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Amplified engagement of prefrontal cortex during control of voluntary action in Tourette syndrome

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Running title: Tourette syndrome intentional inhibition (40 characters)
Abstract (380 words)

Tourette syndrome is characterised by ‘unvoluntary’ tics, which are compulsive, yet often temporarily suppressible. The inferior frontal gyrus (IFG) is implicated in motor control, including inhibition of pre-potent actions through influences on downstream subcortical and motor regions. While tic suppression in Tourette Syndrome also engages the IFG, it is unclear whether such prefrontal control of action is also dysfunctional: Tic suppression studies do not permit comparison with control groups, and neuroimaging studies of motor inhibition can be confounded by the concurrent expression or suppression of tics. Here, patients with Tourette syndrome were directly compared to control participants when performing an intentional inhibition task during fMRI. Tic expression was recorded throughout for removal from statistical models. Participants were instructed to make a button press in response to Go cues, withheld responses to NoGo cues to, and decide whether to press or withhold to ‘Choose’ cues. Overall performance was similar between groups, for both intentional inhibition rates (% Choose-Go) and reactive NoGo inhibition commission errors. A subliminal face prime elicited no additional effects on intentional or reactive inhibition. Across participants, the task activated prefrontal and motor cortices and subcortical nuclei, including pre-supplementary motor area (preSMA), IFG, insula, caudate nucleus, thalamus, and primary motor cortex. In Tourette syndrome, activity was elevated in the IFG, insula, and basal ganglia, most notably within the right IFG during voluntary action and inhibition (Choose-Go and Choose-NoGo), and reactive inhibition (NoGo-correct). Anatomically, the locus of this IFG hyperactivation during control of voluntary action matched that previously reported for tic suppression. In Tourette syndrome, activity within the caudate nucleus was also enhanced during both intentional (Choose-NoGo) and reactive (NoGo-correct) inhibition. Strikingly, despite the absence of overt motor behaviour, primary motor cortex activity increased in patients with Tourette syndrome but decreased in controls during both reactive and intentional inhibition. Additionally, severity of premonitory sensations scaled with functional connectivity of the preSMA to the caudate nucleus, globus pallidus, and thalamus when choosing to respond (Choose-Go). Together, these results suggest that patients with Tourette syndrome use equivalent prefrontal mechanisms to suppress tics and withhold non-tic actions, but require greater IFG engagement than controls to overcome motor drive from hyperactive downstream regions, notably primary motor cortex. Moreover, premonitory sensations may cue midline motor regions to generate tics through interactions with the basal ganglia.

Keywords: basal ganglia; movement disorders: imaging; neuropsychiatry: imaging; tic disorder; Tourette’s syndrome
Introduction

Tourette syndrome is a neurodevelopmental hyperkinetic movement disorder, characterised by motor and phonic tics. A curious feature of these tics is that they are often reported to be semi-voluntary reactions to premonitory urges to move (Kwak et al., 2003; Cavanna and Nani, 2013; Cavanna et al., 2017). Further, patients with Tourette syndrome can often temporarily withhold or suppress them, for example in social contexts (Matsuda et al., 2016). This suggests at least partial volitional control and is distinctive from other hyperkinetic disorders, such as myoclonus (Ganos et al., 2018b). Behavioural therapies, such as exposure and response prevention, capitalise on this capacity for voluntary tic suppression to habituate to and diminish premonitory urges (Frundt et al., 2017; Ganos et al., 2018b).

Dysfunctional interactions within cortico-striato-thalamo-cortical (CSTC) circuits are believed to underlie tic generation (Ganos, 2016), and prefrontal cortex is implicated in their control. For example, functional imaging studies report enhanced activity within lateral prefrontal cortex, particularly the (anterior) inferior frontal gyrus (IFG) during tic suppression (Peterson et al., 1998; Ganos et al., 2014a). This indicates that the active control of tics in Tourette syndrome likely engages the same prefrontal mechanisms as are implicated in stopping or withholding (non-tic) actions (Ganos et al., 2014b; Zapparoli et al., 2015; Rae et al., 2019). Interestingly, patients with Tourette syndrome show greater IFG activity (Zapparoli et al., 2015), and reduced functional connectivity of primary motor cortex, on (non-tic) response inhibition tasks (Thomalla et al., 2014). Together, this suggests that the IFG supports both reactive motor inhibition and volitional tic suppression, in accordance with theoretical notions that volitional tic inhibition may overlap with other forms of motor inhibitory processes, with a ‘neural signature of both internally decided and externally triggered inhibition’, centred on the inferior frontal gyrus (Ganos, Rothwell & Haggard, 2018b). However, in Tourette syndrome greater prefrontal engagement may be necessary to overcome hyper-activity in motor output regions including primary motor cortex (Ganos, 2016; Rae et al., 2019).

The pre-supplementary motor area (preSMA) is also central to action inhibition, interacting with signals from IFG to modulate basal ganglia activity (Rae et al., 2015; Aron et al., 2016). PreSMA is a cardinal substrate for voluntary action decisions, across ‘what-when-whether’
categories (Brass and Haggard, 2008; Zapparoli et al., 2017a). However, fMRI studies of tic expression show supplementary motor area (SMA), rather than preSMA activity prior to tic release (Bohlhalter et al., 2006; Neuner et al., 2014; Zapparoli et al., 2015). This raises questions of whether preSMA activity is altered in Tourette syndrome during the control of voluntary action, and how interactions with the basal ganglia affect tic expression.

fMRI studies characterising neural processes in Tourette syndrome are rarely free of interpretive confounds. Overt tic suppression studies cannot meaningfully compare patients’ brain activity during suppression periods to controls who do not tic (van der Salm et al., 2018). In addition, accidental expression of tics during instructed suppression periods may confound the interpretation of tic suppression versus ‘free ticcing’ studies, while results in task-based studies may be affected by covert tic suppression. Instead, ‘intentional inhibition’ tasks enable direct comparison of Tourette syndrome and control participants, revealing for example heightened dorsal anterior cingulate and striatal activity in Tourette syndrome when participants are instructed to inhibit eye blinks (and suppress ocular tics) (Mazzone et al., 2010; van der Salm et al., 2018).

Here we used an intentional inhibition task during fMRI to compare participants with Tourette syndrome and controls. However, rather than instructing participants not to suppress tics, we used video monitoring time-locked to fMRI acquisition to identify tics. We then used this to construct participant-specific tic regressors to isolate activity related to tic expression from task performance. This approach enabled examination of task effects uncontaminated by tic expression or suppression (Neuner et al., 2007; Thomalla et al., 2014; Rae et al., 2018).

In addition we used a modified Go/NoGo task, to incorporate ‘Choose’ trials, when participants chose whether to act or to withhold a button press (Rae et al., preprint). This allowed simultaneous investigation of voluntary action (on Choose trials when participants elected to act), intentional inhibition (on Choose trials when participants elected to withhold), and reactive inhibition (on NoGo trials). The task also balanced the number of trials across participants, in contrast to tic or blink suppression paradigms, where statistical power may be compromised by subject-level variance in frequency of tics or tic suppression, during scanning.

We predicted that participants with Tourette syndrome show similar patterns of anatomical engagement to controls, in line with the hypothesis that tic suppression uses the same core circuitry for stopping and withholding of (non-tic) movements (Rae et al., 2019). Moreover, we predicted that prefrontal and motor control sites would be hyperactive in Tourette syndrome, against the backdrop of basal ganglia dysfunction and elevated primary motor cortex reactivity
Lastly, we predicted that the strength of interaction between prefrontal and cortical motor planning regions (notably IFG and pre-SMA) with basal ganglia nuclei would determine the severity of Tourette syndrome symptoms (Thomalla et al., 2014; Zapparoli et al., 2017b; Rae et al., 2018).

We previously identified hyperactivity of insular cortex and stronger functional connectivity between insula and motor areas when patients with Tourette syndrome view faces, suggesting that the insula can trigger tic expression during social stimulation (Rae et al., 2018). Insula is also active during ‘whether’ decisions to act or to withhold (Brass and Haggard, 2010), suggesting this region may also cue such motor decisions. We therefore included within our task design a subliminal priming element (Parkinson et al., 2017). We hypothesised that unconscious facial primes might differentially cue ‘Choose’ decisions to act or to withhold responses through effects on insular activation.

Materials and Methods

Participants

Twenty-three participants with Tourette syndrome (13 male; age 18-51, mean 34 years) and 21 controls with no history of major neurological or psychiatric disorder (11 male; age 19-55, mean 35 years) participated. Clinical diagnosis of Tourette syndrome was made by a UK neurologist or psychiatrist specialised in the assessment of Tourette syndrome. Patients were recruited from the Sussex Partnership NHS Foundation Trust (SPFT) Neurodevelopmental Service (psychiatrist H.C.), and via Tourettes Action UK (specifying details of their clinical assessment prior to inclusion). Obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) diagnoses were also recorded.

Tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS, symptom severity: maximum 50; impairment: maximum 50; global total: 100) (Leckman et al., 1989). fMRI analyses used the symptom severity score. Premonitory sensations were assessed using the Premonitory Urge for Tics Scale (PUTS, Woods et al., 2005); OCD severity using the Yale Brown Obsessive Compulsive Scale (YBOCS, Goodman et al., 1989), and ADHD severity using the Adult ADHD Self-Report Scale (ASRS, Kessler et al., 2005).

Two patients were taking dopaminergic medications, six serotonergic medications, and one was taking both dopaminergic and serotonergic medications. One patient on sertraline was
also taking a benzodiazepine. The remaining 14 were unmedicated (one of whom took melatonin as a natural sleep aid remedy).

Table 1 gives demographic details and clinical features (Supplementary Table 1: individual patient data). Participants gave written informed consent. The study was approved by the South East Coast: Brighton National Research Ethics Committee (15-LO-0109).

**Intentional inhibition task**

Participants performed a modified Go/NoGo task in which movement cues (green, red, yellow circles) were presented on a grey background for 800ms (Figure 1). Green Go cues indicated a button press to be made with the right index finger, red NoGo cues indicated the participant should withhold their button press, and yellow ‘Choose’ cues indicated participants should choose whether to press the button or withhold (Rae et al., preprint). There were 864 trials: 432 Go (50%), 144 NoGo (17%), and 288 Choose (33%), presented in a pseudo-randomised order. The higher frequency of Go trials was designed to invoke a pre-potent tendency to go, as in traditional Go/NoGo tasks, and ensure that withholding on NoGo trials was sufficiently challenging to invoke inhibitory control (Rae et al., preprint). Participants were instructed to respond quickly on Go trials, withhold button presses on NoGo trials, and choose quickly, making a fresh decision each time, on Choose trials.

![Figure 1. Intentional inhibition task cues. Following an intertrial interval, on Go trials (50%) green cues instructed participants to make a button press, on NoGo trials (17%) red cues instructed participants to withhold, and on Choose trials (33%) yellow cues indicated participants should choose whether to press or withhold. Stimuli enlarged for illustrative purposes.](image)

To test the secondary hypothesis regarding social context on motor decisions, each trial also involved subliminal presentation of a face prime prior to each movement cue. These face primes (from the NIMSTIM database; Tottenham et al., 2009) portrayed (1) neutral (33%) or (2) angry (33%) expressions, or were (3) scrambled (33%) for a ‘non-social’ control. Three male and three female identities were used over 144 trials (72 Go, 24 NoGo, 48 Choose). Hair
and peripheral features were removed by applying a greyscale circle, leaving only the facial expression. The face primes, presented for 16 ms, were preceded by a scrambled face ‘forward mask’ (32ms), followed by a scrambled face ‘backward mask’ (48ms), to render the face prime consciously imperceptible (Parkinson et al., 2017). Participants were not informed of the face primes before or during the experiment.

A white fixation cross was displayed during intertrial intervals, jittered in duration and optimised using OptSeq (http://surfer.nmr.mgh.harvard.edu/optseq) for event-related design efficiency (35% 1000ms, 30% 1130ms, 20% 1250ms, 10% 1380ms, 5% 1500ms). The task was divided into three blocks of 288 trials, 10 minutes 42 seconds in duration, with breaks in between to reduce fatigue and discomfort.

**Intentional inhibition task statistical analysis**

Indices of motor behaviour (proportion of Choose trials on which participants decided to act i.e. % Choose-Go, NoGo commission errors, Go omissions, reaction times) were compared between Tourette syndrome patients and controls using independent-sample t-tests and Bayesian equivalents (applying default priors) in JASP (https://jasp-stats.org). We examined effects of face priming on intentional inhibition (% Choose-Go) using a 3x2 repeated measures ANOVA (within group factor, face prime: neutral, angry, scrambled; between groups factor: TS, control), and an equivalent Bayesian ANOVA (comparing to a null model). To examine whether task performance changed over the duration of the experiment, and whether this differed between patients and controls, we compared the six motor behaviour indices (%Choose-Go, NoGo commission errors, Go omissions, reaction times) in the first block of trials (1-288) to the final block (trials 577-864) using six 2x2 repeated measures ANOVAs (within group factor: block 1, block 3; between groups factor: TS, control), and equivalent Bayesian ANOVAs (comparing to a null model).

**Face prime subliminality assessment**

To verify that face primes were consciously imperceptible, following the intentional inhibition task two brief behavioural checks were employed (Supplementary Methods).

**MRI acquisition**

fMRI data were acquired on a Siemens Avanto 1.5T (32 channel head coil, T2*-weighted images, repetition time=2520ms, echo time=43ms, 34 ascending 3mm slices , 0.6mm slice gap, in-plane resolution 3x3mm). 255 fMRI volumes were acquired per 10 minute block (765 volumes total). The first five volumes per block were discarded for steady-state magnetisation. A T1-weighted image was acquired for fMRI preprocessing (repetition time=2730ms, echo
time=3.57ms, 1x1x1mm resolution). Participants’ heads were tightly cushioned within the head coil to reduce head movements.

**Tic monitoring**

We did not instruct participants to suppress tics. This was essential to acquire intentional inhibition task fMRI data uncontaminated by simultaneous tic suppression in Tourette syndrome participants. Furthermore, not instructing participants to suppress tics reduces distress and fatigue over the imaging session. To remove BOLD signal relating to generation and expression of tics during the task, we video-recorded tics, time-locked to fMRI data, and included tic expression as a regressor in general linear modelling (Rae et al., 2018). Videos were recorded concurrently with acquisition of neuroimaging data in order to identify the timings of tics, which were used to exclude the effects of tic generation and expression from neuroimaging analyses, but were not used to rate tic severity.

We acquired video using an in-bore MRI compatible camera (MRC Systems, [www.mrc-systems.de](http://www.mrc-systems.de)), mounted on the head coil to view participants’ faces, and an out-of-bore camera to view limbs and body (360x240 resolution, 30 frames per second). Camera feeds and fMRI volume markers were simultaneously relayed to Spike2 physiological recording software (version 7.17, CED). During fMRI acquisition, the researcher (C.R.) watched the live video feeds and noted fMRI volumes at which she observed tics within a written record, in case the video recordings were interrupted, lost or failed in another way. Storage of the video recording failed for three participants; in these cases, the written records alone identified tic onsets and durations in relation to the fMRI timeseries.

For the majority of participants with complete video recordings (n=20), tics were identified in post-hoc video assessment, using the written record as a supplementary guide. Initial tic ratings were conducted by two authors (L.P.: 8 videos, D.L.:12), before a second rater, familiar with each patient’s tic repertoire, conducted a second rating, confirming or rejecting the status of each event as a tic, and identifying any not previously flagged by L.P. or D.L.. An in-house Spike2 script extracted tic onsets and durations, time-locked to fMRI data. Phonic tics were often visible from facial movement, but we did not record sound.

During the 30 minutes of fMRI, an average of 161 tics occurred (range 0-551, standard deviation: 147). The bodily locations at which tics were expressed were on average 40% facial, 8% head, 8% both face and head, 33% body or limbs, and 11% combinations of face, head, body, and limbs.
fMRI preprocessing

fMRI data were preprocessed and analysed using SPM12 (v7219, www.fil.ion.ucl.ac.uk/spm). Preprocessing used default options, including realignment to the mean image, slice-time correction to the middle slice, co-registration with T1 structural and MNI normalisation, and 8mm smoothing.

Task fMRI univariate statistical analysis

A general linear model represented task events, with regressors for onset and duration (500ms) of 1) Go, 2) NoGo-correct, 3) Choose-Go, and 4) Choose-NoGo trials. If participants made Go omissions or NoGo errors, these regressors were added. Because there were no effects of face primes on behaviour (see Results), we collapsed across prime types for all imaging analyses. The general linear model of Tourette syndrome participants contained a further regressor for observed onsets and durations of tics. The fMRI data from the three runs were concatenated (spm_concatenate.m), adding a constant (mean) column for each of the three runs, and a 'block transitions' regressor modelled the transition from end of one block to the start of the next. Six realignment parameter regressors modelled head movement.

Single-regressor T-contrasts were generated for 1) Go, 2) NoGo-correct, 3) Choose-Go, and 4) Choose-NoGo trials, and NoGo errors if made, with implicit baseline of intertrial interval fixation cross. These were entered to a full factorial second-level analysis, with group (Tourette syndrome, control) as independent (between-subjects) factor, and task condition (Go, NoGo-correct, Choose-Go, Choose-NoGo, NoGo-error) as non-independent (repeated measures) factor. Three mean centred covariates modelled medication, ADHD diagnosis, and OCD diagnosis (1/0 yes/no), thus removing potentially confounding variance from individual patient differences in medication status and comorbid ADHD and OCD symptoms.

F-contrasts were generated for all effects ('eye', Figure 3), and group effects (controls versus Tourette syndrome) across all conditions, and for Go, NoGo-correct, Choose-Go, and Choose-NoGo individually. Post-hoc t-tests identified the direction of significant group effects (Figure 3). A conjunction analysis examined overlap of group differences in Choose-Go, Choose-NoGo, and NoGo-correct. Task effect t-contrasts examined volitional action (Choose-Go>Go), intentional inhibition (Choose-NoGo>GoNoGo-correct), volitional action versus intentional inhibition (Choose-Go>Choose-NoGo), and reactive inhibition (NoGo-correct>Go), in controls and Tourette syndrome respectively (Figure 4). Contrast estimate effect size plots for the five trial types were generated for the preSMA, bilateral insula, and M1, at the region's peak co-ordinate in the 'all effects' F-contrast, and for the IFG and caudate nucleus at the
region’s peak co-ordinate in the conjunction (IFG) and Choose-NoGo group difference (caudate nucleus) (Figure 3).

A series of second-level models in Tourette syndrome participants examined correlations between task effects and Tourette syndrome symptom severity. One-sample t-tests of 1) Choose-Go and 2) Choose-NoGo, with 1) YGTSS or 2) PUTS as covariates, created an interaction between task effect and severity score. Medication and comorbidities were entered as covariates. T-contrasts tested for a positive correlation with YGTSS or PUTS.

Three further second-level models examined correlations between task effects relevant to inhibitory control (Choose-NoGo, NoGo-correct) and hyperactivity (Choose-Go) with OCD and ADHD symptom severity. Three one-sample t-tests of 1) Choose-Go, 2) Choose-NoGo, 3) NoGo-correct, with YBOCS and ASRS as covariates, created two interactions between task effect and severity score. Medication status was entered as a covariate. T-contrasts tested for a positive correlation with YBOCS or ASRS. Entering both severity scores to the models simultaneously enabled us to investigate the effects of OCD or ADHD severity while controlling for the other.

To verify that medication status did not affect univariate results, the subgroup of medicated patients (n=9) was compared with the subgroup of unmedicated patients (n=14) (Supplementary Methods).

Statistic images were thresholded at cluster-forming threshold p<0.001 for cluster-wise false discovery rate (FDR) correction for multiple comparisons at p<0.05 (Chumbley et al., 2010; Eklund et al., 2016). Significant clusters were localised using the Anatomy toolbox (v2.2b, Eickhoff et al., 2007) and FSL Harvard-Oxford atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

*Psychophysiological interactions*

A series of psychophysiological interactions (PPIs) investigated how prefrontal cortex modulated activity elsewhere in the brain. We first examined whether preSMA or IFG was associated with changes in functional connectivity when choosing to go and choosing to withhold. Then, in participants with Tourette syndrome, we examined whether the strength of preSMA and IFG functional connectivity during Choose-Go and Choose-NoGo trials related to tic and premonitory sensation severity.
The first eigenvariate (weighted mean of BOLD timeseries) was extracted for the preSMA and IFG, by thresholding an F-contrast for all effects (‘eye’) at p<1 for each individual. A 10mm sphere was extracted at the preSMA peak in the second-level all effects F-contrast (x4, y18, z48), and the IFG peak in the conjunction of group differences (x40, y40, z6).

For each participant, a PPI term was calculated according to task effects (contrast weight: [1] for Choose-Go, and Choose-NoGo, trials respectively), and the timeseries of 1) preSMA and 2) IFG. The Choose-Go and Choose-NoGo PPI terms for 1) preSMA and 2) IFG were each entered to a first-level model, with regressors representing the region’s BOLD activity (PPI.Y) and task effect (PPI.P). The three fMRI runs were concatenated (spm_concatenate.m), adding a constant (mean) column for each run. A ‘block transitions’ regressor modelled the transition from the end of one block to the start of the next. Six regressors modelled head movement, and for Tourette syndrome participants, a regressor of onsets and durations of tics identified in videos. T-contrasts were generated for the PPI term, and entered to second-level models.

Four second-level models examined the PPI of 1) preSMA and 2) IFG, on Choose-Go, and Choose-NoGo trials, in controls and Tourette syndrome participants (two-sample t-tests). F-contrasts and post-hoc t-contrasts tested for group effects (controls versus Tourette syndrome), and t-contrasts individual group effects.

In Tourette syndrome participants, four second-level models (one-sample t-tests) of 1) preSMA and 2) IFG, on Choose-Go, and Choose-NoGo trials, included YGTSS as a covariate; four further models included PUTS as a covariate; creating an interaction between PPI and severity score in all eight models. T-contrasts tested for a positive correlation with YGTSS or PUTS.

As in univariate analyses, PPI second-level models modelled medication, and ADHD/OCD diagnoses (1/0 yes/no), to remove potentially confounding variance from individual patient differences in medication status and comorbid ADHD and OCD symptoms; and contrasts were thresholded at p<0.05 FDRc.

Again in Tourette syndrome participants, two further second-level models (one-sample t-tests) of 1) preSMA on Choose-Go trials and 2) IFG on Choose-NoGo trials included YBOCS and ASRS as covariates, creating two interactions between PPI and severity score. Medication status was entered as a covariate. T-contrasts tested for a positive correlation with YBOCS or ASRS, and were thresholded at p<0.05 FDRc. Entering both severity scores to the models
simultaneously enabled us to investigate the effects of OCD or ADHD severity while controlling for the other.

To verify that medication status did not affect PPI results, the subgroup of medicated patients (n=9) was compared with the subgroup of unmedicated patients (n=14) (Supplementary Methods).

Plots of the preSMA Choose-GoPPI correlation with PUTS were generated in SPM for the caudate nucleus, globus pallidus, and thalamus, at each region’s peak PPI coordinates, using adjusted data.

Data availability
Anonymised demographic, clinical and behavioural data; task code; JASP statistical analyses; tic regressor data and scripts; fMRI analysis scripts, and second-level fMRI models, are available at https://osf.io/94ybj/?view_only=967f59b6dd0f40649982d5d2d3fdecde. Statistic images are in Neurovault (Gorgolewski et al., 2015) at https://neurovault.org/collections/xxxx/. [upon manuscript acceptance following peer review]

Results

Intentional inhibition task
Tourette syndrome participants did not choose to go or withhold more often than controls (%Choose-Go controls: 53%, Tourette syndrome: 56%, t=-0.924, p=0.361, BF_{10}=0.420); nor did they make more NoGo errors (controls: 3%, Tourette syndrome: 3%, t=-0.228, p=0.820, BF_{10}=0.304). Tourette syndrome participants made slightly more Go omissions than controls (controls: 1%, Tourette syndrome: 2%, t=-2.423, p=0.020, BF_{10}=2.920), probably driven by one TS participant. Reaction times did not significantly differ between groups (Table 1, Figure 2).
Figure 2. Behavioural performance on the intentional inhibition task, in control and Tourette syndrome participants. Data visualised using estimation plots (www.estimationstats.com, Ho et al., 2019).

There was no overall effect of face priming on %Choose-Go (F=0.901, p=0.410, BF₁₀=0.162), no group difference (F=0.886, p=0.352, BF₁₀=0.675), and no group by face prime type interaction (F=0.610, p=0.546, BF₁₀=0.022).

From the first block to the final block, the sample as a whole (not separated by group) chose to go more often on Choose trials (+4%, F(1,42)=6.214, p=0.017, BF₁₀=3.088); made more NoGo commission errors (+2%, F(1,42)=7.491, p=0.009, BF₁₀=5.740); and were faster to respond on both Choose-Go (-34ms, F(1,42)=32.857, p<0.001, BF₁₀=14989.073) and Go (-23ms, F(1,42)=18.687, p<0.001, BF₁₀=172.836) trials. There were no block effects on Go omissions (+0.3%, F(1,42)=1.128, p=0.294, BF₁₀=0.370) or NoGo error reaction time (-24ms, F(1,42)=0.023, p=0.882, BF₁₀=0.355). This suggests that as the task progressed, participants as a whole became more impulsive responders, but did not decrease in attention to the task more generally, because they maintained their (high) rates of Go responses (98.5% in Block 1 versus 98.2% in Block 3). We next examined whether there were group effects, such as would indicate the patients becoming more impulsive as the experiment progressed than controls: there was no evidence to that effect, with no significant behaviour*group interactions in the six ANOVAs (%Choose-Go: F(1,42)=0.262, p=0.611, BF₁₀=0.520; NoGo errors:
F(1,42)=0.178, p=0.675, BF_{10}=0.672; Go omissions: F(1,42)=0.511, p=0.479, BF_{10}=0.819; Choose-Go RT: F(1,42)=0.054, p=0.817, BF_{10}=3002.339, large BF_{10} driven by main effect; NoGo error RT: F(1,42)=0.068, p=0.799, BF_{10}=0.081; Go RT: F(1,42)=1.684, p=0.201, BF_{10}=69.584, large BF_{10} driven by main effect). This suggests that any neural group differences are not due to differential changes in attention to the task or changes in impulsivity as the experiment progressed.

**Face prime subliminality assessment**

Behavioural assessment of perception of the face primes suggested that some TS participants were able to detect the presence of a face, although they were unable to discriminate angry from neutral expressions (Supplementary Results).

**Univariate fMRI & contrast estimate effect sizes**

The F-contrast for all effects showed activity associated with Go, NoGo-correct, Choose-Go, Choose-NoGo, and NoGo-error trials in controls and Tourette syndrome participants across prefrontal, parietal, and insula cortices; visual cortices; and cortical and subcortical motor regions (Figure 3, Supplementary Table 2A).

Contrast estimate effect size plots at peak co-ordinates of the all effects F-contrast showed generally elevated activity in Tourette syndrome in preSMA, bilateral insula, and M1 across trial types (Figure 3). This was particularly notable during motor inhibition (Choose-NoGo and NoGo-correct), when primary motor cortex (M1) was suppressed (below 0) in controls but elevated in Tourette syndrome. However, elevated activity in Tourette syndrome did not necessarily pass stringent threshold criteria for significance when tested in the group effect whole-brain contrasts (Figure 4). Contrast estimate effect size plots at peak co-ordinates of group differences (IFG, caudate nucleus) nevertheless demonstrate the hyperactivity of these regions in Tourette syndrome.
Figure 3. Contrast estimate effect size plots of activity during the intentional inhibition task in controls and Tourette syndrome participants in (A) preSMA, (B) right IFG, (C) left insula, (D) right insula, (E) left caudate nucleus, (F) left M1, for (left-to-right) controls (Go, NoGo-correct, Choose-Go, Choose-NoGo, and NoGo-error) and Tourette syndrome (as for controls). Pink bar represents 90% confidence interval. Statistic image shown in (A-F) is the all effects ('eye') F contrast.
Figure 4. Group effects on the intentional inhibition task. Greater activity in Tourette syndrome participants (TS) than controls (CON) (A) across all conditions, and on (B) Choose-Go, (C) Choose-NoGo, and (D) NoGo-correct trials; (E) conjunction of group difference overlap across (B), (C), and (D).

There were significant group effects across all conditions (F-contrast), and for Choose-Go, Choose-NoGo, and NoGo-correct (Supplementary Table 2D, 2F, 2H; Go group contrast not significant). Post-hoc t-tests confirmed Tourette syndrome participants showed greater activity than controls across all conditions in bilateral IFG, right insula, caudate nucleus, putamen, globus pallidus, and thalamus; during Choose-Go in right anterior IFG and subgenual anterior cingulate cortex; during Choose-NoGo in bilateral anterior IFG and caudate nucleus; and during NoGo-correct in right anterior IFG and left caudate nucleus (Figure 4, Supplementary Table 2C, 2E, 2G, 2I). All T-contrasts for greater activity in controls than Tourette syndrome were not significant. A conjunction analysis of group difference overlap across Choose-Go, Choose-NoGo, and NoGo-correct showed anterior IFG and ventromedial prefrontal cortex (Supplementary Table 2J).
Task effect t-contrasts showed activity during volitional action (Choose-Go>Go) in preSMA extending to the rostral cingulate zone, right IFG, bilateral insula, and inferior parietal lobule in both controls and Tourette syndrome (Figure 5A, Supplementary Table 2K, 2L). In addition, there was activity in the thalamus in Tourette syndrome. During intentional inhibition (Choose-NoGo-NoGo-correct), there was activity in the preSMA extending to the rostral cingulate zone, right IFG, bilateral insula, and inferior parietal lobule in both groups (Figure 5B, Supplementary Table 2M, 2N). Contrasting volitional action with intentional inhibition showed M1 in both groups, but to a greater anatomical extent and statistical height in controls (Figure 5C, Supplementary Table 2O, 2P). Finally, during reactive inhibition (NoGo-correct>Go), there was activation of the left inferior frontal junction in both groups, and the right inferior frontal junction and right insula in controls, while Tourette syndrome participants showed additional activity in premotor cortex (Figure 5D, Supplementary Table 2Q, 2R).

**Figure 5.** Task effects on the intentional inhibition task. Activity in controls (CON) and Tourette syndrome participants (TS) for (A) Choose-Go>Go, (B) Choose-NoGo-NoGo-correct, (C) Choose-Go>Choose-NoGo, and (D) NoGo-correct>Go.
Second-level models in patients with Tourette syndrome tested for correlations between task effects (Choose-Go, Choose-NoGo) and Tourette syndrome symptom severity (YGTSS, PUTS). None were significant (p<0.05 FDRc).

Three second-level models in Tourette syndrome participants that tested for correlations between task effects (Choose-Go, Choose-NoGo, NoGo-correct) and OCD or ADHD severity (YBOCS, ASRS) showed no significant effects (p<0.05 FDRc).

Psychophysiological interactions (PPI): preSMA and IFG
Four second-level models examined changes in functional connectivity with 1) preSMA and 2) IFG, according to psychological context of Choose-Go, and Choose-NoGo, in controls and Tourette syndrome.

In the preSMA PPI with Choose-Go, there was a significant effect of group (F-contrast, Supplementary Table 3A), which a post-hoc t-test revealed was due to greater task-induced changes in functional connectivity between preSMA and the superior parietal lobule in Tourette syndrome than in controls (Figure 6A, Supplementary Table 3B). The contrasts for individual group effects were not significant for either controls nor Tourette syndrome. There were no significant effects for the preSMA PPI with Choose-NoGo.

Figure 6. Group psychophysiological interaction (PPI) results. Greater PPI in Tourette syndrome participants (TS) than controls (CON) (A) from preSMA during Choose-Go. IFG PPI with Choose-NoGo in (B) controls and (C) Tourette syndrome.
In the IFG PPI with Choose-NoGo, there were no significant group effects. The contrast testing for a PPI in controls showed early visual cortices (Figure 6B, Supplementary Table 3C); Tourette syndrome participants showed a PPI between the IFG and the frontal pole (Figure 6C, Supplementary Table 3D). There were no significant effects for the IFG Choose-Go PPI.

**Psychophysiological interactions: Premonitory sensation severity (PUTS)**

In Tourette syndrome participants only, four PPI analyses tested whether preSMA and IFG connectivity during Choose-Go and Choose-NoGo trials varied in relation to premonitory sensation severity from PUTS scores. There were no regions where functional connectivity of the IFG varied in proportion to premonitory sensation severity. However, the preSMA PPI showed a significant correlation with PUTS in the caudate nucleus, globus pallidus, and thalamus during Choose-Go (Figure 7A-D, Supplementary Table 3E). The preSMA Choose-NoGo PPI with PUTS was not significant.

**Psychophysiological interactions: Tic severity (YGTSS)**

In Tourette Syndrome participants only, four PPI analyses examined whether preSMA and IFG connectivity during Choose-Go and Choose-NoGo trials varied in relation to tic severity according to YGTSS scores. There were no regions where functional connectivity of the preSMA varied in proportion to tic severity. However, the IFG PPI showed a significant correlation with YGTSS in early visual cortices and V4 during Choose-Go (Figure 7E, Supplementary Table 3F). The IFG Choose-NoGo PPI with YGTSS was not significant.

**Psychophysiological interactions: OCD and ADHD severity**

In Tourette syndrome participants only, two PPI analyses examined whether preSMA connectivity during Choose-Go trials, and IFG connectivity during Choose-NoGo trials, varied in relation to OCD severity (YBOCS) or ADHD severity (ASRS). There were no regions where functional connectivity varied in proportion to OCD severity. However, the IFG PPI showed a significant correlation with ASRS in premotor cortex (Figure 7F, Supplementary Table 3G). The preSMA PPI with ASRS was not significant.
Figure 7. Regions showing a correlation between PPI functional connectivity and premonitory sensations (PUTS), tic severity (YGTSS), and ADHD severity (ASRS). The worse the premonitory sensations, tic severity, or ADHD severity the greater the functional connectivity. (A) preSMA functional connectivity with PUTS during Choose-Go: caudate nucleus, globus pallidus, thalamus; (B) to (D): Correlation plots of preSMA Choose-Go PPI with PUTS in (B) caudate nucleus, (C) globus pallidus, (D) thalamus; (E) right IFG functional connectivity with YGTSS during Choose-Go: early visual cortices and V4; (F) right IFG functional connectivity with ASRS during Choose-NoGo: premotor cortex.

Discussion

Tourette syndrome is characterised by both the ‘unvoluntary’ nature of tics, and the ability of many patients to intentionally suppress tic expression. To uncover the neural mechanisms by
which people with Tourette syndrome control action, we employed an intentional inhibition task, in which participants chose whether to execute or withhold a simple movement. By monitoring patients’ tics we could remove confounding influences of tic expression or suppression on our fMRI measurements. This enabled us to undertake a comprehensive analysis of the interactions between prefrontal and motor regions underpinning control of voluntary action in Tourette syndrome in comparison to a control group without tics.

We found that the neural processes by which Tourette syndrome participants choose to act, or withhold movements, are anatomically similar to controls, encompassing activity in cardinal prefrontal and motor regions including the preSMA. We uncovered further subtleties in these network operations in Tourette syndrome, observing heightened activity in primary motor cortex – even when no action is made – and significantly greater activity than controls in anterior IFG and caudate nucleus when choosing to go, choosing to withhold, and on NoGo trials that captured reactive inhibition. Functional connectivity analyses further elucidated the impact of individual differences in symptom severity. When choosing to go, patients with worse premonitory sensations showed increased connectivity between preSMA and the subcortical nuclei thought critical for tic genesis, highlighting a neural cascade by which stronger premonitory sensations may intensify the urge to move.

Together, these results suggest that the neural processes for action control in people with Tourette syndrome are anatomically similar to those used by which people without tics when choosing to withhold actions. However, in Tourette Syndrome, these processes operate against a backdrop of basal ganglia dysconnectivity and elevated primary motor cortex reactivity. The result is that greater prefrontal leverage is required to modulate downstream subcortical and primary motor cortex activity.

**Prefrontal control of action**

The anatomical pattern of activity when choosing to go, to withhold, or reactively inhibit (NoGo) was similar across Tourette syndrome and control participants, encompassing preSMA, and lateral prefrontal (IFG), insula, and parietal cortices. This ‘pluripotentiality’ of a prefrontal motor control network supporting multiple forms of action control, is perhaps unsurprising given its evolutionary efficiency (Friston and Price, 2003), and the wide spectrum of action choice types from ‘internally-cued’ to ‘externally-cued’ or ‘what-when-whether’ categories (Nachev et al., 2008; Passingham et al., 2010; Zapparoli et al., 2017a). Where participants with Tourette syndrome differed from controls was in the level of activity within these cardinal motor control networks.
In Tourette syndrome participants, activity was generally elevated across several regions, including the IFG, right insula, basal ganglia (caudate nucleus, putamen, globus pallidus) and thalamus. On trials specifically involving motor inhibition, anterior IFG and caudate nucleus were significantly hyperactive compared to controls. A more posterior IFG site (pars opercularis) is commonly associated with reactive motor inhibition, for example on the stop signal task (Aron et al., 2004; Rae et al., 2015). However, anterior IFG was linked to tic suppression in a previous study comparing suppression to ‘free ticcing’ (Ganos et al., 2014a). Meta-analyses of reactive inhibition also reveal multiple clusters of IFG activity along the extent of the gyrus (Rae et al., 2014; Guo et al., 2018). It is also notable that multiple cognitive domains beyond motor inhibition are associated with IFG function, and relevant to symptoms of Tourette syndrome, such as vocalisation and stimulus salience processing (Amunts and Zilles, 2012; Hampshire and Sharp, 2015), although these were not explicitly manipulated in the present study. Together, these data suggest that IFG, including more anterior segments, is hyperactive in Tourette syndrome, and likely underpins volitional withholding of tics and non-tic actions. Compared to controls, greater activity is required to overcome subcortical and primary motor cortex circuitry tipped towards a state of motor execution.

Further evidence for a heightened state of motor excitability in Tourette syndrome came from examining primary motor cortex. Here, the effect size plots showed that when controls inhibited actions (on both NoGo and Choose-NoGo trials) primary motor cortex activity was suppressed. In contrast, primary motor cortex activity was not suppressed in participants with Tourette syndrome (mean contrast estimates were above zero, even though participants were not moving). This finding cannot be attributed to tic expression, which was controlled for within the analytic models. Moreover, tic expression would have affected the implicit baseline (inter-trial intervals) against which task events and hence NoGo and Choose-NoGo contrasts were computed. This intriguing finding of elevated primary motor cortex activity in Tourette syndrome extends transcranial magnetic stimulation data showing heightened primary motor cortex excitability in Tourette syndrome during NoGo states (Draper et al., 2015), and greater reduction in primary motor cortex excitability during tic suppression in patients best able to withhold tics (Ganos et al., 2018a). These data also support the hypothesis that tonic regulation of excitability within motor pathways may underlie remission of tics in adolescents whose tics reduce with age (Jackson et al., 2015), while heightened motor cortex excitability remains in those who express tics into adulthood.

PreSMA activity was not significantly different between Tourette syndrome and control participants when choosing whether to act or withhold. PreSMA is a principal site of voluntary action; electrical stimulation here elicits the urge to move (Fried et al., 1991) and focal
activation underscores ‘what-when-whether’ decisions during fMRI (Zapparoli et al., 2017a). Curiously, prior fMRI studies have shown SMA (rather than preSMA) activity prior to release of tics (Bohlhalter et al., 2006; Neuner et al., 2014): We proposed that the role of the preSMA in tics may be ascribing a ‘somewhat intended’ or ‘unvoluntary’ experience to ‘explain away’ motor prediction errors, arising from the release of tics fostered by SMA and basal ganglia dysfunction (Rae et al., 2019). We argue that during tic suppression, the preSMA may signal to subcortical structures, in particular the subthalamic nucleus, to pause motor outflow, while the IFG amplifies this inhibitory effect (Rae et al., 2015; Rae et al., 2019). Both these propositions imply that the preSMA is not a site of overt dysfunction in Tourette syndrome relative to controls, while basal ganglia and lateral prefrontal sites are implicated in tic genesis and suppression respectively. Meta-analyses show that across tasks, both IFG and SMA, but not preSMA, are hyperactive in Tourette syndrome (Polyanska et al., 2017). Future application of multivariate pattern analysis techniques (Haxby et al., 2014) hold potential to determine whether sub-populations of preSMA neurons underpinning choices to move or withhold (Fedota et al., 2014) are functionally different in patients with Tourette syndrome. More fine-grained neuroimaging (at higher field strength than employed here) will be valuable in exploring interactions between IFG and the subthalamic nucleus. This may delineate more precisely how hyperactivity within IFG and caudate nucleus contribute to pausing of basal ganglia outflow to primary motor cortex.

**Psychophysiological interactions**

We used functional connectivity analyses to explore how prefrontal and motor planning regions, namely the IFG and preSMA, interact with downstream regions, including basal ganglia. Greater functional connectivity was observed from the preSMA during Choose-Go (but not Choose-NoGo) trials, and from the IFG during Choose-NoGo (but not Choose-Go) trials. These results indicate that the preSMA perhaps makes a stronger contribution to movement production and the IFG a stronger contribution to movement withholding (Aron et al., 2016). Next, we examined how preSMA and IFG interactions scale according to disorder severity in Tourette syndrome. Notably, when choosing to go, preSMA functional connectivity to the caudate nucleus, globus pallidus, and thalamus was stronger in patients with worse premonitory sensations. Thus, pathways driving volitional production of movement appear hyper-connected in individuals with greater premonitory sensations, which may be underscored by structural connectivity of white matter tracts connecting preSMA to the basal ganglia (Worbe et al., 2015).

We did not observe increased preSMA functional connectivity with the insula, a region implicated in generating premonitory sensations that can foster tic production through outputs
to midline motor regions (Jackson et al., 2011; Cavanna et al., 2017; Conceicao et al., 2017). Speculatively, this may reflect greater insular inputs to the SMA, rather than preSMA (Rae et al., 2019). Also, our task modelled ‘whether’ decisions to release or withhold movements, and correspondingly elicited activity in canonical voluntary action regions. However, this arguably has different ecological validity compared to blink suppression tasks (Mazzone et al., 2010; van der Salm et al., 2018), which might engender stronger feelings of urge and premonitory sensations.

There were a few relationships identified for IFG connectivity, in terms of tic severity (visual cortices) and ADHD severity (premotor cortex). The fact that higher severity of ADHD symptoms was associated with greater connectivity between the IFG and premotor cortex when choosing to inhibit suggests that stronger leverage of prefrontal resources to motor preparation cortices for the volitional withholding of action may be required in patients with worse ADHD (regardless of diagnostic status). We did not observe any relationships between univariate task effects or connectivity with OCD severity, suggesting that severity of obsessive compulsive symptoms did not affect the main findings of IFG and striatal hyperactivity in the patient group compared to controls (nor OCD diagnostic status, which was entered as a covariate in group analyses). Employing symptom severity scales alongside recording diagnostic status can be useful in order to distinguish overall clinical cohort effects from effects of within-group heterogeneity.

Subliminal face perception in TS
Our paradigm included an exploratory ‘face priming’ element, in which motor cues were preceded by brief (16ms) presentations of neutral, angry, or scrambled faces. Social context clearly influences tic expression, provoking echophenomena, or exacerbating tic expression through social scrutiny (Eapen et al., 1994; Ganos et al., 2012). We previously found that supraliminal (i.e. consciously perceived) face stimuli – portraying neutral or angry expressions – evoke insula hyperactivity in Tourette syndrome, and further, that insula to basal ganglia functional connectivity scaled with the severity of premonitory sensations (Rae et al., 2018). This suggests that the insula is a tic trigger site, cueing motor responses to affective stimuli. However, here we observed no effect of masked face primes on how frequently participants chose to act; nor significant group differences. We therefore collapsed across face prime types in fMRI analyses to increase statistical power. Although we intended the face primes to be subliminal (unconscious), our subsequent detection checks found that patients with Tourette syndrome detected their presence, despite the forward-and-backward masking. This
heightened perceptual ability may represent a core feature of Tourette syndrome, or alternatively may arise experientially after years of often uncomfortable social scrutiny.

**Study limitations and future directions**

We selected the intentional inhibition task as an exemplary paradigm for measuring voluntary action, voluntary inhibition, and reactive inhibition within the same experimental session. This is distinct from tic suppression studies, for which a direct comparison task to control participants is not possible. Blink suppression paradigms bridge this gap, in addition to capturing the urge nature of both tics and blinks, but generate different numbers of trials, and unbalance data across individuals and groups, impacting statistical power. Hence, the present task offers a purer index of voluntary action control for group comparisons. It may be valuable for future investigations to incorporate all three types of task within a single study, enabling evaluation across dimensions of naturalistic urge with equivalent information sampling between participants.

Several patient participants reported feeling fatigued after completion of the study. Therefore, we checked for possible differences in attention to the task in the patients versus controls, in case neural differences observed in Tourette syndrome were due to differential changes in behaviour as the experiment progressed. From the first to the final block, participants as a whole chose to go more often, made more NoGo commission errors, and were faster to respond on Choose-Go and Go trials, but maintained their high rates of Go responses. This suggests that as the task progressed, participants became more impulsive responders, but did not decrease in their attention to the task for generally. Although there were significant block effects on impulsivity, the numerical changes were not vast: thus the changes in impulsive responding in the sample as a whole were subtle, but significant. However, there were no group by time interactions, such that the patients did not become more impulsive as the experiment progressed than controls. This gives confidence that the neural hyperactivity seen in the Tourette syndrome participants is not due to differential changes in attention to the task or changes in impulsivity.

Deployment of an intentional inhibition task requires that participants are not simultaneously attempting to suppress tics, since this would impact fMRI measurements of motor inhibition networks. Therefore, we allowed participants to tic and applied the alternative strategy of using video recordings of participants’ face and limbs to generate ‘tic regressors’ and thus remove the influence of tic expression on fMRI analyses (Neuner et al., 2007; Thomalla et al., 2014; Rae et al., 2018). Although this approach was as comprehensive as conceivably feasible, it remains possible that some phonic tics were not captured. Following Thomalla et al (2014),
we monitored the live video feeds to note observed tics in the first instance, and then conducted a thorough offline tic rating procedure, incorporating multiple raters, to ensure optimum fidelity of the tic timelines that were entered to fMRI statistical models. Such additional challenges are important to consider when studying movement disorder populations who may be expressing symptoms during scanning, especially hyperkinesias.

We accounted for comorbidities and medications by including these as covariates in statistical analyses. The ‘TS spectrum’ ranges from ‘pure TS’, characterised by simple tics alone, to ‘full-blown TS’ in which the motor symptoms are accompanied by complex tic expressions (such as echo- and coprophenomena) and multiple comorbidities, often including ADHD, autism and OCD (Robertson and Eapen, 2014; Martino et al., 2017). In a mixed sample, it may be difficult to disentangle whether prefrontal hyperactivation (for example) is inherently due to Tourette syndrome, or related to a comorbid neurodevelopmental disorder also involving frontostriatal circuits. Nevertheless, we feel studying a cohort that spans the full ‘TS spectrum’ is essential, since it is likely ‘not a unitary condition’ (Robertson, 2015). Using covariates is one approach to tackle confounding influences of ADHD and OCD while, in larger samples, patient stratification into sub-groups would enable greater insight.

Decisions on how to model and analyse fMRI data, including how to control for comorbidities and investigate the impacts of symptom severity, all influence researcher degrees of freedom. Given the number of possible analytic permutations in neuroimaging studies, these can be very large. One useful way to limit such degrees of freedom is to pre-register an fMRI analysis plan before the data are observed and/or analysed. If we had done so for our study, we could have formally defined in advance (for example) when compensatory neural processes to evoke similar behavioural performance to controls, such as we observed with the IFG, were expected. This enables one to demonstrate effects via ‘confirmatory’ tests. If not formally specified in advance via a pre-registered plan, analyses can be conceptualised as exploratory tests instead.

Modelling behavioural data, as well as neural activity, can bring useful insights, especially if model parameters are then reapplied to neuroimaging analyses. Such methods have yet to be widely applied in Tourette syndrome (Maia and Conceicao, 2017). Drift diffusion modelling offers one promising approach to understand how the motor system is tipped towards cortical excitability, and modulated under reactive motor inhibition (Draper et al., 2015) and intentional tic suppression (Ganos et al., 2018a). Voluntary decisions to move or withhold can be explained by accumulation of activity to motor thresholds (Sebastian et al., 2018). Altered thresholds or accumulation rates can differentiate other patient groups, including Parkinsonian
sub-types (Zhang et al., 2016). It is plausible that patients with worse premonitory sensations or tic severity are distinguished by lower thresholds and faster accumulation rates for choices to go, and that such parameters correlate with activity in CSTC circuitry.

Conclusions
People with and without Tourette syndrome use similar neuroanatomical architecture in the release and intentional withholding of actions. However, greater prefrontal engagement is required in Tourette syndrome to prevent release of movements arising from hyperactivity within downstream motor regions, notably primary motor cortex. Midline motor regions typically associated with voluntary action interact with the basal ganglia in proportion to the severity of premonitory sensations, highlighting how individuals with greater premonitory urges experience hyper-connectivity of networks that underpin volitional movement.

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Conflicts of interest
None declared.

Supplementary material
Supplementary material is available at Brain Communications online.
References


Parker J, Garfinkel S, Critchley H, Dienes Z, Seth AK. Don't make me angry, you wouldn't like me when I'm angry: Volitional choices to act or inhibit are modulated by subliminal perception of emotional faces. Cognitive, affective & behavioral neuroscience 2017; 17(2): 252-68.


Tables

**Table 1.** Demographic details of participants, clinical features of patients, and behavioural performance on the intentional inhibition task. Data are presented as means (SD). Group difference \( P \)-values refer to two-tailed \( t \)-tests or chi-squared for number of males/females. OCD=obsessive compulsive disorder; ADHD=attention deficit hyperactivity disorder; YGTSS=Yale Global Tic Severity Scale; PUTS=Premonitory Urge for Tics Scale; YBOCS=Yale-Brown Obsessive Compulsive Scale; ASRS=Adult ADHD Self-Report Scale.

<table>
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<tr>
<th>Features / measures</th>
<th>Control (n=21)</th>
<th>Tourette Syndrome (n=23)</th>
<th>Group difference</th>
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<tbody>
<tr>
<td>Number of males / females</td>
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<td>13 / 10</td>
<td>( x^2=0.439, \ p=0.932 )</td>
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<td>Age</td>
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<td>34 (11)</td>
<td>( t=0.356, \ p=0.724, BF_{10}=0.313 )</td>
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<td>Years of education</td>
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<td>14 (2)</td>
<td>( t=-0.010, \ p=0.992, BF_{10}=0.298 )</td>
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<td>Number with OCD</td>
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<td>10</td>
<td></td>
</tr>
<tr>
<td>Number with ADHD</td>
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<td>6</td>
<td></td>
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<td>YGTSS: symptom severity</td>
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<td></td>
</tr>
<tr>
<td>YGTSS: impairment</td>
<td>-</td>
<td>19 (13)</td>
<td></td>
</tr>
<tr>
<td>YGTSS: total (symptom severity &amp; impairment)</td>
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<td>45 (19)</td>
<td></td>
</tr>
<tr>
<td>PUTS</td>
<td>-</td>
<td>23 (7)</td>
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<tr>
<td>ASRS</td>
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<td>4 (2)</td>
<td>( t=-4.474, \ p&lt;0.001, BF_{10}=351.15 )</td>
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<tr>
<td>YBOCS</td>
<td>6 (6)</td>
<td>15 (10)</td>
<td>( t=-3.457, \ p&lt;0.001, BF_{10}=25.70 )</td>
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<tr>
<td>% Choose-Go</td>
<td>53% (10%)</td>
<td>56% (13%)</td>
<td>( t=-0.924, \ p=0.361, BF_{10}=0.420 )</td>
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<tr>
<td>% NoGo errors</td>
<td>3% (3%)</td>
<td>3% (4%)</td>
<td>( t=-0.228, \ p=0.820, BF_{10}=0.304 )</td>
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<tr>
<td>% Go omissions</td>
<td>1% (1%)</td>
<td>2% (2%)</td>
<td>( t=-2.423, \ p=0.020, BF_{10}=2.920 )</td>
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<td>Choose-Go reaction time (ms)</td>
<td>477 (45)</td>
<td>488 (43)</td>
<td>( t=-0.887, \ p=0.380, BF_{10}=0.409 )</td>
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<td>NoGo error reaction time (ms)</td>
<td>371 (182)</td>
<td>370 (166)</td>
<td>( t=0.018, \ p=0.985, BF_{10}=0.326 )</td>
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<tr>
<td>Go reaction time (ms)</td>
<td>419 (37)</td>
<td>434 (40)</td>
<td>( t=-1.289, \ p=0.204, BF_{10}=0.579 )</td>
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</table>
Amplified engagement of prefrontal cortex during control of voluntary action in Tourette syndrome

SUPPLEMENTARY INFORMATION

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Supplementary Methods

Face prime subliminality assessment
To verify that face primes were consciously imperceptible, following the intentional inhibition task, two brief behavioural checks were employed.

Firstly, participants undertook a detection task, comprising 72 trials, presented in a random order. On ‘face present’ trials (n=36), neutral (18) or angry (18) faces were displayed for 16 ms, forward and backward-masked (in the same manner described in the main manuscript), while on ‘face absent’ trials (36), scrambled faces were presented. Following each stimulus, participants answered “Was there a face?” by indicating YES or NO with a left or right button press.

Participants then undertook a discrimination task, comprising 72 trials, presented in a random order. On half the trials, neutral faces were displayed for 16 ms, forward and backward-masked, while on the other half of the trials, angry faces were displayed. Following each stimulus, participants answered, “Was the face angry or neutral?” by indicating ANGRY or NEUTRAL with a left or right button press.

We assessed conscious perception according to significantly greater than chance performance at (1) detecting the presence of a face in the detection task, and (2) detecting the expression of a face in the discrimination task. We calculated participants’ d’ score on each task, according to z-scored hit rate minus z-scored false alarm rate, comparing these to 0 (i.e. chance performance) in a 2x2 repeated measures ANOVA (within group factor: detection score versus 0; between group factor: TS, control), and an equivalent Bayesian ANOVA.

One participant with Tourette syndrome withdrew from the study after the intentional inhibition task but before these tasks, and one participant with Tourette syndrome withdrew prior to the discrimination task; we therefore present subliminality assessment data on the remaining 22 / 21 TS participants.

Effects of medication on univariate fMRI results
To verify that medication status did not affect univariate results, the subgroup of medicated patients (n=9) was compared with the subgroup of unmedicated patients (n=14).

First, participants’ response at the peak IFG co-ordinate in the three key univariate group difference results (Choose-Go, Choose-NoGo, NoGo-correct) was plotted, separating by medication status (Supplementary Figure 1A-C).

The data were then analysed at the second-level separating by medicated (n=9) and unmedicated (n=14) patients (Supplementary Figure 1 lower pane).

Effects of medication on PPI results
To verify that medication status did not affect PPI results, the subgroup of medicated patients (n=9) was compared with the subgroup of unmedicated patients (n=14).
We considered the effect of medication status on the key PPI result: increased connectivity from the preSMA to the basal ganglia on Choose-Go trials, in proportion to premonitory sensation severity (PUTS). First, the PUTS-PPI correlation at the three basal ganglia locations illustrated in Figure 7 of the main manuscript (caudate nucleus, globus pallidus, thalamus) was plotted, separating by medication status (Supplementary Figure 2A-C).

The data were then analysed at the second-level separating by medicated (n=9) and unmedicated (n=14) patients (Supplementary Figure 2 lower pane).
Supplementary Results

Face prime subliminality assessment
When comparing d’ scores at detecting presence or absence of a face versus chance performance (0), there was an overall effect, suggesting that participants could detect the presence of forward-and-backward masked 16ms faces (F=6.988, p=0.012, BF₁₀=8.459). The group effect was not significant (F=1.163, p=0.287), and nor was the group by detection interaction (F=1.163, p=0.287), but the Bayes Factor for overall effect + group effect suggested anecdotal evidence (BF₁₀=3.331). Two post-hoc one-way t-tests showed that control participants did not detect faces above chance (t=1.149, p=0.264, BF₁₀=0.407), but Tourette syndrome participants did (t=2.552, p=0.019, BF₁₀=2.978).

When comparing discrimination task d’ scores to chance performance (0), there was no overall effect (F=0.118, p=0.733, BF₁₀=0.252), suggesting that while some participants were able to detect the presence of a face, they were not able to discriminate whether it was angry or neutral. There was also no effect of group (F=0.437, p=0.513, BF₁₀=0.311), or group by discrimination interaction (F=0.437, p=0.513, BF₁₀=0.027).

Effects of medication on univariate fMRI results
The peak IFG co-ordinate response plots (Supplementary Figure 1A-C) show considerable overlap in IFG activity levels between the medicated and unmedicated participants, with the unmedicated group appearing to show slightly higher mean activation here across all three trial types than the medicated. If anything, this suggests that the overall result in the full sample – that the TS group as a whole show hyperactivations here relative to controls – is not driven by medication status, since the medicated group in fact have slightly lower IFG activity, according to the plots.

The second-level analyses separating medicated (n=9) and unmedicated (n=14) patients (Supplementary Figure 1 lower pane) show that in general, the unmedicated group tend to show greater IFG activity on the three trial types, in terms of statistical height and anatomical extent of activations. However, the group difference contrasts do not pass correction for multiple comparisons. Thus, this suggests that removing the nine medicated patients did not fundamentally alter the results in terms of observing IFG hyperactivation relative to the control group, but did substantially lower the power, such that those contrasts are no longer significant after correcting for multiple comparisons.
Supplementary Figure 1. Effects of medication status on IFG activity (plotted at peak co-ordinate x40, y40, z6, in A-C; and crosshairs centred on this co-ordinate). Contrasts that did not pass correction for multiple comparisons shown at p<0.001 uncorrected; otherwise thresholded at p<0.05 FDRc with cluster-defining threshold of p<0.001.

Effects of medication on PPI results
The preSMA PPI correlation plots (Supplementary Figure 2A-C) show that the medicated group entirely overlap with unmedicated patients. This suggests that the overall result in the full sample – a correlation of PUTS with the preSMA PPI – is not driven by medication status.
Supplementary Figure 2. Effects of medication status on preSMA PPI connectivity correlation with PUTS (plotted at three peak co-ordinates of the caudate nucleus, globus pallidus, and thalamus in A-C). The contrast for correlation with PUTS did not pass correction for multiple comparisons in either the medicated or unmedicated samples (shown at p<0.001 uncorrected in both), although bearing resemblance to the corrected (p<0.05 FDRc) result in the full sample (crosshairs centred on caudate nucleus peak co-ordinate in full sample).

The second-level analyses separating medicated (n=9) and unmedicated (n=14) patients (Supplementary Figure 2 lower pane) indicate that the correlation with basal ganglia connectivity was still observable in the larger unmedicated sub-sample, although it did not reach correction for multiple comparisons. The correlation with PUTS was also (just) recognisable in the medicated sample in the caudate nucleus (at p<0.001 uncorrected). Thus, this suggests that removing the nine medicated patients did not fundamentally alter the results in terms of observing a correlation between preSMA-basal ganglia connectivity and PUTS, but did substantially lower the power, such that correlation with PUTS in (either the medicated or unmedicated group) is no longer significant after correcting for multiple comparisons.

Therefore, we conclude that the key results are not overtly different in terms of neural mechanisms between medicated and unmedicated participants, but reducing the sample
size by excluding either group leaves the analysis underpowered, relative to the full patient sample (n=23).
**Supplementary Table 1.** Patient clinical features and medications. OCD = obsessive compulsive disorder; ADHD = attention deficit hyperactivity disorder; YGTSS = Yale Global Tic Severity Scale; PUTS = Premonitory Urge for Tics Scale; YBOCS = Yale-Brown Obsessive Compulsive Scale; ASRS = Adult ADHD Self-Report Scale.

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<th>YGTSS: total (symptom severity &amp; impairment)</th>
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Supplementary Table 2. Univariate fMRI: Local maxima of significant clusters per contrast, localised according to the Anatomy toolbox (v2.2b, Eickhoff et al 2007, *Neuroimage*) in SPM12, and the FSL Harvard-Oxford cortical and subcortical atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) where the Anatomy toolbox did not contain a label (indicated by *). (L = left hemisphere, R = right hemisphere; x, y, z = co-ordinates of maximum activated voxel in standard MNI152 space, $F / t = F / t$ stat at this voxel. Peaks are listed at p<0.05 FDR cluster corrected (cluster-forming threshold: p<0.001).

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B Group main effect (F-contrast)
(Controls all conditions versus Tourette syndrome all conditions)

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**D** Group effect NoGo correct (F-contrast)
(Controls NoGo correct versus Tourette syndrome NoGo correct)

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**E** Group effect NoGo correct (T-contrast)
(Tourette syndrome NoGo correct > Controls NoGo correct)

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**F** Group effect Choose-Go (F-contrast)
(Controls Choose-Go versus Tourette syndrome Choose-Go)

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**G** Group effect Choose-Go (T-contrast)
(Tourette syndrome Choose-Go > Controls Choose-Go)

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**H Group effect Choose-NoGo (F-contrast)**

(Controls Choose-NoGo versus Tourette syndrome Choose-NoGo)

<p>| 1     | Middle frontal gyrus | R  | 42 | 48 | 16  | 50.20 |
|       | Insula               | R  | 44 | 16 | 0   | 48.67 |
|       | Insula               | R  | 34 | 22 | 4   | 47.27 |
|       | Middle frontal gyrus | R  | 40 | 42 | 32  | 44.67 |
|       | Middle frontal gyrus | R  | 34 | 50 | 20  | 44.27 |
|       | Middle frontal gyrus | R  | 44 | 42 | 26  | 43.33 |
|       | Middle frontal gyrus | R  | 44 | 44 | 22  | 42.82 |
|       | Middle frontal gyrus | R  | 44 | 38 | 28  | 42.40 |
|       | Middle frontal gyrus | R  | 40 | 44 | 26  | 41.78 |
|       | Middle frontal gyrus | R  | 30 | 48 | 30  | 41.56 |
|       | Middle frontal gyrus | R  | 34 | 30 | 34  | 35.81 |
| 2     | Precuneus            | L  | -14| -58| 16  | 40.15 |
|       | Precuneus            | R  | 8  | -52| 18  | 33.42 |
|       | Cuneus (area hOc2, V2) | L  | -6 | -96| 16  | 33.25 |
|       | Middle occipital gyrus (area PGp, IPL) | L  | -38| -82| 30  | 33.15 |
|       | Angular gyrus (area PGp, IPL) | L  | -46| -76| 30  | 28.62 |
|       | Cuneus               | L  | -12| -72| 30  | 28.34 |
|       | Cuneus               | L  | -12| -70| 22  | 27.18 |
|       | Calcarine gyrus (area hOc1, V1) | R  | 12 | -80| 4   | 24.68 |
|       | Cuneus (area hOc2, V2) | L  | 2  | -90| 16  | 23.83 |
|       | Cuneus               | R  | 22 | -60| 20  | 21.02 |
|       | Cuneus               | L  | -8 | -86| 36  | 20.13 |
| 3     | Superior parietal lobule | R  | 48 | -42| 58  | 42.75 |
|       | Supramarginal gyrus (area hIP2, IPS) | R  | 48 | -40| 44  | 39.10 |
|       | Angular gyrus        | R  | 40 | -58| 42  | 36.58 |
|       | Angular gyrus        | R  | 42 | -56| 38  | 36.10 |
|       | Inferior parietal lobule (area PFm, IPL) | R  | 52 | -54| 38  | 31.19 |
|       | N/A                  | R  | 30 | -46| 36  | 26.56 |
|       | N/A                  | R  | 32 | -48| 34  | 24.21 |
|       | Superior parietal lobule (BA 7a) | R  | 40 | -54| 58  | 23.89 |
|       | Middle occipital gyrus | R  | 30 | -62| 36  | 18.00 |
|       | Angular gyrus (BA 7a) | R  | 34 | -68| 52  | 16.85 |
|       | Supramarginal gyrus (area PF, IPL) | R  | 62 | -36| 28  | 12.77 |
| 4     | Cerebellum (lobule VIIa, crus II) | L  | -34| -62| -44 | 43.72 |
|       | Cerebellum (lobule VIIa, crus II) | L  | -36| -66| -46 | 41.95 |
|       | Cerebellum (lobule VIIa, crus I) | L  | -30| -62| -32 | 40.79 |
|       | Middle occipital gyrus (area hOc4lp, V4) | L  | -28| -90| 0   | 37.72 |
|       | Middle occipital gyrus (area hOc4lp, V4) | L  | -22| -96| 4   | 36.90 |</p>
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**Group effect Choose-NoGo (T-contrast)**

(Tourette syndrome Choose-NoGo > Controls Choose-NoGo)

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**Middle frontal gyrus**

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**Superior medial gyrus**

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**Inferior frontal gyrus**

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**Anterior cingulate cortex**

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**Conjunction analysis**

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+ (Tourette syndrome Choose-Go > Controls Choose-Go)
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**L** Tourette syndrome Choose-Go > Tourette syndrome Go (T-contrast)

<p>| 1 | Superior medial gyrus | R | 6 | 22 | 42 | 7.51 |
| Superior frontal gyrus | R | 24 | 8 | 60 | 7.47 |
| Inferior frontal gyrus (pars opercularis, BA 44) | R | 50 | 12 | 18 | 6.63 |
| Insula | R | 40 | 20 | 0 | 6.62 |
| Inferior frontal gyrus (pars opercularis, BA 44) | R | 52 | 12 | 8 | 6.20 |
| Inferior frontal gyrus (pars opercularis) | R | 50 | 18 | -2 | 6.19 |
| Inferior frontal gyrus (pars opercularis) | R | 48 | 14 | 38 | 5.35 |
| Middle frontal gyrus | R | 38 | 8 | 54 | 4.61 |
| Middle frontal gyrus | R | 40 | 10 | 52 | 4.52 |
| Middle frontal gyrus | R | 38 | 20 | 40 | 3.96 |
| Posterior-medial frontal | R | 10 | 16 | 64 | 3.45 |
| 2 | Inferior parietal lobule (area hIP3, IPS) | R | 42 | -44 | 54 | 6.46 |
| Inferior parietal lobule (area PFm, IPL) | R | 52 | -38 | 52 | 6.28 |
| Precuneus | R | 10 | -66 | 46 | 5.67 |
| Angular gyrus | R | 48 | -54 | 38 | 5.52 |
| Inferior parietal lobule (area hIP1, IPS) | R | 44 | -52 | 40 | 5.45 |
| Supramarginal gyrus | R | 52 | -38 | 38 | 5.42 |
| Inferior parietal lobule (area hIP1, IPS) | R | 38 | -54 | 42 | 5.39 |
| Inferior parietal lobule (area hIP3, IPS) | R | 32 | -48 | 42 | 5.27 |
| Supramarginal gyrus (area PF, IPL) | R | 60 | -38 | 28 | 4.72 |
| Angular gyrus | R | 28 | -64 | 44 | 4.64 |
| Supramarginal gyrus (area PFm, IPL) | R | 58 | -42 | 28 | 4.63 |
| 3 | Middle frontal gyrus | R | 44 | 42 | 24 | 6.61 |
| Middle frontal gyrus | R | 30 | 48 | 12 | 6.17 |
| Middle orbital gyrus | R | 36 | 56 | -4 | 5.56 |
| Middle frontal gyrus | R | 32 | 52 | 22 | 4.61 |
| Middle frontal gyrus | R | 32 | 52 | 26 | 4.51 |
| Superior orbital gyrus | R | 22 | 46 | -12 | 4.36 |
| 4 | Insula | L | -34 | 18 | 4 | 7.13 |
| Inferior frontal gyrus (pars opercularis, BA 44) | L | -52 | 10 | 12 | 5.44 |
| Insula | L | -30 | 24 | -8 | 4.49 |
| Precentral gyrus | L | -46 | 8 | 32 | 4.17 |
| Inferior frontal gyrus (pars opercularis, BA 44) | L | -46 | 8 | 28 | 4.09 |
| 5 | Middle frontal gyrus | L | -38 | 40 | 30 | 6.05 |
| Middle frontal gyrus | L | -38 | 42 | 20 | 5.65 |
| Middle frontal gyrus | L | -36 | 42 | 16 | 5.64 |
| Middle frontal gyrus | L | -38 | 44 | 14 | 5.62 |
| Middle frontal gyrus | L | -28 | 48 | 16 | 4.65 |
| 6 | Inferior parietal lobule | L | -44 | -42 | 44 | 4.92 |
| Inferior parietal lobule (area hIP2, IPS) | L | -44 | -46 | 46 | 4.89 |
| Inferior parietal lobule (area hIP2, IPS) | L | -46 | -44 | 48 | 4.82 |
| Inferior parietal lobule (area PF, IPL) | L | -54 | -40 | 52 | 4.75 |</p>
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### Controls Choose-NoGo > Controls NoGo correct (T-contrast)

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**Note:**
- R: Right side
- L: Left side
- X, Y, Z: Coordinates
- T: Statistical significance (p-value)
**Supplementary Table 3.** Psychophysiological interactions: Local maxima of significant clusters per contrast, localised according to the Anatomy toolbox (v2.2b, Eickhoff et al 2007, Neuroimage) in SPM12, and the FSL Harvard-Oxford cortical and subcortical atlases ([https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases](https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases)) where the Anatomy toolbox did not contain a label (indicated by *). (L = left hemisphere, R = right hemisphere; x, y, z = co-ordinates of maximum activated voxel in MNI152 space, \( F / t = F / t \) stat at this voxel. Peaks are listed at \( p<0.05 \) FDR cluster corrected (cluster-forming threshold: \( p<0.001 \)).

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