RESEARCH ARTICLE

Rapid Compensation for Noisy Voluntary Movements in Adults with Primary Tic Disorders

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ABSTRACT: Background: It has been proposed that tics and premonitory urges in primary tic disorders (PTD), like Tourette syndrome, are a manifestation of sensorimotor noise. However, patients with tics show no obvious movement imprecision in everyday life. One reason could be that patients have strategies to compensate for noise that disrupts performance (ie, noise that is task-relevant).

Objectives: Our goal was to unmask effects of elevated sensorimotor noise on the variability of voluntary movements in patients with PTD.

Methods: We tested 30 adult patients with PTD (23 male) and 30 matched controls in a reaching task designed to unmask latent noise. Subjects reached to targets whose shape allowed for variability either in movement direction or extent. This enabled us to decompose variability into task-relevant versus less task-relevant components, where the latter should be less affected by compensatory strategies than the former. In alternating blocks, the task-relevant target dimension switched, allowing us to explore the temporal dynamics with which participants adjusted movement variability to changes in task demands.

Results: Both groups accurately reached to targets, and adjusted movement precision based on target shape. However, when task-relevant dimensions of the target changed, patients initially produced movements that were more variable than controls, before regaining precision after several reaches. This effect persisted across repeated changes in the task-relevant dimension across the experiment, and therefore did not reflect an effect of novelty, or differences in learning.

Conclusions: Our results suggest that patients with PTD generate noisier voluntary movements compared with controls, but rapidly compensate according to current task demands. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: primary tic disorders; Tourette syndrome; sensorimotor integration; sensorimotor noise; movement variability

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Tics in primary tic disorders (PTD), such as Tourette syndrome (TS), are repetitive, stereotypic movements and vocalizations that occur unrelated to their context.[1] There is strong interest in the idea that neural noise in the sensorimotor system may be elevated in PTD, and may contribute to the generation of tics.[2-5] In healthy individuals, random subthreshold fluctuations in neuronal activity play an important role in voluntary action, specifically for the decision (when) to move.[6] Elevated noise in tic patients could thus increase the likelihood that subthreshold activity in the sensorimotor system results in overt movement.[2] Higher noise levels may also impair the ability to discriminate intention from noise, and non-voluntary from voluntary movement.[4] In line with a "neural noise account", electroencephalography has revealed increased 1/f noise in patients with tics.[3]

Elevated noise should increase voluntary movement variability.[2,7] However, research on motor performance in patients has provided inconsistent findings, ranging from low[8] to even above-average performance.[9] One reason could be that patients employ compensatory strategies to mitigate the effects of elevated motor noise. Compensatory strategies aid in tic control,[10-12] and influence movement execution, or trial-by-trial learning,[13-15] in patients with PTD. Tics tend to decrease in frequency during task engagement,[16] possibly because task engagement involves strategies that suppress noise and, thus, tics.

Voluntary movements are characterized by a high degree of redundancy – the same goal (eg, reaching out to a door handle) can be achieved with many different motor commands (eg, resulting in many variations of hand position on the handle).[17] We hypothesized that elevated neural noise in PTD may not manifest as enhanced movement variability in tasks that constrain redundancy, when high precision is required and compensatory strategies to reduce noise are encouraged.[5] Instead, elevated noise may only surface as voluntary movement variability when a task includes redundant (ie, less task-relevant) movement dimensions.[18] For example, if compensation takes time, elevated noise may temporarily surface as movement variability when a previously task-irrelevant (redundant) spatial dimension becomes newly task-relevant.

To quantify unmitigated motor noise, we asked patients with PTD and controls to reach to partially redundant visual targets, shaped either as an arc (allowing for variability in movement direction) or as a radial line (allowing for variability in movement extent). Target shape alternated between blocks, allowing us to investigate movement variability when a previously less task-relevant dimension became newly task-relevant.[18,19] To limit compensation for movement variability, we minimized sensory feedback and emphasized fast movements. We expected higher movement variability in patients compared with controls when compensation was less likely, or (still) incomplete, ie, either in the redundant dimension, or, transiently at the beginning of a new block, in the dimension that had just become task-relevant.

Methods

Participants

A total of 30 adult patients with a PTD were recruited from the outpatient clinic of the Department of Neurology at Charité University Medicine, Berlin. A total of 30 age-matched healthy participants were included as a control sample. All participants gave their written informed consent prior to the study, which was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee (Charité University Medicine Berlin, Germany, EA2/082/18). Two participants (one patient and one control) were excluded because they produced movements that fell below a predefined velocity threshold (see later) in >20% of trials.

Included patients had a mean age of 28.5 years (standard deviation [SD}: 7.8 years; 23 were male). Included matched controls had a mean age of 28.6 years (SD: 9.3 years; 21 were male). Diagnosis of PTD was confirmed in a semi-structured interview and clinical examination (author C.G.) based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria.[20] Nine patients (31%) were diagnosed with a chronic motor tic disorder and 20 (69%) had TS. Table 1 provides further clinical characteristics, compared between groups using independent-samples *t*-tests (for continuous variables), and chi-square test (for categorical variables; SPSS, IBM).

Apparatus

Participants sat at at a three-leveled experimental table (Fig. 1 and Video 1). A graphics tablet (Intuos 4XL; Wacom, Kazo, Japan; 5080 lines per inch, sampled at 200 Hz, active area of 48.8 × 30.5 cm) was placed on the lowest level. The uppermost level held a downward-facing LCD monitor displaying visual stimuli (60 Hz) which participants saw in a mirror placed at the middle level, facing upwards. The distances between the monitor and the mirror, and between the mirror and the tablet, were identical, creating the illusion that visual stimuli appeared in the same plane as the tablet. The task used Presentation (Neurobehavioral Systems).

Experimental Task

We examined variability in reaching movements in a task that dissociates highly task-relevant and less task-relevant movement dimensions while minimizing compensatory strategies that reduce motor noise. Participants performed rapid center-out reaching

TABLE 1 *Clinical characteristics*

Characteristic	Primary tic disorders	Controls	*P*-value
Gender, male (n (%))	23 (79)	21 (70)	0.539
Age, years (mean ± SD)	28.5 ± 7.8	28.6 ± 9.3	0.952
Age at first manifestation of tics, years (mean ± SD)	7.7 ± 4.2	–	-
Tics of dominant arm/shoulder (n (%))	21 (72)	–	–
YGTSS (mean ± SD)	48.4 ± 20.5	–	–
TTS (mean ± SD)	22.9 ± 8.8	–	–
PUTS (mean ± SD)	22.8 ± 6.2	–	–
GTS-QoL (±SD)	25.6 ± 18.6	–	–
Antipsychotic medication (n (%))	8 (28)	0	–
Comorbid diagnoses (n (%))	16 (55)	0	–
ADHD (n (%))	11 (38)	0	–
OCD (n (%))	11 (38)	0	–
Depression (n (%))	7 (24)	0	–
YBOCS (mean ± SD)	14.7 ± 9.8	5.3 ± 6.7	0.0001
CAARS (mean ± SD)	13.8 ± 7.5	7.3 ± 4.5*	0.0004
BDI-II (mean ± SD)	10.2 ± 6.6	3.9 ± 4.5*	0.0001
Years of education (mean ± SD)	15.9 ± 3.5	17.8 ± 3.9	0.059
Left-handedness (n (%))[21]	0 (0)	2 (7)*	0.136

Abbreviations: SD, standard deviation; YGTSS, Yale Global Tic Severity Scale[22]; TTS, total tic score; PUTS, Premonitory Urge for Tics Scale[23]; GTS-QoL, Gilles de la Tourette Syndrome–Quality of Life Scale[24]; ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder; YBOCS, Yale–Brown Obsessive Compulsive Scale[25]; CAARS, Conners' Adult ADHD Rating Scale[26]; BDI-II, Beck's Depression Inventory[27].
*Data from three controls missing (questionnaires not returned).

movements. Visual targets were either straight radially oriented lines, or lines that formed circumferential segments of a circle, both centered on the hand position (Fig. 1, right panel; Videos 2 and 3). This arrangement effectively decomposes reaching control into a task-relevant and less task-relevant dimension: when the target is a radially oriented line, any variability in movement direction must be controlled, while variability in movement extent is less problematic. When the target is arc-shaped, the reverse is true. Thus, we could distinguish between motor noise that required compensation, and motor noise that did not.

Importantly, all targets of a given block (60 trials) had the identical shape (radial lines or arcs), while target shape alternated between blocks (six blocks in total). Therefore, the highly task-relevant dimension changed from block to block. This allowed us to examine how subjects adjusted movement variability to the current target shape at the beginning of each block, when compensation for noise may not yet take effect.

To minimize trial-to-trial motor corrections, and adjustments to ongoing movements, we removed visual feedback of hand position during the reach. In addition, the task emphasized movement speed, further minimizing adjustment of ongoing movements.[28] To prevent stereotypical reaching, targets appeared in three possible locations, straight ahead, 30° to the right, or 30° to the left.

We report details of trial timing, visual stimulation, and training, in the Supplementary Methods S1.

Data Analysis

Data were analyzed using custom-written scripts in MATLAB (The MathWorks Inc.). Criteria for trial exclusion are reported in the Supplementary Methods, and excluded trials are displayed in Fig. S1.

We computed movement variability in direction and extent, movement initiation time, peak velocity, and movement accuracy. Movement initiation time was defined as the time interval between target presentation and the time at which the stylus left the home position. Peak velocity was computed from the temporal derivative of stylus position after smoothing with a second-order Savitzky–Golay filter (frame length of 31 samples,

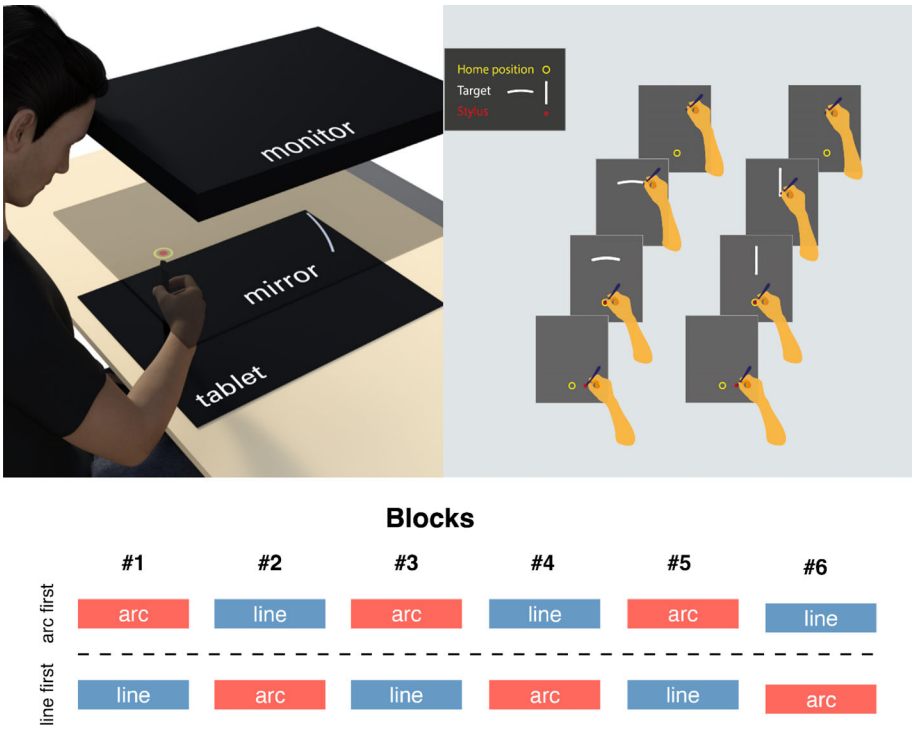

FIG. 1. Apparatus and schematic of the experimental task. Left upper panel: set-up of three-leveled experimental table, with a graphics tablet at the lowest level, an upward facing mirror at the middle level (here depicted as semi-transparent so that the lower level can be seen), and a monitor facing downward at the upper level. Participants sat in front of the table, moved a stylus with their dominant hand across the tablet in three directions in a center-out reaching task, and looked at the mirror's reflection of visual stimuli presented by the monitor. They could not see their hand because it was hidden by the second level of the experimental table, and the arms and shoulders were covered by a cape worn around the neck (not shown) attached to the second level of the table. Right upper panel: schematic of events during individual trials. For illustration purposes, the hand and arm are shown on top of the visual stimuli. During the actual experiment, participants could not see their arm and hand. Participants first moved a red dot to a home position (a yellow ring). A two-dimensional target was presented, which could be an arc (left) or a radial line (right), shown straight ahead (as illustrated here), or 30° to the right or left. The task was to move the stylus to any point on the target. Arc-shaped targets therefore allowed for more variable movement direction than movement extent, and vice versa for radially oriented line targets. As the stylus moved out of the home position, the red dot and the home position were extinguished, reappearing shortly after movement offset to guide participants back to the home position. Lower panel: blocks of arc-shaped targets alternated with blocks of radially oriented line-shaped targets. The order (starting with arc-shaped targets or radially oriented line-shaped targets) was counterbalanced across subjects within each group. [Color figure can be viewed at wileyonlinelibrary.com]

corresponding to 155 ms[29]). Movement accuracy was computed as the shortest Euclidean distance from movement endpoint to the nearest point on the target (always positive).

Movement direction was computed as the angle between endpoint and home position. For separate analyses, we re-computed movement direction as the angle between stylus location at the time of maximum velocity and the home position. Movement extent was the Euclidean distance between endpoint and home position.

Movement variability was computed as the variance of endpoints in each dimension, demeaned for each block and target location. For separate analyses, blocks were divided into consecutive bins (20 trials/bin, ie, three bins). To ensure robustness of these analyses, we alternatively split blocks into bins of 12 trials/bin, 15 trials/bin, or 30 trials/bin (corresponding to fifths, quarters, and a median split). Bin-wise movement variability was computed after demeaning endpoints per block, target location, and bin.

Video 1. Experimental setup. The video illustrates the three levels of the experimental table.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.29775

Statistical Analysis

We conducted mixed-effects repeated-measures ANOVAs with Greenhouse–Geisser correction (JASP[30]). Pearson's correlation tested for a relation between task performance and clinical symptoms/comorbidities.

Video 2. Experimental task – example trials with radial lines as targets. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.29775

Video 3. Experimental task – example trials with arc-shaped targets. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.29775

Results

Intact Movement Accuracy in Patients

Across the experimental task, patients produced movements that showed accuracy similar to control levels. Figure 2A displays 68% confidence ellipses of movement endpoints for controls (left column) and patients (right column), separately for line-shaped targets (upper row) and arc-shaped targets (lower row). There was no difference between PTD and control subjects in a mixed-effects repeated-measures ANOVA with movement accuracy as dependent variable and target shape as a second factor (main effect of group: $F_{(1,56)} = 0.3$, $P = 0.6$, $\eta^2 = 0.003$, $\eta_p{}^2 = 0.005$; Fig. 2B). Both groups displayed a slight overreach, which is consistent with earlier observations.[31] Both PTD patients and controls performed significantly more accurately in blocks with radial lines ($F_{(1,56)} = 30.3$, $P < 0.001$, $\eta^2 = 0.13$, $\eta_p{}^2 = 0.35$). Additional analyses of movement initiation time revealed no group differences in initiation time, while movement speed was significantly higher in patients compared with controls (Fig. S2).

Movement Variability in Highly Task-Relevant and Less Task-Relevant Dimensions

We then examined how target shape affected movement variability in the two groups. Both groups adjusted variability in movement direction according to target shape (arc vs. radial line; $F_{(1,56)} = 65.2$, $P = 0.002$, $\eta^2 = 0.038$, $\eta_p{}^2 = 0.166$; Fig. 3A). Both groups equally limited variability in movement direction when moving to radial line-shaped targets compared with arc-shaped targets (Fig. 3B, left), with no differences across groups ($F_{(1,56)} = 0.02$, $P = 0.9$, $\eta^2 < 0.001$, $\eta_p{}^2 < 0.001$), and no significant group × target shape interaction ($F_{(1,56)} = 2.4$, $P = 0.13$, $\eta^2 = 0.008$, $\eta_p{}^2 = 0.041$). Variability in movement direction was therefore sensitive to our experimental manipulation

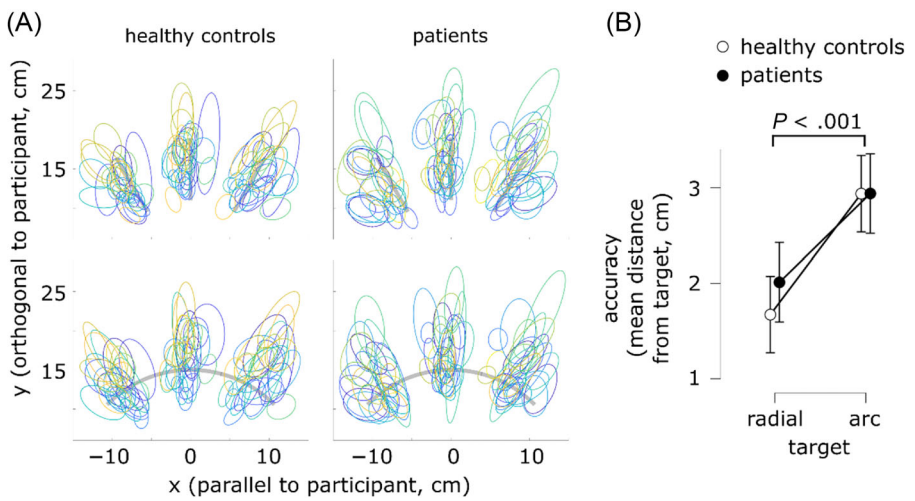

FIG. 2. Movement endpoint spread around targets (A), and accuracy (B). (A) 68% (~one standard deviation) confidence ellipses for each control participant (left column) and each patient (right column), both for radial line-shaped targets (upper row) and arc-shaped targets (lower row) in three different locations. Each color represents one individual. Targets are shown as semi-transparent grey rectangles (radial line-shaped targets, upper row) and arcs (arc-shaped targets, lower row). (B) Accuracy of movement endpoints for each group and target shape, collapsed across target locations. Accuracy was computed as the mean distance between movement endpoints and the target. Error bars represent 95% confidence intervals. [Color figure can be viewed at wileyonlinelibrary.com]

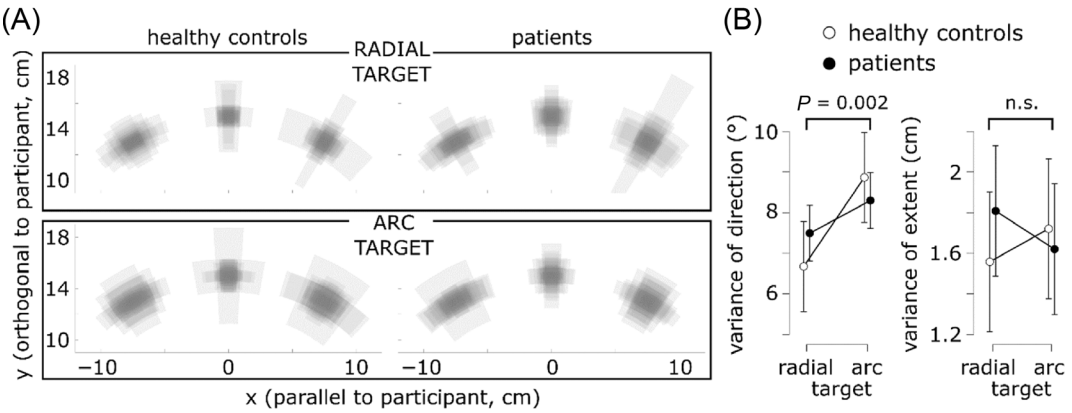

FIG. 3. Spread of movement endpoint direction and extent as a function of group and target shape. (A) Semi-transparent arcs represent variance in movement direction (measured at movement endpoint; indicated by the "width" of the arc, ie, the angle subtended by an arc relative to the home position), and variance in movement extent (indicated by the "height" of the arc, ie, its thickness in the radial direction, relative to the home position). Variance is shown separately for each individual (one semi-transparent arc corresponds to one individual) in the control group (left column) and patient group (right column), and separately for radial line-shaped targets (upper row) and arc-shaped targets (lower row). Note that movement direction is more variable for arc-shaped targets than for radial line-shaped targets in both groups. Note also that panel A does not depict movement endpoints, but merely their spread (compare with Fig. 2A). (B), Variance in movement direction (left) and extent (right) as a function of group and target shape. Error bars represent 95% confidence intervals.

of target shape across groups, and, thus, under experimental control. Conversely, neither of the two groups adjusted movement extent (in cm) to target shape ($F_{(1,56)} = 0.06$, $P = 0.9$, $\eta^2 < 0.001$, $\eta_p{}^2 < 0.001$; Fig. 3B, right; additional Bayesian analyses reported in Supplementary Results). This indicates that our manipulation of target shape yielded no, or only insufficient, experimental control over variability in movement extent. For the following analyses we, therefore, focus on variability in movement direction.

Unmasking Elevated Movement Variability in PTD

The block-wise change of target shapes in our experiment allowed us to explore transient group differences in movement variability at the beginning of each block. To this end, we divided each block into three bins of 20 consecutive trials each. We then computed a group × target shape × bin (first, second, third bin) mixed-effects repeated-measures ANOVA with variance of movement direction at movement endpoint as dependent variable. This revealed a significant main effect of target shape ($F_{(1,56)} = 26.3$, $P < 0.001$, $\eta^2 = 0.069$, $\eta_p{}^2 = 0.319$), and a significant main effect of bin ($F_{(2,112)} = 8.4$, $P < 0.001$, $\eta^2 = 0.014$, $\eta_p{}^2 = 0.13$), but no significant main effect of group (Fig. 4A). Importantly, there was a significant three-way interaction between target shape, group, and bin ($F_{(2,112)} = 9.8$, $P = 0.03$, $\eta^2 = 0.005$, $\eta_p{}^2 = 0.061$; all two-way interactions were not significant).

We examined this triple interaction further in two separate group × bin ANOVAs for each target shape. We found a significant group × bin interaction only for radial line-shaped targets, not for arc-shaped targets (radial line-shaped targets: $F_{(1.66,93.1)} = 13.3$, $P = 0.005$, $\eta^2 = 0.018$, $\eta_p{}^2 = 0.098$, Greenhouse–Geisser correction; arc-shaped targets: $F_{(2,112)} = 0.3$, $P = 0.7$, $\eta^2 = 0.001$, $\eta_p{}^2 = 0.006$). Follow-up *t*-tests to the significant two-way interaction observed for radial targets, comparing variance in movement direction between groups for each of the three bins, revealed that movement direction was significantly more variable in the first bin for patients, compared with controls ($P = 0.04$, false discovery rate [FDR]-corrected). Follow-up linear regression analyses, testing for a linear trend across bins within each group, additionally revealed a significant decrease in movement direction variance from the first to the third bin for patients ($P < 0.001$, FDR-corrected), but not for controls ($P = 0.45$). To ensure robustness of results, different criteria for binning data within each block (quarters, fifths, or halves) were applied in separate control analyses. These analyses consistently showed elevated variance in movement direction in PTD in the first bin (Supplementary Results).

Similar results were obtained when examining variance in movement direction at the point of maximum velocity (heading angle). This indicates that the patterns of variability that we observed were present early in the movement, and not only at the end of the reach, and may thus reflect variability in movement planning, rather than execution (Fig. 4B). Specifically, we found a significant group × bin interaction effect on variance of movement direction (measured at maximum velocity, in degrees) in blocks with radial line-shaped targets ($F_{(2,112)} = 4.4$, $P = 0.02$, $\eta^2 = 0.019$, $\eta_p{}^2 = 0.072$). Follow-up *t*-tests to this two-way interaction, comparing variance in movement direction at maximum velocity between groups for each of the three bins, revealed that movement direction was significantly more variable in the first bin for patients, compared with controls

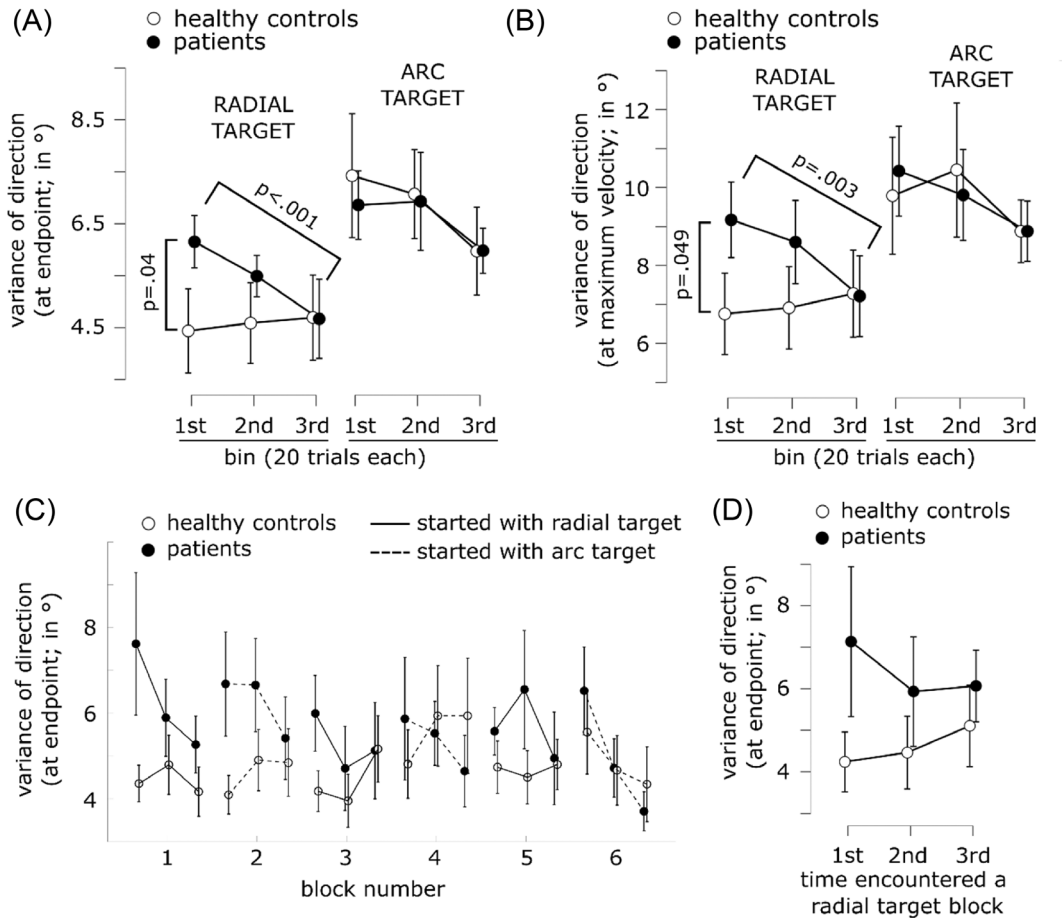

FIG. 4. Variability of movement direction as a function of group, target shape, and trial bin. For each block (60 trials each), data were binned into thirds (20 trials per bin) to examine transient group differences in movement variability at the beginning of a block. Variability (variance) in movement direction, measured at movement endpoint (A) or at the point of maximum velocity (B; heading direction) is shown as a function of group, target shape, and bin. Error bars in (A) and (B) represent 95% confidence intervals. *P*-values are obtained via post-hoc *t*-tests and are FDR-corrected. (C) Variability (variance) in movement direction at movement endpoints in blocks with radial line-shaped targets as a function of group (black markers, patients; white markers, controls), block (values on the x-axis) and bin (consecutive datapoints for each block, from left (first third) to right (last third)). The order of blocks (arc-shaped target blocks, radial line-shaped target blocks) was counterbalanced across individuals (separately for each group). Data shown in (C) represent movement direction variability in blocks with radial line-shaped targets only (for which a group × target shape interaction was observed, see (A) and (B)). Therefore, data for even blocks come from different participants compared with data from odd blocks. Panel (C) distinguishes between these counterbalancing groups by solid versus dashed lines. Error bars in (C) represent standard errors of the mean. Panel (D) shows variance of movement direction from the first bin of trials from the radial target blocks, merged across the two counterbalancing groups based on the number of times a radial line-shaped target block had been encountered (x-axis). For example, the first datapoint ('1st' on x-axis) represents data from the first bin of trials in the first block for the group indicated by solid lines in (C), as well as data from the first bin of trials in the second block for the group indicated by dashed lines in (C). Error bars represent 95% confidence intervals.

($P = 0.049$, FDR-corrected). Linear regression analyses, testing for a trend across bins within each group, additionally revealed a significant decrease in movement direction variance from the first to the third bin for patients ($P = 0.003$, FDR-corrected), but not for controls ($P = 0.3$). Thus, even though variance of movement direction (and total endpoint spread, ie, variance computed across both spatial dimensions) across the entire experiment did not differ between patients and controls, we did observe initial transiently elevated variance in movement direction in patients, compared with controls, irrespective of the binning procedure, and irrespective of how movement direction was computed (see Supplementary Results).

We next examined whether the difference in variability of movement direction between patients and controls in the first bin of trials existed only at the onset of the experiment, and diminished across blocks, or whether the difference persisted. We therefore conducted a group (patients, controls) × encounter (first, second, third) mixed-effects repeated-measures ANOVA, with variance in movement direction in the first bin of trials, measured at movement endpoint, as dependent variable. Here, "encounter" represents the number of times a block with radial line-shaped targets had been encountered so far. Given that the order of blocks (radial line-shaped targets, arc-shaped targets) was counterbalanced across

individuals within each group (patients, controls), data were collapsed across counterbalancing groups (Fig. 4C).

We observed a significant main effect of group ($F_{(1,56)} = 6$, $P = 0.02$, $\eta^2 = 0.055$, $\eta_p{}^2 = 0.097$), but no significant main effect of encounter ($F_{(1.65,92.6)} = 0.4$, $P = 0.6$, $\eta^2 = 0.003$, $\eta_p{}^2 = 0.008$, Greenhouse–Geisser correction). Importantly, the group × encounter interaction was not significant ($F_{(1.65,92.6)} = 1.6$, $P = 0.2$, $\eta^2 = 0.012$, $\eta_p{}^2 = 0.028$, Greenhouse–Geisser correction). A Bayesian ANOVA provided evidence in favor of the hypothesis that the group (patients vs. controls) difference in variance of movement direction in the first bin of trials did not change across the experiment ($BF_{excl} = 13.8$ for the factor "encounter" and $BF_{excl} = 12$ for the interaction between "group" and "encounter"; Fig. 4D).

We report movement initiation time, peak velocity, and movement accuracy across bins in the Supplementary Results (including Fig. S3).

Correlation analyses between either variance in movement direction in the first bin, or the difference in variance in movement direction between the first and third bin, and total tic score (TTS), Yale–Brown Obsessive Compulsive Scale (YBOCS) (the latter across controls and patients), and Conners' Adult ADHD Rating Scale (CAARS) did not yield any significant associations (all $P > 0.1$). Comparing subgroups of patients with attention deficit hyperactivity disorder (ADHD) (11 patients) versus without ADHD (18 patients), we found evidence against the idea that the observed variability in movement direction at the beginning of radial line blocks is driven by ADHD comorbidity (Supplementary Results & Fig. S4).

Discussion

We provide evidence that the variability of voluntary movements is elevated in patients with PTD, compared with matched controls, consistent with recent proposals of increased sensorimotor noise in PTD.[2] However, this difference is confined to early stages of skilled motor performance, which may indicate that patients implicitly employ goal-directed compensation strategies to ensure sufficient movement precision.[32] These findings are concordant with largely unimpaired motor functioning of PTD patients in everyday life, and the meta-analysis of performance in motor skill tasks.[9]

Our experiment used targets that created strong control demands on movement direction but not movement amplitude, or vice versa. In line with the idea that patients with primary tics compensate for elevated noise, and that compensation takes time, we observed initial transiently elevated variability in movement direction when direction had just become task-relevant, followed by a progressive increase in precision to levels of control participants. This may hint towards specific compensatory mechanisms during different states of motor preparation and execution in people with tics. Conversely, we did not observe a general increase in "task-irrelevant" movement variability in PTD. There may be several reasons for this. Our manipulation of target shape did not provide tight experimental control over how individuals interpreted the redundant spatial dimension of targets. Participants were asked to stop their reach underneath any part of a given target, but not beyond any of its limits, so that the less task-relevant dimension was never fully task-irrelevant. We do not know how much "risk" participants would accept in allowing movement variability to accumulate in the less task-relevant dimension. As a result, we believe that the influence of such uncontrolled, "random" effects may have masked group differences in task-irrelevant movement variability in our study.

This contrasts with the unambiguous relevance to goal achievement of the highly task-relevant spatial dimension, for which we observe the expected effects. In blocks with radial line-shaped targets, for which movement direction variability was paramount, we saw a significant initial elevation in movement variability followed by a significant improvement in precision in patients. This compensation explains why we observed no general group difference in variability when computed across the entire experiment. This effect did not seem to reflect general novelty or learning processes, because we found no evidence that the initial variability effect in the PTD group reduced over the course of the experiment.

Several factors could contribute to elevated noise in patients with PTD, potentially involving attention. Inattention often leads to increased variability and decreased precision in task performance. ADHD is a common comorbidity in patients with PTD,[33] including in our cohort. While we found no correlation between task performance and ADHD symptom severity measured by CAARS in our study, patients did have significantly higher scores (patients 13.8 ± 7.5 vs. controls 7.3 ± 4.5; P-value $= 0.0004$). However, our results provide evidence against a major influence of ADHD on movement variability in our task (Fig. S4). Attention to tasks has been shown to reduce tics, while attention to tics enhances tic frequency.[16] Inattention would typically result in both imprecision and inaccuracy, yet movement accuracy was not significantly different between groups. Instead, in the first bin of trials, patients exhibited higher movement variability (Fig. 4A) but also higher accuracy compared with later bins (Fig. S3). Finally, it seems counterintuitive to assume inattention at the onset of a new block, after a break, followed by increase in attention throughout the block – it is more commonly assumed that sustained attention decays over time, which is at odds with the pattern of accuracy we observe across the block (Fig. S3). However, more studies are needed to

definitely exclude the possibility that ADHD drives effects on movement variability in PTD, for example, by including an additional control group with ADHD. While Fig. S4 provides an encouraging starting point for such studies, our study is likely underpowered for detecting subgroup effects (11 patients with ADHD).

Overall, the initial transiently elevated movement variability in patients with PTD is more likely attributed to an increase in stochastic fluctuations in motor planning processes, independent of any attention deficits. The lack of association between variability of voluntary motor output and tic severity suggests that variability may serve as a trait behavioral marker rather than a direct consequence of tic severity.

Our study shows that in adults with PTD elevated sensorimotor noise may be unmasked at the offset of motor execution but is progressively diminished with task repetition. On one account, the reduction of variability over time may indicate a transition from a default tic state to a voluntary action state.[12,34] This transition, observed even in the absence of sensory feedback, suggests that patients can modulate sensorimotor noise levels by engaging in voluntary tasks. However, block-wise changes in task demands, or short breaks between blocks, may transiently return the system to the default tic state. The state-dependent nature of motor control is supported by previous studies using transcranial magnetic stimulation.[12,35]

These results add an important temporal dimension in motor research in tic disorders and may, thereby, reconcile discrepant findings in previous studies that also explored the concept of a noisy sensorimotor system in tic disorders. A longitudinal study that compared tic severity between childhood and adulthood revealed that impaired fine motor skills in childhood were a strong predictor of tic persistence in the future.[36] Similarly, in a proprioceptive matching task, patients exhibited elevated proprioceptive variability, suggesting noisier afferent signals in TS.[37] In contrast, many other studies did not replicate similar findings.[9,34,38,39] A double-step reaching task in adults TS patients showed no differences to controls in movement accuracy and variability in the first goal-directed outward movement.[5] However, by design, that study could not exclude online or trial-to-trial movement corrections that may help compensate for noise.[32] It has been proposed that patients with TS use compensatory strategies such as enhanced cognitive control over motor output,[10-12,34] or by correcting movements based on sensory feedback.[32] Our task was designed to remove the possibility of visually guided online corrections and error-based learning. Participants' movement direction and amplitude depended on some combination of an initial motor plan and a visual–proprioceptive feedback loop. We therefore suggest that the elevated initial noise of the PTD group, and its subsequent compensation, arise in one of these two processes.

Limitations

We found that neither patients nor controls adjusted variability in extent to target shape (see also Supplementary Results for Fig. 3b). It could be that emphasis on fast movements made it difficult for participants to control movement extent sufficiently, especially in the absence of visual feedback. Movement velocity is a not task-irrelevant parameter, and interacts with movement extent, with fast movements being less precise and more variable in nature.[18] The spread of movement endpoints is typically elongated in extent, indicating that variability in movement extent may be more difficult to control, possibly because execution noise contributes to total noise more in movement extent.[18] Because target shape yielded insufficient or no experimental control over variability in movement extent, the factors that drive variability in movement extent in our study are unknown, and are difficult to interpret. We therefore focused on variability in movement direction throughout the study, which we could control via target shape, and, thus, interpret. Finally, while our cohort size is comparable to, or exceeds,[5,40,41] many recent studies examining PTD, effects of target shape on movement extent variability may be too small to be detectable in 60 subjects (30 per group).

Conclusions

The key finding of this study is initially elevated movement direction variability in patients with PTD, which decreased progressively across repetition of a task. Our study supports the concept of elevated neural noise in PTD and underscores the role of compensatory strategies that may mask underlying pathophysiology.

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Data Availability Statement

All data and analysis scripts are available upon reasonable request.

References

1. Ganos C, Münchau A, Bhatia KP. The semiology of tics, Tourette's, and their associations. Mov Disord Clin Pract 2014;1(3):145–153. https://doi.org/10.1002/mdc3.12043
2. Münchau A, Colzato LS, AghajaniAfjedi A, Beste C. A neural noise account of Gilles de la Tourette syndrome. NeuroImage 2021;30:102654. https://doi.org/10.1016/j.nicl.2021.102654
3. Adelhöfer N, Paulus T, Mückschel M, et al. Increased scale-free and aperiodic neural activity during sensorimotor integration—a novel facet in Tourette syndrome. Brain Commun 2021;3(4):fcab250. https://doi.org/10.1093/braincomms/fcab250
4. 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. https://doi.org/10.1016/j.cortex.2014.09.016

5. Kim S, Jackson GM, Dyke K, Jackson SR. Impaired forward model updating in young adults with Tourette syndrome. Brain 2019; 142(1):209–219. https://doi.org/10.1093/brain/awy306
6. Schurger A, Sitt JD, Dehaene S. An accumulator model for spontaneous neural activity prior to self-initiated movement. Proc Natl Acad Sci U S A 2012;109(42):E2904–E2913. https://doi.org/10.1073/pnas.1210467109
7. Faisal AA, Selen LPJ, Wolpert DM. Noise in the nervous system. Nat Rev Neurosci 2008;9(4):292–303. https://doi.org/10.1038/nrn2258
8. Sweet RD, Solomon GE, Wayne H, Shapiro E, Shapiro AK. Neurological features of Gilles de la Tourette's syndrome. J Neurol Neurosurg Psychiatry 1973;36(1):1–9. https://doi.org/10.1136/jnnp.36.1.1
9. Kalsi N, Tambelli R, Aceto P, Lai C. Are motor skills and motor inhibitions impaired in Tourette syndrome? A review. J Exp Neurosci 2015;9:57–65. https://doi.org/10.4137/JEN.S25095
10. Mueller SC, Jackson GM, Dhalla R, Datsopoulos S, Hollis CP. Enhanced cognitive control in young people with Tourette's syndrome. Curr Biol 2006;16(6):570–573. https://doi.org/10.1016/j.cub.2006.01.064
11. Jung J, Jackson SR, Parkinson A, Jackson GM. Cognitive control over motor output in Tourette syndrome. Neurosci Biobehav Rev 2013; 37(6):1016–1025. https://doi.org/10.1016/j.neubiorev.2012.08.009
12. Draper A, Jude L, Jackson GM, Jackson SR. Motor excitability during movement preparation in Tourette syndrome. J Neuropsychol 2015;9(1):33–44. https://doi.org/10.1111/jnp.12033
13. Nashed JY, Crevecoeur F, Scott SH. Rapid online selection between multiple motor plans. J Neurosci 2014;34(5):1769–1780. https://doi.org/10.1523/JNEUROSCI.3063-13.2014
14. Smith MA, Brandt J, Shadmehr R. Motor disorder in Huntington's disease begins as a dysfunction in error feedback control. Nature 2000;403(6769):544–549. https://doi.org/10.1038/35000576
15. Shadmehr R, Mussa-Ivaldi F. Adaptive representation of dynamics during learning of a motor task. J Neurosci 1994;14(5):3208–3224. https://doi.org/10.1523/JNEUROSCI.14-05-03208.1994
16. Misirlisoy E, Brandt V, Ganos C, Tübing J, Münchau A, Haggard P. The relation between attention and tic generation in Tourette syndrome. Neuropsychology 2015;29(4):658–665. https://doi.org/10.1037/neu0000161
17. Todorov E, Jordan MI. Optimal feedback control as a theory of motor coordination. Nat Neurosci 2002;5(11):1226–1235. https://doi.org/10.1038/nn963
18. van Beers RJ, Brenner E, Smeets JBJ. Random walk of motor planning in task-irrelevant dimensions. J Neurophysiol 2013;109(4): 969–977. https://doi.org/10.1152/jn.00706.2012
19. van Beers RJ, Haggard P, Wolpert DM. The role of execution noise in movement variability. J Neurophysiol 2004;91(2):1050–1063. https://doi.org/10.1152/jn.00652.2003
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, D.C: American Psychiatric Association; 2013. http://doi.org/10.1176/appi.books.9780890425596.
21. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97–113.
22. Leckman JF, Riddle MA, Hardin MT, 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(4):566–573. https://doi.org/10.1097/00004583-198907000-00015
23. Rössner V, Müller-Vahl K, Neuner I. PUTS-premonitory urge tics scale: Fragebogen für Kinder. Tourette-Syndrom und andere Tic-Erkrankungen im Kindes-und Erwachsenenalter. Berlin: MWV Medizinische Wissenschaftliche Verlagsgesellschaft; 2010.
24. Cavanna AE, Schrag A, Morley D, et al. The Gilles de la Tourette syndrome-quality of life scale (GTS-QOL): development and validation. Neurology 2008;71(18):1410–1416. https://doi.org/10.1212/01.wnl.0000327890.02893.61
25. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46(11):1006–1011.
26. Conners CK, Erhardt D, Epstein JN, Parker JDA, Sitarenios G, Sparrow E. Self-ratings of ADHD symptoms in adults I: factor structure and normative data. J Atten Disord 1999;3(3):141–151. https://doi.org/10.1177/108705479900300303
27. Beck AT, Steer RA, Brown G. Beck Depression Inventory–II. Washington, D.C: APA PsycTests; 1996. http://doi.org/10.1037/t00742-000.
28. Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol 2007;98(1):54–62. https://doi.org/10.1152/jn.00266.2007
29. Wong AL, Marvel CL, Taylor JA, Krakauer JW. Can patients with cerebellar disease switch learning mechanisms to reduce their adaptation deficits? Brain 2019;142(3):662–673. https://doi.org/10.1093/brain/awy334
30. JASP Team. JASP (Version 0.16.3); 2022. Computer software.
31. de Graaf JB, van den Broek JFM, Bekkering H, Sittig AC. The visual estimation of the left hand position is shifted towards the body midline. Vision et adaptation. Paris: Elsevier 1995;183–192.
32. Stenner MP, Ostendorf F, Ganos C. Forward model deficits and enhanced motor noise in Tourette syndrome? Brain 2019;142(10): e53. https://doi.org/10.1093/brain/awz266
33. Song JH. The role of attention in motor control and learning. Curr Opin Psychol 2019;29:261–265. https://doi.org/10.1016/j.copsyc.2019.08.002
34. Neuner I, Arrubla J, Ehlen C, et al. Fine motor skills in adult Tourette patients are task-dependent. BMC Neurol 2012;12(1):120. https://doi.org/10.1186/1471-2377-12-120
35. Ganos C, Rocchi L, Latorre A, et al. Motor cortical excitability during voluntary inhibition of involuntary tic movements: the motor neurophysiology of tic inhibition. Mov Disord 2018;33(11):1804–1809. https://doi.org/10.1002/mds.27479
36. Bloch MH, Sukhodolsky DG, Leckman JF, Schultz RT. Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome: fine motor skill deficits predict future symptom severity in Tourette's syndrome. J Child Psychol Psychiatry 2006;47(6):551–559. https://doi.org/10.1111/j.1469-7610.2005.01561.x
37. Cothros N, Medina A, Martino D, et al. Children with tic disorders show greater variability in an arm-position-matching proprioceptive task. Mov Disord 2021;36(3):782–784. https://doi.org/10.1002/mds.28413
38. Buse J, August J, Bock N, Dörfel D, Rothenberger A, Roessner V. Fine motor skills and interhemispheric transfer in treatment-naive male children with Tourette syndrome: motor skills in Tourette syndrome. Dev Med Child Neurol 2012;54(7):629–635. https://doi.org/10.1111/j.1469-8749.2012.04273.x
39. Georgiou N, Bradshaw JL, Phillips JG, Bradshaw JA, Chiu E. Advance information and movement sequencing in Gilles de la Tourette's syndrome. J Neurol Neurosurg Psychiatry 1995;58(2): 184–191. https://doi.org/10.1136/jnnp.58.2.184
40. Larsh TR, Huddleston DA, Horn PS, et al. From urges to tics in children with Tourette syndrome: associations with supplementary motor area GABA and right motor cortex physiology. Cereb Cortex 2023;33(7): 3922–3933. https://doi.org/10.1093/cercor/bhac316
41. Stenner MP, Baumgaertel C, Heinze HJ, Ganos C, Müller-Vahl KR. Intact automatic motor inhibition in patients with tourette syndrome: automatic inhibition in Tourette syndrome. Mov Disord 2018;33(11):1800–1804. https://doi.org/10.1002/mds.27493

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