants were required on each trial to execute two movements in turn, each directed to a remembered target location without visual feedback. Importantly, we assumed that to perform accurately on the second (return) movement it would be necessary to update any forward model to take account errors made during the first (outward) movement. Here we demonstrate that while the Tourette syndrome group were equally accurate, and no more variable, than the matched control group in executing aiming movements to the first (outward) target location. They were significantly less accurate, and exhibited greater movement variability, than controls when executing the second (return) movement. Furthermore, we show that for the return movement only, movement accuracy and movement variability were significantly predicted by the Tourette syndrome group's clinical severity scores. We interpret these findings as consistent with the view that individuals with Tourette syndrome may experience a reduction in the precision of the forward model estimates thought necessary for the accurate planning and control of movements.

Introduction

Recent theories of motor control have emphasised how the brain may use internal models of the body to ensure accurate control of movements (Wolpert and Ghahramani, 2000). One such internal model - referred to as a forward model - is thought to generate an estimate of the next motor state and/or the sensory consequences of an upcoming movement. Specifically, it is proposed that whenever a motor command is issued, a copy of that command is passed to the appropriate forward model predictor, which then generates an estimate of the sensory consequences of that movement. A fundamental role for such models is to allow movement errors to be monitored through a comparison of estimated (i.e., predicted) sensory outcomes with actual sensory outcomes. Prediction errors can be used to update forward models and so improve the accuracy of future predictions. Importantly, the predicted sensory consequences of an action can also provide a means by which to determine a sense of agency for our movements (Frith and Done, 1989), i.e., the (conscious) sense of authorship and control over our actions.

Tourette syndrome is a childhood-onset neurological condition characterised by an evolving repertoire of chronic motor tis 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. Importantly, the voluntary or involuntary nature of tics has been the subject of considerable debate and it is noteworthy that in a recent study that examined sense-of-agency in adults with Tourette syndrome, it was demonstrated that individuals with Tourette syndrome exhibited illusions of agency, relative to matched controls, in circumstances where their actions were artificially enhanced by an external agent (Delorme et al., 2016). Furthermore, the illusion of agency in such circumstances was associated with disease severity.

Most individuals with Tourette syndrome, particularly adults, report that their tics are preceded by premonitory sensory phenomena (PSP), sometimes referred to as premonitory urges (PU), that are described as uncomfortable cognitive or bodily sensations that precede the execution of a tic and are experienced as a strong urge for motor discharge (Cohena et al., 2013). It has been proposed by some that PSP do not merely precede the execution of tics but instead precipitate them by acting as aversive stimuli to which tics are the learnt response (see Cavanna, Black, Hallett, Voon, 2017). Within this view tics are often assumed to be *voluntary* responses to aversive sensory stimulation and it has been argued that PSP may in fact be the core symptoms

of Tourette syndrome (Cavanna et al., 2017). Consistent with this proposal, there is now accumulated evidence to indicate that individuals with Tourette syndrome experience heightened sensitivity to external stimuli in all five senses and that this may arise due to a breakdown in sensory gating mechanisms (Patel et al. 2014). It should be noted however that sensory thresholds are typically within the normal range in Tourette syndrome, indicating that alterations in patients' perceived sensation most likely arise due to altered central processing of sensory stimuli (Patel et al. 2014). Brain imaging evidence has demonstrated that there are widespread increases in cortical and sub-cortical brain activity that immediately precede the execution of tics in TS (Bohlhalter et al., 2006; Lerner et al., 2007; Stern et al., 2000): involving in particular, limbic sensory (insular cortex) and motor (cingulate cortex) areas and cortical motor regions (primary somatosensory cortex and supplementary motor area). Nonetheless, it is very important to note that tics often occur completely outside of awareness and should in these circumstances be viewed as involuntary movements.

Individuals with Tourette syndrome will often report that their tics can be voluntarily suppressed; but that it can be uncomfortable and stressful to suppress tics and that the urge to tic becomes uncontrollable after a period of suppression. Therefore, an alternative perspective on PU is that they occur primarily in circumstances in which tics may need to be suppressed or their execution deferred (Jackson et al., 2011). Specifically, a distinguishing feature of urges, as distinct from involuntary actions, may be that urges are chiefly associated with actions that cannot be realised immediately and must be held in check until an appropriate time when they might be released (Jackson et al., 2011). It has been suggested therefore that tics should be viewed as occupying a grey zone that lies between involuntary and voluntary action (Belluscio et al., 2011).

It has been argued that volitional actions may be accompanied by a distinctive subjective experience, and as a result they feel different from physically similar involuntary movements (Ganos et al., 2015). Furthermore, it is proposed that the presence of tics in Tourette syndrome may result in the blurring of the boundary between voluntary and involuntary movements, and result in an "impaired perception of the different subjective experiences accompanying these two distinct kinds of action" (Ganos et al., 2015). More specifically, these authors see involuntary movements as challenge for perceptual learning: during development a child must learn to recognise the signals that distinguish voluntary actions from the sensorimotor noise that may

accompany involuntary action. It is suggested that for individuals with Tourette syndrome: the level of sensorimotor noise that accompanies tics is particularly high; and that tics may be difficult to distinguish from volitional movements as they may depend upon the same motor circuits within the brain (Ganos et al., 2015).

In the current study we investigated whether the mechanisms associated with the internal monitoring of movements were impaired in individuals with Tourette syndrome, relative to a matched group of typically-developing individuals, using a task that involved executing double-step aiming movements of a hand-held robot manipulandum. The task involved reaching from a randomly determined start position to a remembered visually-defined target location and then returning as accurately as possible to the remembered start location for that trial. Importantly, on each trial visual information about the target location (outward movement) and the start position (the target for the second, return, movement) was presented only very briefly, prior to movement onset, and was not available thereafter. Proprioceptive information signalling the start location was also available prior to movement onset and proprioceptive/kinesthetic information available during the movement could be used to signal the location of the movement endpoint for the outward movement. We take the view that, in order to perform accurately on the return movement it would be optimal to update any forward model used to plan/control the movement to take account of any mismatch between estimated target location of the outward movement and the actual movement endpoint (i.e. prediction error). We hypothesise that, if individuals with Tourette syndrome have difficulty in generating accurate forward models of their movements due to the high levels of movement-related sensory noise that accompany the occurrence of tics, then they should experience difficulty in successfully updating their movement plans in the double-step reaching task and should exhibit decreased endpoint accuracy and increased endpoint variability for the return movements.

Methods

Participants

23 young adults with a confirmed clinical diagnosis of Tourette syndrome and *25* typically developing (CS) age-matched young adults participated in the study. However, *1* CS and *2* Tourette syndrome participants were excluded from the analysis due to high error rates (See Analysis section). The ages of the remaining participants were as follows: Tourette syndrome

group = 12.52 ± 1.8 years; CS group = 12.81 ± 1.86 years. The characteristics of the Tourette syndrome participants included for analysis are shown in Table 1. None of the CS group exhibited tics or reported experiencing tics. Current tic severity was measured in the Tourette syndrome group using the Yale Global Tic Severity Scale (YGTSS, Leckman, Riddle, Hardin, et al., 1989). As Attention deficit/hyperactivity disorder is highly co-morbid with Tourette syndrome, and individuals with co-occurring Attention deficit/hyperactivity disorder symptoms were not excluded from the study, we measured Attention deficit/hyperactivity disorder symptoms from both the Tourette syndrome and CS groups using the Connors Comprehensive Behavior Rating Scale (Connors, 2008). IQ was measured using the revised Wechsler Abbreviated Scale of Intelligence (WASI, Weschsler, 1999).

Table 1 about here

Apparatus

The participants performed planar reach-and-return movements using a 2D robot manipulandum (vBot-2D; Howard et al., 2009). The setup of the robot manipulandum was identical to that reported in Kim et al. (2014). Briefly, the handle of the robot manipulandum was positioned beneath a mirror such that participants could not see their hand during the task. A projector screen was positioned directly above the mirror and aligned with the robot manipulandum such that stimuli (i.e., visual stimuli marking the start and/or target locations on each trial) presented on the projection screen appeared to lie within the movement plane of the robot manipulandum.

Task

An invisible square (4 x 4 cm^2) was located at the bottom of the screen. For each trial, the home location for that trial was pseudo-randomly chosen from among four corners of the invisible square. The target location for that trial was also chosen pseudo-randomly from among four possible locations that were 15 cm apart from the centre of the invisible square, and angled -45, -15, +15, +45 degrees from midline (See **Error! Reference source not found.**). Participants were asked to hold the handle of the robot manipulandum to begin each trial. Once the participant took hold of the handle, the robot moved their hand to the home location for that trial and the trial commenced when the handle was located at the home location for over 1 second. A

white circle and a red circle (radius: 7 mm) appeared to indicate the position of the home and target locations for that trial. The white and red circles were presented for a brief period (500 ms) and then disappeared accompanied by an auditory warning (a beep). Participants were instructed that, on hearing the beep, they should move the handle of the robot to the target location as accurately as possible and within 3 s. Once they had reached their estimated target location for that trial and had ceased moving (see Analysis section below), a double beep was presented which instructed the participant to move the robot handle back to home location as accurately as possible within 3 s period. It is important to note that visual feedback of the hand position, or the location of the visual target or home position, was not provided either during the reach-toward-target movement (i.e. outward reaching movement) or during the return-to-home movement (i.e. return movement). Prior to the task, participants had the opportunity to practice the task until they reported that they fully understood the task (up to 16 trials). Following the practice session all the participants completed 64 trials.

Insert Figure 1 about here

Analysis

Outward and return movements were analysed separately. Only movements whose velocity exceeded 5 cm/s were included in the analysis and the endpoint of each movement was defined as the location at which tangential velocity of the movement fell below 5 cm/s. *Outward reaching errors* were measured in cm as the distance between the target and the endpoint of the outward reaching movement, and *return errors* were measured in cm as the distance between start location for that trial and endpoint of the return movement. The trials in which the participants did not finish their movement within 3 s in either the outward or return movement, or the trials with errors larger than 10 cm were excluded. *2* Tourette syndrome and *1* CS participant were excluded from the further analysis as more than 20 trials out of 64 trials were excluded from their data. In addition to the accuracy measures, the variability of the movement endpoints was also quantified in each individual. All the targets were combined by drawing a virtual line between home and target for each trial, and rotating all the outward/return movements so that they can be aligned along the y axis with target/start location set as (0,0). Principal component analysis (PCA) was applied for the outward movements and the return

movements separately. An example of single participant performance (See Fig 1b) and PCA results (See Figure 1c and 1d) are shown in Figure 1. The largest eigenvalue was taken as an index of the variability in amplitude, and the smallest eigenvalue was taken as an index in the variability in direction (Contreras-Vidal, 2006).

To examine the relationship between reaching movement performance and the clinical symptoms of Tourette syndrome, correlation analyses (Pearson) were conducted for the Tourette syndrome group only to investigate any association between reaching accuracy/variability and tic severity (as measured by the YGTSS).

Results

Preliminary analyses

Preliminary analyses confirmed that the Tourette syndrome group and the control group did not differ in age (means: Tourette syndrome group = 12.52 ±1.8 years, CS group = 12.81 ±1.86 years; $t < 1$, $P = 0.6$). The mean age-adjusted IQ scores differed slightly between the groups, however the mean IQ for both groups was above average (TS group = 109.76 ± 13.3, CS group = 117.87 ± 12.31; $t = 2.1$, $P < 0.05$). Finally, preliminary analyses demonstrated that the Tourette syndrome and CS groups differed in their mean Connors (Attention deficit/hyperactivity disorder) score (Tourette syndrome group = 67.6 ± 14.6, CS group = 52.0 ± 10.0; $t = 4.2$, $P < 0.0001$). Note that, with regard to identify Attention deficit/hyperactivity disorder risk, scores of 60-69 are considered to reflect 'elevated' risk while a score of 70+ is considered to reflect a 'very elevated' risk.

Reaching accuracy and variability to first target location

Analyses were completed using a restricted set of *a priori* planned contrasts between groups. Analysis of the reaching error scores (i.e., the Euclidian distance between the target location and the kinematically-defined movement end point) revealed that there were no between-group differences in reaching accuracy (Tourette syndrome group = 3.74 ±1.22 cm, CS group = 3.91 ± 1.37 cm; $t < 1$, $P = 0.44$). Analyses were also conducted for reaching endpoint variability, as indexed by the magnitude of the largest eigenvalue (variability in movement amplitude) and the smallest eigenvalue (variability in movement direction). These analyses revealed that there were

no between-group differences in either the variability in movement amplitude (Tourette syndrome group = 4.68 ± 0.52 cm, CS group = 4.20 ± 0.65 cm; $t < 1$, $p > 1$) or the variability in movement direction (Tourette syndrome group = 2.40 ± 1.45 cm, CS group = 1.79 ± 1.03 cm; $t = 1.64$, $p > 1$). Finally, we calculated the area of the error ellipse defined by the two eigenvalues and tested for between group differences in the mean area of the error ellipse. This analysis revealed that there were no such between-group differences (Tourette syndrome group = 41.68 ±41.15 cm^2, CS group = 29.74 ± 40.40 cm^2; $t < 1$, $p > 1$). Relevant means are presented in Figure 2.

For the Tourette syndrome group only, additional analyses were conducted to determine whether there was an association between clinical measures of tic severity (i.e., YGTSS motor or global scores) and measures of reaching accuracy or variability. Pearson correlation coefficients were calculated in each case. These analyses confirmed that there were no significant correlations between individual measures of reaching accuracy or variability and individual clinical tic severity scores (maximum $R = 0.36$, $P = 0.11$).

Insert Figure 2 about here

Reaching accuracy and variability for return movement to start location

An identical set of analyses to those outlined above were conducted for the return movements to the start position. Analysis of the reaching error scores (Euclidian distance between target location and kinematically-defined movement endpoint) revealed that the return movements for the Tourette syndrome group were significantly less accurate than those of the CS group (Tourette syndrome group = 2.88 ± 0.89 cm, CS group = 2.37 ± 0.68 cm; $t = 2.47$, $P < 0.02$). Analysis of movement endpoint variability was based upon the magnitudes of the largest and smallest eigenvalues. The between-group analysis of the magnitude of the largest eigenvalue (i.e., variability in movement amplitude) revealed that movement endpoints for the Tourette syndrome group was significantly more variable than those of the CS group (Tourette syndrome group = 4.99 ± 2.22 cm, CS group = 3.88 ± 2.03 cm; $t = 2.09$, $P < 0.05$). Similarly, the between-group analysis of the magnitude of the smallest eigenvalue (i.e., variability in movement direction) revealed that movement endpoints for the Tourette syndrome group was significantly more variable than those of the CS group (Tourette syndrome group = 2.93 ± 1.80 cm, CS group

= 2.09 ± 1.37 cm; t = 2.09, $P < 0.05$). We also calculated the area of the error ellipse defined by the two eigenvalues and tested for between group differences in the mean area of the error ellipse. This analysis revealed that the area of the endpoint error ellipse was marginally larger for the Tourette syndrome group compared to the CS group (Tourette syndrome group = 56.29 ± 60.16 cm^2, CS group = 32.69 ± 41.88 cm^2; t 1.89, $P < 0.07$). Relevant means are presented in Figure 2.

For the Tourette syndrome group only, additional analyses were again conducted to determine whether there was an association between clinical measures of tic severity (i.e., YGTSS motor or global scores) and measures of reaching accuracy or variability. Pearson correlation coefficients were calculated in each case. These analyses confirmed that there were no significant correlations between individual measures of reaching accuracy or variability and individual clinical tic severity scores (maximum R = 0.34, $P = 0.13$).

Effect of clinical/IQ measures on reaching performance

The CS group did not exhibit tics or report having experience tics and for this reason clinical measures of tic severity (YGTSS) were not obtained for the CS group. YGTSS scores were obtained for the Tourette syndrome group and, as noted above, these measures were shown not to be associated with either reaching accuracy or reaching variability.

IQ was measured using the revised WASI scale and, while the mean IQ score for both groups was above the norm (Tourette syndrome group = 109.76 ± 13.3, CS group = 117.87 ± 12.31), IQ differed between the groups.

Attention deficit/hyperactivity disorder risk was assessed using the Conners Comprehensive Behavior Rating Scale and was obtained from the parents of all participants irrespective of whether they had a TS diagnosis. As noted above, the mean Connors scores differed significantly between groups (Tourette syndrome group = 67.6 ± 14.6, CS group = 52.0 ± 10.0; t = 4.2, $P < 0.0001$) with Connors scores of > 60 considered to indicate elevated risk of Attention deficit/hyperactivity disorder.

In order to investigate the influence of IQ and Attention deficit/hyperactivity disorder score on reaching accuracy and variability a series of stepwise multiple regression analyses were conducted with the following variables entered as predictor variables: Group (Tourette syndrome

vs. CS); IQ score; and Connors score. In each case the order of entry of variables was forced with Group being entered first. Relevant data are presented in Figure 3.

Insert Figure 3 about here

Reach accuracy: outward movement

The analysis revealed that none of the variables were significant predictors of reaching endpoint error scores for the outward reaching movement (all $t < 1$, $p > 0.6$).

Reach variability: outward movement

The analysis revealed that none of the variables were significant predictors of the area of the error ellipse for reaching endpoint error scores for the outward reaching movement (maximum $t = 1.82$, $P = 0.08$).

Reach accuracy: return movement

The analysis revealed that both group ($t = -2.18$, $P = 0.04$) and Connors score ($t = 2.4$, $P = 0.02$) were significant predictors of reaching endpoint error scores for the return reaching movement. However, when Group was entered into the model first then Connors score ceased to significantly predict any additional variance.

Reach variability: return movement

The analysis revealed that Connors score ($t = 2.8$, $P = 0.009$) was a significant predictor of the area of the error ellipse for reaching endpoint error scores for the return movement. When Group was entered into the model first the Connors score continued to be a significant predictor of additional variance ($R^2 = 0.15$, adj-$R^2 = 0.11$, $F = 3.72$, $P = 0.033$).

Estimation of internal model updating

In the current study, visual information about the target location (outward movement) and the start position (the target for the second, return, movement) was presented briefly prior to movement onset and was not available thereafter. Proprioceptive information signalling the start location was also available prior to movement onset and proprioceptive/kinaesthetic information would be available during the movement and could be used to signal the location of the

movement endpoint for the outward movement and the continuous position of the limb during the movements. It might be argued that, in order to perform accurately on the return movement, it would be optimal to update any forward model used to plan/control the outward movement to take account of any mismatch between estimated target location and the actual movement endpoint (i.e. prediction error).. Alternatively, participants could instead simply execute the return movement based solely on the information presented prior to movement onset. We chose to assess whether participants exhibited evidence of internal model updating (i.e., that their endpoint errors for the return movement showed evidence of having adjusted for the endpoint of their outward reaching movement). To do this we completed the following steps (Figure 4 provides an illustration with respect to a single trial).

First, assuming that the participant had *not* adjusted for any inaccuracy in the endpoint of their outward movement, we calculated the straight-line path from the outward movement endpoint to the estimated return target location assuming that the return movement had been planned based upon the information that was available to the participant prior to movement onset and this plan had not been updated (the cyan dotted line in Figure 4b). We then re-computed the accuracy of the end point of the return movement by calculating a direction error and an amplitude error relative to this straight-line path.

Insert Figure 4 about here

Second, assuming that the participant had in fact accounted for any inaccuracy in their outward movement by updating their internal model during the trial, we calculated the estimated straight-line path from the outward movement endpoint to the actual return target location (the magenta dotted line in Figure 4b) and we re-computed the accuracy of the end point of the return movement by calculating a direction error and an amplitude error relative to this straight-line path.

Third, to determine which of these proposals best accounts for the variability in the endpoint errors of the return movements, we conducted separate stepwise multiple regression analyses with the following variables entered as predictor variables: Group (Tourette syndrome vs. CS); Estimated amplitude error (cm); and estimated direction error (degrees). In each case the order of entry of variables was fixed with Group being entered first.

When the data that assumed that forward model updating had not occurred were entered into the model the analysis revealed that Group ($t = -2.2$, $P < 0.04$) and amplitude error ($t = 4.77$, $P < 0.0001$) were significant predictors of the endpoint errors for the return movement. Furthermore, when Group was entered into the model first the amplitude error continued to be a significant predictor of additional variance ($R^2 = 0.38$, adj-$R^2 = 0.35$, $F = 12.72$, $P = 0.0001$).

When the data were entered that assumed that forward model updating had occurred, the analysis revealed that Group ($t = -2.2$, $P < 0.04$) and amplitude error ($t = 6.09$, $P < 0.0001$) were significant predictors of the endpoint errors for the return movement. When Group was entered into the model first, the amplitude error continued to be a significant predictor of additional variance ($R^2 = 0.47$, adj-$R^2 = 0.45$, $F = 18.77$, $P = 0.0001$). Relevant data are presented in Figure 5. These analyses indicate that 45% of the variance in the endpoint error of the return movement can be explained by a model that assumes that movement amplitude planning has been updated to some extent to take into account the endpoint of the outward movement. Furthermore, this model appears to provide a better fit of the data that a model which assumes that no forward model updating occurs (Figure 5).

Insert Figure 5 about here

To further investigate this issue we conducted two additional analyses. First, we calculated the difference between the updated-model error and the non-updated model error for both groups and tested whether the mean difference varied from zero. Specifically, we assumed that the mean difference will have a mean of zero where model updating do not occur, but will have some scalar value where model updating occurs to some extent. This was the case for both the Tourette syndrome ($t(20) = -5.32$, $P < 0.001$) and the CS ($t(23) = -5.67$, $P < 0.001$) groups indicated that model-updating occurred for both groups. Next we tested whether there were between-group differences using a mixed group (CS v Tourette syndrome) by error-estimate-type (updated-model error v non-updated model error) ANOVA. This ANOVA revealed a significant main effect of Group ($F(1,43) = 4.331$, $P < 0.05$) and a significant main effect of

error-estimate-type ($F(1,43) = 60.36$, $P < 0.0001$). The Group x error-estimate-type was not significant.

Discussion

In light of the proposal that, as a consequence of increased levels of sensory noise that may accompany their tics, individuals with Tourette syndrome may blur the boundary between voluntary and involuntary movements (Ganos et al., 2015). We reasoned that this would most likely lead to less precise forward models and poorer internal monitoring of movements in individuals with TS. We examined the accuracy and variability of aiming movements, measured using a hand-held robot manipulandum, within a double-step aiming task. Within the task participants were required on each trial to execute two movements in turn, each directed to a remembered target location without visual feedback. Importantly, we assumed that to perform accurately on the second (return) movement, it would first be necessary to update any forward model used to plan/control the movement, in order to take account of any mismatch between the estimated target location of the outward movement and the actual movement endpoint. We hypothesised that individuals with TS would have difficulty in successfully updating their movement plans and would therefore exhibit decreased movement accuracy and increased movement variability for the second (return) movement in the double-step reaching task. The main results of the study are summarised below.

First, individuals with Tourette syndrome were no less accurate, and no more variable, than a matched group of typically-developing individuals when executing aimed movements to the remembered location of the first target. Furthermore, reaching accuracy and reaching variability for the first (outward) movement was not associated with any clinical measure. This is an important finding in our view insofar as it demonstrates that the Tourette syndrome group are equally accurate, and no more variable, at reaching to the initial remembered target location. From this we infer that their ability to hold the initial target information in memory is no worse than that of the matched controls, and that they are no worse than controls at constructing an appropriate movement plan to reach the first target location. This finding is consistent with previous findings demonstrating that individuals with Tourette syndrome, when compared to

matched controls, are not impaired at executing fast, goal-directed, reaching (aiming) movements (Georgiou et al., 1997).

By contrast, the Tourette syndrome group were shown to be significantly less accurate than the matched control group when executing the second (return) movement and their movements were also significantly more variable than those of the controls with respect to both movement amplitude and movement direction. This finding is consistent with the proposal that sensorimotor noise is increased in individuals with Tourette syndrome due to the occurrence of tics (Ganos et al., 2015) and with our proposal that as a consequence forward model estimation, thought to be a critical component for updating movement plans, may be less effective in individuals with Tourette syndrome. This finding is also consistent with the recent demonstration that individuals with Tourette syndrome exhibit increased illusions of agency in circumstances where their actions are artificially enhanced by an external agent (Delorme et al., 2016). In that study, the propensity to report illusions of agency was associated with disease severity, however in the current study we found no significant association between tic severity and movement accuracy or variability. However, we did demonstrate that for the return movement only, both movement accuracy and movement variability were significantly predicted by Attention deficit/hyperactivity disorder symptoms (Connors score). In the case of movement accuracy this association was not independent of group. However, in the case of movement variability Attention deficit/hyperactivity disorder symptomatology remained a significant predictor of movement variability after group had been entered into the regression model. In some respects, this finding is not that surprising and is consistent with previous reports that children with Attention deficit/hyperactivity disorder are impaired, compared to matched controls, when executing reaching (aiming) movements, and that their movements are more variable (Yan and Thomas, 2002). Nonetheless, it is unclear how best to interpret this finding. The prevalence of co-occurring psychiatric conditions in individuals with a diagnosis of Tourette syndrome is extremely high (~86%); most often Attention deficit/hyperactivity disorder or Obsessive-compulsive disorder (~72%) (Hirschtritt, et al., 2015). This suggests that the co-occurrence of Attention deficit/hyperactivity disorder with Tourette syndrome should be viewed as the norm rather than an exception. Furthermore, alterations in the structure and neurochemistry of cortical-striatal-thalamic-cortical circuits have frequently been implicated in the pathophysiology of Tourette syndrome, Obsessive-compulsive disorder, and Attention deficit/hyperactivity disorder

(Felling and Singer, 2011) and this is supported by recent animal models of Tourette syndrome which indicate that localised disinhibition within striatum may be a common pathological mechanism for Tourette syndrome, Attention deficit/hyperactivity disorder and Obsessive-compulsive disorder (Worbe et al., 2009). For this reason it is currently unclear whether we should view such Tourette syndrome, Obsessive-compulsive disorder and Attention deficit/hyperactivity disorder as separate but highly co-occurring conditions, or instead view them as diverse manifestations of a common underlying pathophysiology.

To assess whether participants exhibited evidence of internal model updating in our study we compared movement errors that were estimated in two different ways. In the first, we assumed that the participant had *not* adjusted for any inaccuracy in the endpoint of their outward movement, and that the return movement was planned using the information that was available to the participant prior to movement onset. By contrast, in the second estimate, we assumed that the participant had taken into account any inaccuracy in their outward movement by updating their internal model. In each case we calculated separate direction and amplitude error estimates and used stepwise multiple regression analyses, in each case, to determine which assumption provided the best fit of the observed endpoint accuracy and variability data for the second (return) aiming movements. These analyses confirmed that in both cases, group and movement amplitude error were statistically significant, and independent, predictors of the endpoint accuracy of the second (return) movement. Importantly however, it was clear that the error estimates that assumed that the participant had taken into account any inaccuracy in their outward movement by updating their internal model provided a superior fit of the data (see Figure 5). We interpret this finding as consistent with the view that as a consequence of their tics, individuals with Tourette syndrome may experience increased levels of sensorimotor noise (Ganos et al., 2015), and that this noise is likely to lead to a reduction in the precision of the forward model estimates that are thought necessarily for the accurate planning and control of movements. Such forward model estimates are held to be particularly important for accurate judgements of agency - the (conscious) sense of authorship and control over our actions, and we note that the interpretation of our findings as indicating a loss of precision in forward model estimates, is consistent with the recent demonstration that agency judgements are significantly impaired in individuals with Tourette syndrome (Delorme et al., 2016).

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Competing interests

The authors report no competing interests.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

References

Belluscio BA, Tinaz S, Hallett M. Similarities and differences between normal urges and the urge to tic. *Cognitive Neuroscience* 2011; 2: 245-246.

Bohlhalter S, Goldfine A, Matteson S, Garraux G, Hanakawa T, Kansaku K, … Hallett M. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. *Brain: A Journal of Neurology* 2006; *129*(Pt 8): 2029–37. http://doi.org/10.1093/brain/awl050

Cavanna AE, Black KJ, Hallett M, Voon V. Neurobiology of the Premonitory Urge in Tourette's Syndrome: Pathophysiology and Treatment Implications. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2017; appi.neuropsych. http://doi.org/10.1176/appi.neuropsych.16070141

Cohena SC, Leckman JF, Bloch MH. Clinical assessment of Tourette syndrome and tic disorders. Neuroscience and Biobehavioral Reviews 2013; 37: 997–1007.

Conners CK. The Conners 3rd Edition (Conners 3). North Tonawanda: Multi-Health system, 2008.

Contreras-Vidal JL. Development of forward models for hand localization and movement control in 6- to 10-year-old children. *Human Movement Science* 2006; 23: 634–645.

Delorme C, Salvador A, Voon V, Roze E, Vidailhet M, Hartmann A, et al. Illusion of agency in patients with Gilles de la Tourette Syndrome. *Cortex* 2016; 77: 132–140.

Draper A, Jackson GM, Morgan PS, Jackson SR. Premonitory urges are associated with decreased grey matter thickness within the insula and sensorimotor cortex in young people with Tourette syndrome. *Journal of Neuropsychology* 2015; 10: 143-153.

Felling RJ. & Singer HS. Neurobiology of Tourette syndrome: current status and need for further investigation. *Journal of Neuroscience* 2011; 31: 12387–12395.

Frith CD & Done DJ. Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. *Psychol. Med*. 1989; 19: 359–363

Ganos C, Asmuss L, Bongert J, Brandt V, Münchau A, Haggard P. Volitional action as perceptual detection: Predictors of conscious intention in adolescents with tic disorders. *Cortex* 2015; 64: 47-54 .

Georgiou N, Bradshaw JL, Phillips JG, Cunnington R, Rogers MA. Functional asymmetries in the movement kinematics of patients with Tourette's syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 1997; 63: 188–195.

Hirschtritt ME, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry* 2015; 72: 325–33.

Howard IS, Ingram JN, Wolpert DM. A modular planar robotic manipulandum with endpoint torque control. *J. Neurosci. Methods* 2009; 181: 199–211.

Jackson SR, Parkinson A, Kim, SY, Schuermann, M, Eickhoff SB. On the functional anatomy of the urge- for-action. *Cognitive neuroscience* 2011; 2: 227-243.

Kim S, Stephenson MC, Morris PG, Jackson SR. tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: A 7 T magnetic resonance spectroscopy study. *NeuroImage* 2014; 99: 237-243.

Leckman JF. Tourette's syndrome. *Lancet* 2002; 360: 1577-1586.

Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic severity scale: initial testing of a clinician rated scale of tic severity. *J. Am Acad Child Adolesc Psychiatry* 1989; 28: 566–73.

Lerner A, Bagic A, Boudreau EA, Hanakawa T, Pagan F, Mari Z, Bara-Jimenez W, Aksu M, Garraux G, Simmons JM, Sato S, Murphy DL, Hallett M. Neuroimaging of neuronal circuits involved in tic generation in patients with Tourette syndrome. *Neurology* 2007; 68: 1979 –1987.

Patel N, Jankovic J, Hallett M. Sensory aspects of movement disorders. *Lancet Neurology* 2014; 13(1): 100–112.

Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, Frith CD, Frackowiak RS, Dolan RJ. A functional neuroanatomy of tics in Tourette syndrome. *Arch Gen Psychiatry* 2000; 57: 741–748.

Tinaz S, Malone P, Hallett M, Horovitz SG. Role of the right dorsal anterior insula in the urge to tic in tourette syndrome. *Movement Disorders* 2015; http://doi.org/10.1002/mds.26230

Wechsler D. Wechsler Abbreviated Scale of Intelligence (WASI) manual. *San Antonio, Psychological Corporation*, 1999.

Wolpert DM. & Ghahramani Z. Computational principles of movement neuroscience. *Nature Neuroscience* 2000; 3: 1212–1217.

Yan JH & Thomas JR. Arm movement control: Differences between children with and without attention deficit hyperactivity disorder. *Research Quarterly for Exercise and Sport* 2002; 73(1): 10–18.

Captions

Table 1 Characteristics of the TS sample. Including: age, IQ, tic severity, medication status, and any diagnosed co-morbidities.

Figure 1 A graphical representation of the task

Illustrates A. display with four possible start locations (white circles) and four different target positions (red circles). B. An example of outward and return movement endpoint distributions for a representative TS participant in native space. Outward (C) and return (D) movements were rotated so that they can be aligned along the y axis and error ellipses fitted. Note, the endpoint for individual trials are represented by the small open circles in (C) and (D) and the colour of each small circle denotes the particular target location.

Figure 2 Differences in movement accuracy and variability

Illustrates between-group differences in movement endpoint error (upper left panel), variability in movement amplitude (upper right panel), variability in movement direction (bottom left panel), and area of the movement endpoint error ellipse (bottom right panel). Reaching to the first (visual) target are represented by open squares whereas return movements are represented by open circles. Error bars are the standard error of the mean.

Figure 3 Movement accuracy/variability and Attention deficit/hyperactivity disorder symptoms

Illustrates the relationship between movement accuracy (upper panels) / movement variability (lower panels) and Attention deficit/hyperactivity disorder symptoms as measured by the Connors t-score. The left hand panels show data for the outward reaching movement and the right hand panels for the return movement. Black circle symbols represent scores for the typically-developing control group and blue square symbols scores for the TS group.

Figure 4 Estimating forward model updating

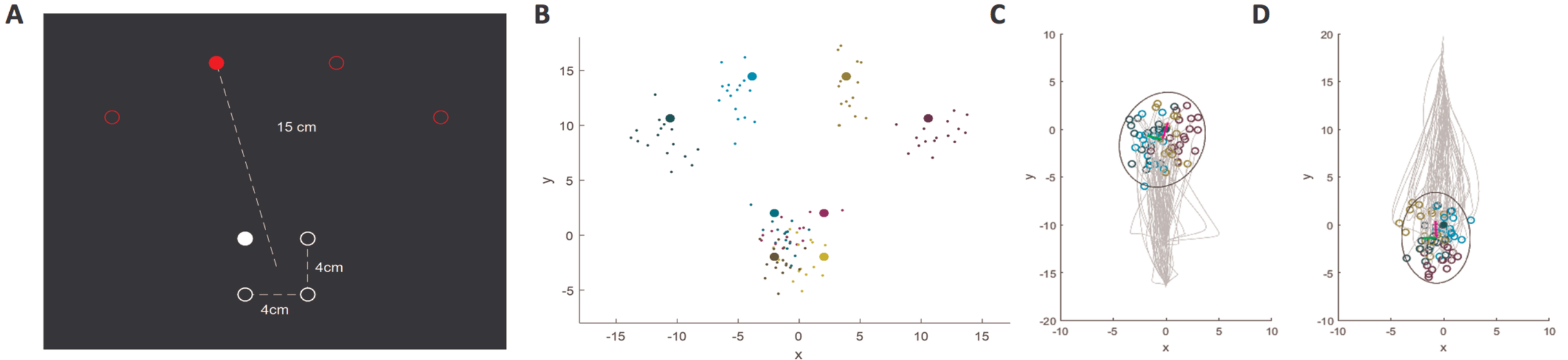
Illustrates how direction and amplitude errors were estimated based upon the assumption that an internal model used to plan and control movements was or was not updated (see text for further explanation). **A**. The paths shown (blue and red lines) illustrate representative data from a single trial. The square symbols indicate the home (unfilled) and target (filled) locations for that trial respectively and the broken black line indicates a straight line between the home location and the location of the outward target. The blue line represents the hand path from the home position toward the first target location and the blue circle indicates the movement endpoint. The red line represents the hand path of the return-to-home movement and the red circle indicates the endpoint of the return movement. **B**. Illustrates how amplitude and direction errors may be calculated. The cyan line illustrates the movement path that might be planned if the error in the end point of reach-to-target movement (blue path) was not taken into account and the original movement plan was executed. The magenta line illustrates the movement path that might be planned if the error in the end point of reach-to-target movement (blue path) was accounted for

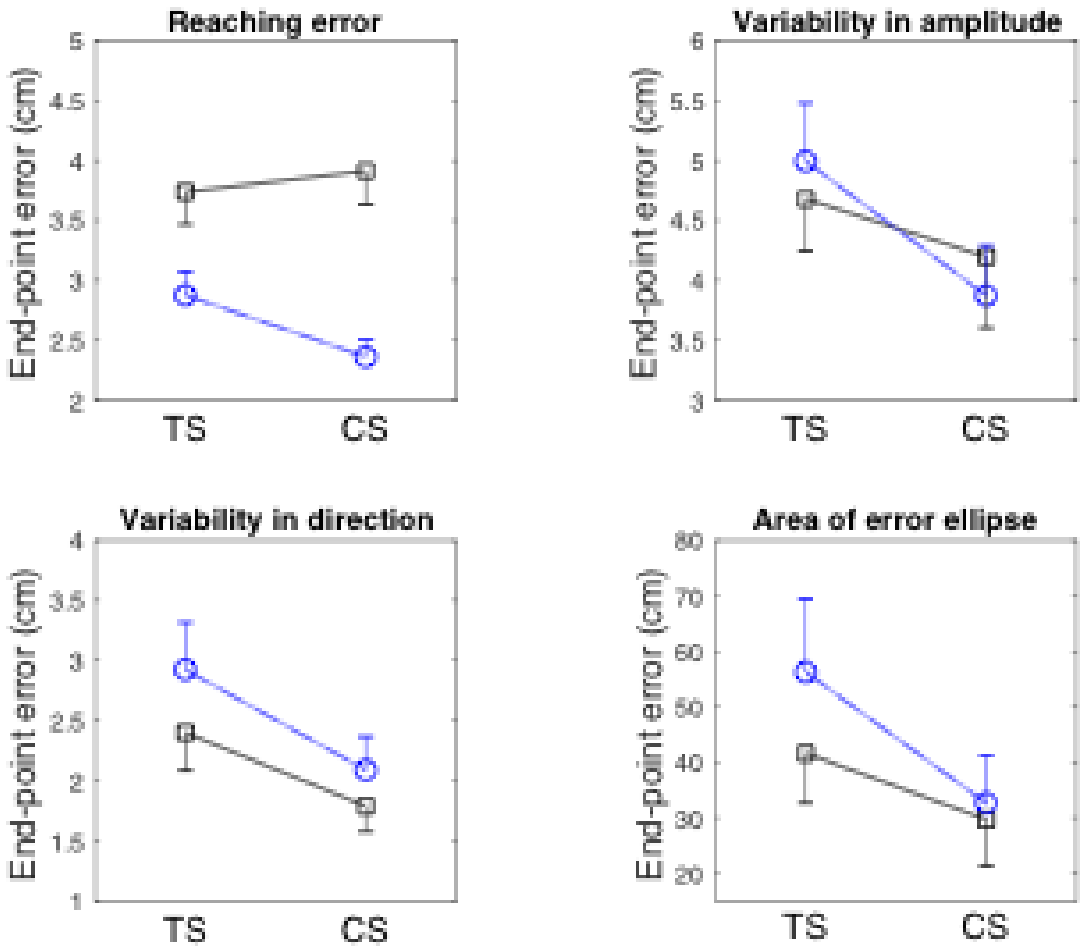
by any forward model controller and the return movement plan was changed accordingly. Circles indicate the end point of each movement.

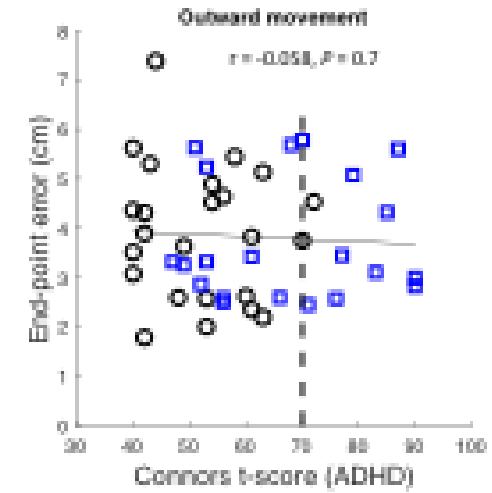
Figure 5 Associating movement accuracy/variability with estimates of forward model updating

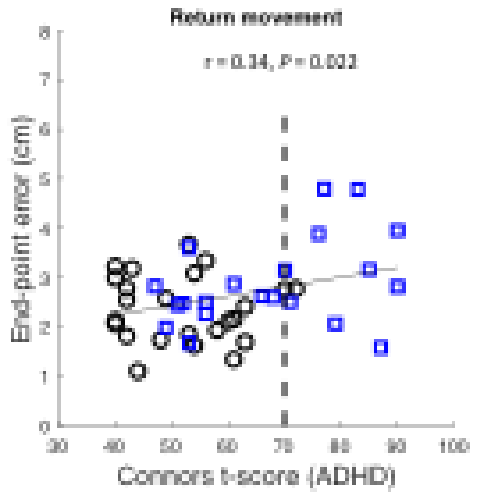
Scatter plot illustrating the association between observed movement endpoint errors (Euclidian distance), sorted according to increasing magnitude (x-axis), and estimated movement amplitude errors (y-axis). The left panel shows estimated amplitude errors that assume that forward models were updated to take into account the endpoint of the outward movement (See text for clarification) and the right panel shows estimated amplitude errors that assume that forward models were not updated. Individuals with TS are represented by open blue circles and matched controls by open black square symbols.

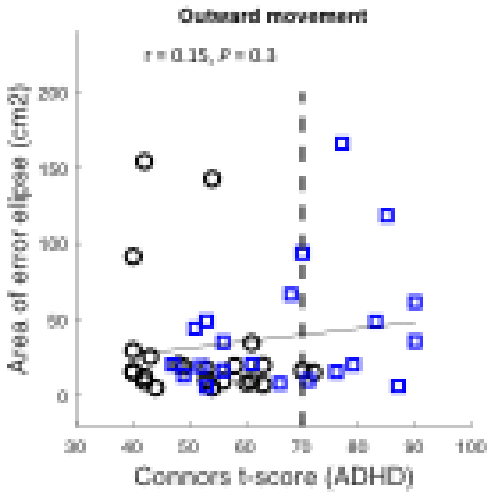
							WASI	Connors
ID	***Age in years***	**YGTSS Motor score**	**YGTSS Phonic score**	**YGTSS Global score**	**Medication**	**Comorbidity (diagnosed)**	**IQ score**	**t-score**
TS01	*11.2*	17	17	54			118	90
TS02	*15.7*	15	8	53	Sertraline	OCD, Anxiety	101	66
TS03	*12.2*	16	22	68	Sertraline (125mg), Risperidone (0.25mg) , Atomoxetine (50mg)	ADHD, OCD	118	83
TS04	*13.1*	19	18	67			92	79
TS05	*11.4*	21	14	45	Sertraline (75mg)		129	61
TS06	*11.6*	18	17	55	Clonidine (50mg)		120	90
TS07	*11.6*	17	8	35		Aspergers	121	53
TS08	*13.8*	17	10	47	Melatonin (for sleep)		96	70
TS09	*13.8*	15	0	25			102	47
TS10	*9.3*	14	0	24			106	52
TS11	*14.2*	16	5	26	Clonidine (125mg, 4* a day)		120	56
TS12	*12.3*	13	7	40	Elvanse (30mg)	ADHD	96	76
TS13	*10.7*	12	10	32			108	71
TS14	*15.5*	8	5	18			133	49
TS15	*13.0*	10	7	27	Clonidine (175mg)		99	56
TS16	*11.5*	7	8	25			126	53
TS17	*14.8*	14	9	53	Aripiprazole	ASD	97	68
TS18	*12.8*	22	22	84		ADHD	100	85
TS19	*9.5*	10	0	20			124	51
TS20	*10.9*	9	10	39	Clonidine (10mg)		88	77
TS21	*14.1*	15	7	52	Sertraline (75mg), Guanfacine	OCD, Anxiety	111	87
Mean	**12.52**	**14.52**	**9.71**	**42.33**			**109.76**	**67.62**
Std	**1.80**	**4.08**	**6.54**	**17.83**			**13.32**	**14.59**

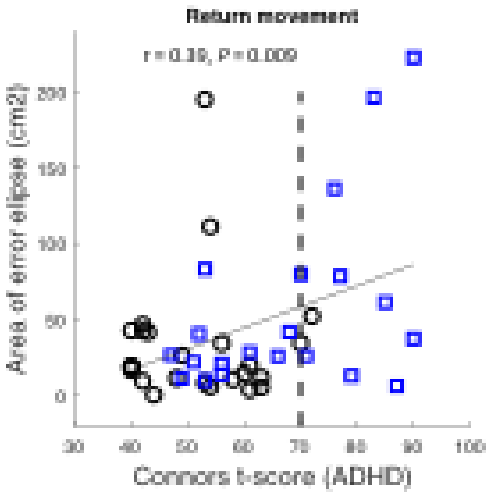

A
15 cm
4cm
4cm
B
C
D
x
y


Reaching error
End-point error (cm)
5
4.5
4
3.5
3
2.5
2
TS
CS
Variability in amplitude
End-point error (cm)
6
5.5
5
4.5
4
3.5
3
TS
CS
Variability in direction
End-point error (cm)
4
3.5
3
2.5
2
1.5
1
TS
CS
Area of error ellipse
End-point error (cm)
80
70
60
50
40
30
20
TS
CS

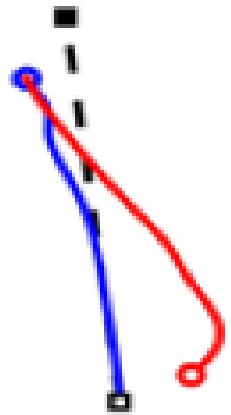

Outward movement
r = -0.058, P = 0.7
End-point error (cm)
Connors t-score (ADHD)


Return movement
r = 0.34, P = 0.022
End-point error (cm)
Connors t-score (ADHD)

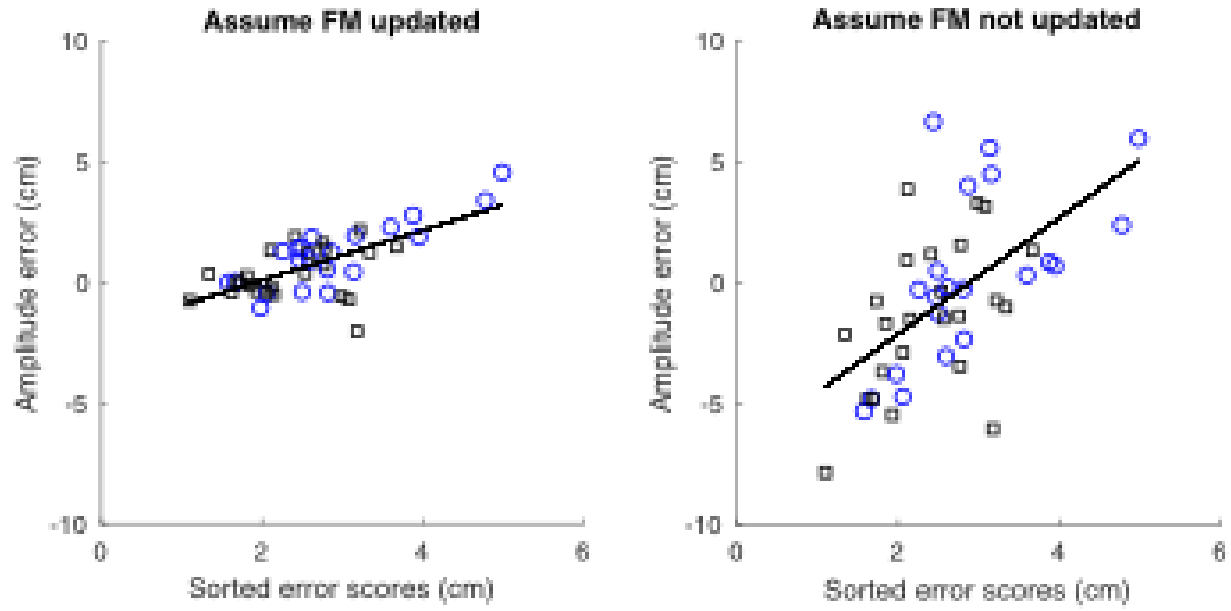

Outward movement
r = 0.15, P = 0.3
Area of error ellipse (cm2)
Connors t-score (ADHD)


Return movement
r = 0.39, P = 0.009
Area of error ellipse (cm2)
Connors t-score (ADHD)

A



B


Assume FM updated
Amplitude error (cm)
Sorted error scores (cm)
10
5
0
-5
-10
0
2
4
6
Assume FM not updated
Amplitude error (cm)
Sorted error scores (cm)
10
5
0
-5
-10
0
2
4
6