Perspectives on functional and hyperkinetic movement disorders

Phenomenology & pathophysiology

van der Salm, S.M.A.

Citation for published version (APA):
Chapter 7

LINKING MOTION TO EMOTION IN FUNCTIONAL MOVEMENT DISORDERS USING COMBINED ELECTROMYOGRAPHY AND FUNCTIONAL MRI

S.M.A. van der Salm
A.F. van Rootselaar
M.J. Edwards
A.W.G. Buijink
J.N. van der Meer
P.F.C. Groot
J.H.T.M. Koelman
D.C. Cath
A.J. Nederveen
D.J. Veltman
M.A.J. Tijssen

Submitted
Chapter 7

**ABSTRACT**

**BACKGROUND**
Patients with functional, formerly known as ‘psychogenic’, movement disorders (FMD) have difficulty performing a simple voluntary movement task such as finger tapping. Patients with FMD report a decreased sense of control (also known as self-agency) over movement execution, while performing a voluntary task. In this functional Magnetic Resonance Imaging study we test the hypothesis that impaired voluntary task execution during finger tapping in FMD patients relates to alterations in the voluntary motor control network. Specifically, we hypothesize changes in the parietal cortex related to altered perceptual integration and changes in limbic areas related to altered drive to move.

**METHODS**
Seven patients with FMD and 18 healthy control subjects were included; in addition we included 12 patients with Tourette syndrome serving as a hyperkinetic control group. Our functional Magnetic Resonance Imaging study included a finger tapping task monitored with simultaneous video recordings and electromyography. Task analysis was based on electromyography on- and offset times. Functional connectivity analysis was used to investigate the neural network involved in task execution.

**RESULTS**
Patients with FMD had a significantly lower tapping frequency compared to healthy control subjects \((p = 0.041)\). In FMD patients decreased activation of bilateral parietal cortices (Brodmann area 31 and 7) and left dorsolateral prefrontal cortex was detected compared to Tourette patients during tapping. Functional connectivity was increased in patients with FMD compared to both Tourette patients and healthy controls between the left primary motor cortex, the left putamen and left limbic circuit (including the hippocampus, parahippocampal and cingulate gyrus and the amygdala).

**CONCLUSIONS**
We demonstrate that parietal perceptual integration is decreased during voluntary task execution in FMD patients compared to hyperkinetic controls. This might explain the decreased sense of agency and lack of experienced control over voluntary movements of FMD patients. The decreased activation of the parietal praxis area suggests that the difficulty to execute a voluntary motor task could be explained as ‘functional apraxia’, which is a novel interpretation. The increased functional connectivity between primary motor cortex and limbic areas in hyperkinetic functional movement disorder patients implicates a functional link between the emotional and voluntary motor network in FMD patients, and has therapeutic implications for this difficult to treat patient group.
INTRODUCTION

Psychogenic or functional movement disorders (FMD) are a specific subtype of conversion disorder, and are commonly encountered in neurological clinical practice. (1) While the aetiological significance of previous traumatic life events is often highlighted, the diagnosis is made primarily on the presence of a specific type of disordered movement. (2) FMD is characteristically altered by attentional focus: when attention is distracted, movements transiently normalise. Conversely when attention is focussed on to movement, for example during neurological examination, movement is more impaired. This phenomenon forms the basis for bedside and investigational diagnostic tests in FMD, best exemplified in the diagnosis of functional tremor. (3, 4)

Understanding the neural correlate of this key clinical characteristic is potentially important in advancing our understanding of the pathophysiology of FMD. However, the heterogeneity of the abnormal movements in patients with FMD makes experimental study difficult. Previous experimental studies have found that when patients with FMD perform a voluntary movement in an explicit or pre-prepared manner, the movement is abnormal both in its quality (reaction time, movement speed, presence of visual monitoring of the moving limb), in its subjective experience with regard to sense of control or agency, and in an experimental marker thought to reflect sense of agency (perceived timing of intention to move). (4-9) This suggests that assessment of brain function during performance of an explicit movement task in people with FMD may provide useful information regarding the mechanism of FMD, as well as providing a controllable experimental paradigm.

The primary aim of our study was therefore to use the known difficulty in executing voluntary movements in patients with FMD to inform our understanding of the pathophysiology of FMD itself.

During the execution of a finger tapping task, we compared FMD patients to healthy controls and to patients with Gilles de la Tourette syndrome (GTS) with predominant motor tics, included as a movement disorder control group. The rationale for inclusion of GTS patients is based on previously conducted studies in same cohort of patients with jerky FMD and motor tics (GTS). (9-13) In a clinical video study we observed that FMD patients have difficulty in performing a finger tapping task, and GTS patients do not, in line with previous reports. (4, 11, 13-19) Several studies demonstrated that internally driven motor performance and task execution are normal in GTS. (19) Of note, in GTS multiple large sample imaging studies found no difference in finger tapping performance or neuro-imaging activations in the voluntary motor circuit between patients and controls, which makes GTS patients an ideal comparison group to control for non-specific effects of having intermittent involuntary movement. (19)

When investigating the difficulty to perform a voluntary task in FMD patients the neurobiological model of normal movement generation needs to be considered. (Figure 1,
based on (5,20-22)) In this model, the drive to move originates in the prefrontal and limbic areas and is executed by the voluntary motor system (pre-SMA, mesial motor areas, DLPFC and SMA) via consecutive steps of the decision to move and motor planning. The perceptual integrator (parietal cortex) receives feedforward input from the areas involved in intentional motor planning, and feedback after the movement has occurred. Feedforward and feedback are integrated and weighted against prior beliefs of movement by the parietal perceptual integrator. When these forward and feedback signals match, this results in the feeling of being in control of one’s own actions (self-agency).

Based on previous experimental and theoretical work, we hypothesised that compared to healthy controls and patients with GTS, patients with FMD would have impaired performance of a finger tapping task, and that this would be associated with alterations in frontal and limbic connectivity with motor areas and activation of brain areas involved in comparison of expected vs actual sensory feedback, in particular parietal areas involved in perceptual integration.
Chapter 7

Based on (5, 20-22)) In this model, the drive to move originates in the prefrontal and limbic areas and is executed by the voluntary motor system (pre-SMA, mesial motor areas, DLPFC and SMA) via consecutive steps of the decision to move and motor planning. The perceptual integrator (parietal cortex) receives feedforward input from the areas involved in intentional motor planning, and feedback after the movement has occurred. Feedforward and feedback are integrated and weighted against prior beliefs of movement by the parietal perceptual integrator. When these forward and feedback signals match, this results in the feeling of being in control of one’s own actions (self-agency).

Based on previous experimental and theoretical work, we hypothesised that compared to healthy controls and patients with GTS, patients with FMD would have impaired performance of a finger tapping task, and that this would be associated with alterations in frontal and limbic connectivity with motor areas and activation of brain areas involved in comparison of expected vs actual sensory feedback, in particular parietal areas involved in perceptual integration.

Figure 1 Conceptual framework for the generation of internally driven normal volitional movements (based on (5, 20-22)). The limbic or prefrontal cortices generate the incentive to move. This drive to move is transmitted via the pre-supplementary cortex (pre-SMA), mesial motor areas and dorsolateral prefrontal cortex (DLPFC) to the supplementary motor cortex (SMA), whereby the “the decision to move” and the motor plan is made. Next, the SMA activates the primary motor cortex resulting in a movement. The resulting movement is fed back via a sensory feedback loop to a “perceptual integrator”. This perceptual integrator, presumably located in the parietal cortex, compares beliefs and expectations of movements with the received proprioceptive feedback. The “forward model” of volitional motor control proposes that generation of the motor command during motor planning in the brain also involves generation of an efference copy (feedforward signal) which is send to the perceptual integrator. (22) The efference copy is then compared to proprioceptive feedback. If mismatch is detected between the feedback and the efference copy of the intended movement, the movement can be corrected, even during execution of the movement itself. The feedforward and feedback information are integrated and weighted against prior beliefs of movement. When these match, this results in the feeling of being in control of one’s own actions, known as ‘self-agency’. DLPFC= dorsolateral prefrontal cortex. SMA= supplementary motor area.
METHODS
PARTICIPANTS
The present study is embedded within a larger study on FMD and GTS using video recordings, EEG recordings measuring the BP and fMRI evaluations, details of which have been reported previously. (9-13) Inclusion criteria for FMD and GTS patients were age older than 18 years, jerks/motor tics of the trunk, arms or legs. FMD patients were evaluated by experienced clinicians and classified as ‘clinically established’ FMD based on the Fahn and Williams criteria.(23) All included GTS patients met the DSM-IV-TR criteria for Gilles de la Tourette syndrome. Patients with excessive head movements, based on pre-MRI EEG-EMG recordings were excluded for the fMRI study. Healthy controls were included who were free of neuro- or psychiatric co-morbidity and were not using psycho-active drugs. Healthy controls were matched as a group to the FMD patients for age, gender, handedness and educational level. For the determination of subjects’ handedness the standard Edinburgh Handedness Inventory was used.(24) Education was classified using the 7-point Dutch Verhage educational scale, scoring: “1 = less than 6 years of education Dutch primary school” to “7 = specialized degree on University-level”. Psychiatric co-morbidity in patients was assessed with the Mini International Neuropsychiatric Interview (M.I.N.I.) plus.(26) To measure self-agency or the perception of voluntariness in FMD and GTS patients, a custom-made questionnaire was used.(9) The perceived degree of ‘agency’ (phrased as: the jerks are mine/ I feel the jerks belong to me) and the perceived degree of control were rated by the patients on a Visual Analogue Scale (VAS) ranging from 0 (absent/fully disagree) to 100 (present/fully agree).

The local medical ethics committee of the Academic Medical Center of the University of Amsterdam (AMC) approved the study (Helsinki declaration). Written informed consent was obtained from all participants.

EXPERIMENTAL PARADIGM
Participants had to repeatedly tap the thumb upon the index finger, middle finger, ring finger, little finger and back in reverse order with their right hand. Tapping task start and rest instructions were projected on a screen, located outside the scanner bore and visible by a mirror, to instruct subjects when to perform the task during scanning. Patients received no specific instructions regarding their abnormal movements (in other words no specific instructions to suppress or release FMD or tics).

Outside the scanner room, participants practised the task during EMG recording. Surface EMG sets were placed on the tapping muscles (the Flexor Carpi Radialis muscle (FCR), Exensor Carpi Radialis muscle (ECR), and First Dorsal Interosseus muscle (FDI)) of the right arm in all subjects.
The participants were scanned at rest and during right sided finger tapping. Task blocks lasted for 25.7 sec (= 10 functional images) and were repeated 7 times, followed by a final 5 scans period of rest at the end of the task to allow the BOLD signal to return to baseline. A total of 145 (20*7+5) functional images were recorded.

**DATA acQUISITION**

Functional images were acquired on a 3T MRI-scanner (Intera, Philips Healthcare, Best, the Netherlands) with a SENSE 8-channel head receive coil. For fMRI a T2* weighted EPI sequence was used (TR = 2.53 s, TE = 25 ms, Flip angle = 90, SENSE-factor = 2.4, 96 x 96 matrix, FOV = 214x214 mm, slice thickness = 2.7 mm, interslice gap = 0.3 mm, voxel size=2.3x2.3x3 mm³) with 45 sagittal slices covering the entire brain. In addition to functional data, a structural T1-weighted 3D image of the entire brain was obtained (TR = 25 ms, TE = 4.6 ms, SENSE-factor = 2.5, 256 x 256 matrix, FOV = 256x256 mm², 170 slices, slice thickness = 1 mm, sagittal slice orientation). Foam padding and a head strap were applied to minimize head motion.

EMG data were recorded with an MRI compatible EEG amplifier (SD MRI 64, MicroMed, Treviso, Italy) and an MRI compatible surface EMG cable unit providing 16 Ag/AgCl electrodes usable for up to 8 bipolar EMG derivations. Wires were twisted to minimize gradient artefacts and contained current-limiting electrodes of 12 kOhm. (26) Reference and ground electrodes were placed on the wrist (Ulnar Styloid Process). The sampling frequency was 2048 Hz. The EMG was synchronised in time to the MR scanning sequence, and in addition video recordings of the participants and scanner environments were made time-locked to the EMG acquisition.

**EMG DATA ANALYSIS**

Offline, the MR scanner artefact was removed from the EMG signal using an average artefact template subtraction algorithm with modifications for obtaining better performance in the EMG frequency band (30-200 Hz) and to increase adaptability during movements inside the scanner.(27) Following MR artefact removal, the EMG signal of the ECR and FDI was used to accurately determine the onset and offset of task performance for each participant using Brainvision analyser (version 1.03). The video recordings were used to further interpret the EMG signals (tapping performance vs. other movements). Spectral analysis of the EMG (Fast Fourier Transform) was used to quantify the peak frequency of participants’ performance of the motor tasks during scanning.
BEHAVIOURAL ANALYSES
Baseline characteristics and tapping performance were compared between study groups with non-parametric Kruskall Wallis and Mann Whitney U tests and in the case of dichotomous variables chi-squared tests. A significance threshold of $p<0.05$ was applied using the IBM Statistical Package for the Social Sciences software (SPSS Version 19.0).

IMAGE ANALYSIS
Pre-processing and data analysis was carried out using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks, Sherborn, MA). EPI images were spatially realigned using a least squares approach and a six parameter (rigid body) spatial transformation to the first EPI image and co-registered to the T1-weighted anatomical image. Images were resampled at 2x2x2 mm$^3$ and smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel. The on- and off-sets of the task, as determined by the EMG and video recordings, were used to temporally adjust the task regressor, which was subsequently convolved with a canonical hemodynamic response function. Movement induced effects were modelled using the 6 rigid-body motion parameters (first level analysis SPM) and by including the Volterra expansion consisting of linear and quadratic effects, and spin-history effects of the motion parameters, resulting in a total of 24 regressors added as nuisance covariates in the design matrix of a General Linear Model (GLM) in addition to task regressors.(28, 29) In the second-level analysis, between group comparisons were performed. All activations were reported for voxels detected at whole brain cluster-forming threshold $P<0.005$, cluster-wise interference $P<0.05$ (False Discovery Rate (FDR)-corrected). (30) The results were visualized using xjView toolbox (www.alivelearn.net/xjview), mricron (http://people.cas.sc.edu/rorden/mricron/index.html) and the Anatomy toolbox (www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMANATOMYToolbox).
Results

Participants
Thirteen FMD patients, 15 GTS patients and 19 control subjects were scanned. Ten participants had to be excluded from fMRI analysis due to motion artefacts. Thus, 7 FMD patients, 12 GTS patients and 18 control subjects were included in final analyses. Table 1 summarizes the clinical characteristics of the remaining patients and controls. The median age was 50 years (range 38-65, 4 males) for FMD patients, a median age of 32 years (range 20-46, 10 males) for GTS patients, and a median age of 52.5 years (range 21-77, 11 males) for healthy control subjects. In each group one subject was ambidextrous and the other participants were right-handed. Median educational level was 5 in FMD patients (range 5-6), 6 in GTS patients (range: 3-7) and 5.5 in control subjects (range: 1-7).

Although the exclusion of participants that were originally matched on age resulted in a wider range of age distribution, there was no significant difference between all groups for age (Kruskal Wallis p=0.106), gender (p=0.436), handedness (p=0.778) or educational level (p=0.906). There were no significant differences for age, gender, handedness or educational level upon pairwise comparisons (Mann Whitney U tests between FMD & GTS, FMD & controls, GTS & controls).

Disease duration was significantly longer in GTS (median 19.5 years, range: 5-32) compared to FMD patients (median 6 years, range: 3-12) (p= 0.005).

Psychiatric co-morbidity is listed in Table 1. One GTS patient had co-morbid attention deficit hyperactivity disorder. This GTS patient was on medication (methylphenidate) and was continued during scanning. The same patient used alprazolam or clonazepam and one FMD patient occasionally used diazepam, from which they both abstained for >24 hours before scanning. All other patients were medication free during testing (see Table 1).

There was a significant difference between FMD and GTS patients regarding the perceived degree of ‘self-agency’ and control over the movements induced by their disorder. FMD patients rated the degree of perceived agency (I feel the jerks belong to me) with a median of 8 on a 100 point scale (0=completely absent) and GTS as 81 on a 100 scale (p=0.028). FMD patients rated the degree of perceived control over the movements with a median of 4 on a 100 point scale (0=completely absent) and GTS as 45 on a 100 scale (p=0.007).
### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Group</th>
<th>Age</th>
<th>Gender</th>
<th>Handedness</th>
<th>Medication</th>
<th>Psychiatric co-morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FMD</td>
<td>44</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>OCD, generalised anxiety, depression (past), dysthymic disorder, social phobia, alcohol dependence</td>
</tr>
<tr>
<td>2</td>
<td>FMD</td>
<td>65</td>
<td>M</td>
<td>A</td>
<td>-</td>
<td>Depression (past), alcohol dependence</td>
</tr>
<tr>
<td>3</td>
<td>FMD</td>
<td>65</td>
<td>F</td>
<td>R</td>
<td>Diazepam</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>FMD</td>
<td>50</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>FMD</td>
<td>53</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>Depression (past)</td>
</tr>
<tr>
<td>6</td>
<td>FMD</td>
<td>38</td>
<td>F</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>FMD</td>
<td>38</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>GTS</td>
<td>41</td>
<td>F</td>
<td>R</td>
<td>-</td>
<td>OCD, panic disorder</td>
</tr>
<tr>
<td>9</td>
<td>GTS</td>
<td>39</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>GTS</td>
<td>20</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>Depression (past), OCD, alcohol dependence, manic episode (past)</td>
</tr>
<tr>
<td>11</td>
<td>GTS</td>
<td>29</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>Depression (past), OCD, alcohol dependence, generalised anxiety</td>
</tr>
<tr>
<td>12</td>
<td>GTS</td>
<td>46</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>GTS</td>
<td>35</td>
<td>F</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>GTS</td>
<td>23</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>GTS</td>
<td>23</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>GTS</td>
<td>42</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>GTS</td>
<td>39</td>
<td>M</td>
<td>A</td>
<td>-</td>
<td>Depression (past), OCD, substance dependence, social phobia</td>
</tr>
<tr>
<td>18</td>
<td>GTS</td>
<td>29</td>
<td>M</td>
<td>R</td>
<td>Methylphenidate, clonazepam / alprazolam</td>
<td>OCD, ADHD</td>
</tr>
<tr>
<td>19</td>
<td>GTS</td>
<td>25</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>OCD</td>
</tr>
</tbody>
</table>

Medians are reported for age (years). M= male, F= female, FMD= functional movement disorders, GTS = Gilles de la Tourette syndrome, R=right, A=ambidexter, OCD= obsessive compulsive disorder, ADHD= attention deficit hyperactivity disorder.
**Performance and EMG Results**

Evaluation of the video and EMG signal revealed that all participants were able to perform the sequential finger tapping task correctly. The mean tap frequency was 1.94 Hz (SD 0.86) in FMD, 2.38 Hz (SD 0.89) in GTS and 2.85 Hz (SD 0.77) in controls. There was no overall significant difference in tapping frequency between all groups (p=0.100 Kruskal Wallis), but FMD patients had a significantly lower tap frequency compared to controls (Mann Whitney U p=0.041). An illustrative example of an EMG recording is shown in Supplementary Figure 1.

Supplementary Figure 1 EMG trace during rest and finger tapping in an FMD patient before (upper panel) and after (lower panel) correction for scanner artefact (10 second epoch; black dotted vertical line at 2.5 sec: task instruction to start finger tapping; red dotted vertical line: actual start indicated by EMG of right sided m. extensor carpi radialis (ECR) and first dorsal interosseous). In the uncorrected EMG signal (top panel) determining the onset of the task execution is impossible. After removal of the scanner artefacts (lower panel), muscle activity associated with task execution is easily detected. Note the tenfold scale difference of the Y axis between the upper and lower panel (10000 and 1000 mV respectively).
**FUNCTIONAL IMAGING RESULTS**

Within group analyses of the main effect of the tapping task (ANOVA of FMD, GTS & controls, all FDR corrected) showed the strongest BOLD activations for ‘tapping’ conditions in the bilateral (left > right) primary and pre-motor cortex (Brodmann area 4, p<0.001) and SMA, right and left cerebellum (p<0.001), and left putamen and pallidum (p<0.001), all part of the voluntary motor circuitry. In addition, the left inferior parietal area showed significant activity (Brodmann area 40, p<0.001). Results of the main effect of the tapping task across all groups are shown in Table 2 and Figure 2A.

Between group comparisons of the main effect of the tapping task (ANOVA of FMD, GTS & controls) revealed no significant differences between groups. Between group comparisons (two sample t-tests, FDR corrected) showed no differences between groups, except for the comparison between GTS and FMD (GTS > FMD). (Table 3, Figure 2B) Increased activation during tapping in was found in GTS compared to FMD patients in the left parietal lobe, precuneus and cingulate gyrus (Brodmann area 7 and 31, p= 0.001 left hemisphere and p<0.001 right hemisphere), the left medial frontal cortex and DLPFC (Brodmann area 8 and 9, p=0.001), left temporal lobe and superior temporal gyrus (Brodmann area 38, p=0.012), right precuneus (Brodmann area 7, p=0.05) and the middle temporal gyrus (Brodmann area 21, p=0.05).

Contrast estimates indicated that the differences between GTS and FMD resulted from consistent increased activation in GTS and consistent decreased activation in FMD. (Figure 3)
FUNCTIONAL IMAGING RESULTS

Within group analyses of the main effect of the tapping task (ANOVA of FMD, GTS & controls, all FDR corrected) showed the strongest BOLD activations for 'tapping' conditions in the bilateral (left > right) primary and pre-motor cortex (Brodmann area 4, p<0.001) and SMA, right and left cerebellum (p<0.001), and left putamen and pallidum (p<0.001), all part of the voluntary motor circuitry. In addition, the left inferior parietal area showed significant activity (Brodmann area 40, p<0.001). Results of the main effect of the tapping task across all groups are shown in Table 2 and Figure 2A.

Between group comparisons of the main effect of the tapping task (ANOVA of FMD, GTS & controls) revealed no significant differences between groups. Between group comparisons (two sample t-tests, FDR corrected) showed no differences between groups, except for the comparison between GTS and FMD (GTS > FMD). (Table 3, Figure 2B) Increased activation during tapping in was found in GTS compared to FMD patients in the left parietal lobe, precuneus and cingulate gyrus (Brodmann area 7 and 31, p= 0.001 left hemisphere and p<0.001 right hemisphere), the left medial frontal cortex and DLPFC (Brodmann area 8 and 9, p=0.001), left temporal lobe and superior temporal gyrus (Brodmann area 38, p=0.012), right precuneus (Brodmann area 7, p=0.05) and the middle temporal gyrus (Brodmann area 21, p=0.05).

Contrast estimates indicated that the differences between GTS and FMD resulted from consistent increased activation in GTS and consistent decreased activation in FMD. (Figure 3)

Table 2 Main effect of tapping task

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Side</th>
<th>BA</th>
<th>Cluster size</th>
<th>MNI Coordinates</th>
<th>Peak z</th>
<th>P Value (FDR corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary motor cortex, SMA, Premotor cortex</td>
<td>L&gt;R</td>
<td>4,6</td>
<td>10191</td>
<td>-38 -18 52</td>
<td>&gt;8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>-</td>
<td>842</td>
<td>18 -54 -20</td>
<td>&gt;8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior parietal lobe</td>
<td>L</td>
<td>40</td>
<td>110</td>
<td>-52 -38 24</td>
<td>5.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>-</td>
<td>250</td>
<td>-24 -58 -22</td>
<td>5.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Putamen and pallidum</td>
<td>L</td>
<td>-</td>
<td>142</td>
<td>-22 0 8</td>
<td>5.58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2 Main effects of the tapping task across all participants (ANOVA, FDR corrected for multiple comparisons). FMD= functional movement disorder; GTS= Gilles de la Tourette; L = left, R= right, BA= Brodmann area.
**Table 3** Imaging findings comparing Gilles de la Tourette (GTS) with FMD patients during finger tapping.

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Side</th>
<th>BA</th>
<th>Cluster size</th>
<th>MNI Coordinates</th>
<th>Peak Z</th>
<th>P Value (FDR corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal and limbic lobe, precuneus and cingulate gyrus</td>
<td>L</td>
<td>7 &amp; 31</td>
<td>257</td>
<td>-2</td>
<td>-66</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>31</td>
<td>554</td>
<td>6</td>
<td>-40</td>
<td>40</td>
</tr>
<tr>
<td>Medial frontal cortex</td>
<td>L</td>
<td>8</td>
<td>256</td>
<td>-46</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>DLPFC</td>
<td></td>
<td>9</td>
<td></td>
<td>-20</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Superior temporal gyrus/ angular gyrus</td>
<td>L</td>
<td>38</td>
<td>171</td>
<td>-48</td>
<td>10</td>
<td>-26</td>
</tr>
<tr>
<td>Parietal lobe, precuneus</td>
<td>R</td>
<td>7</td>
<td>119</td>
<td>-66</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe, middle temporal gyrus</td>
<td>R</td>
<td>21</td>
<td>120</td>
<td>62</td>
<td>0</td>
<td>-8</td>
</tr>
</tbody>
</table>

**Table 3** displays significant differences between Gilles de la Tourette syndrome (GTS) and FMD patients during the tapping task across all participants (t-test, FDR corrected for multiple comparisons). DLPFC = dorsolateral prefrontal cortex.
**Table 3** Imaging findings comparing Gilles de la Tourette (GTS) with FMD patients during finger tapping.

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Side</th>
<th>BA</th>
<th>Cluster Size</th>
<th>MNI Coordinates</th>
<th>Peak Z</th>
<th>P Value (FDR corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal and limbic lobe, p-recuneus and cingulate gyrus</td>
<td>L</td>
<td>7 &amp; 31</td>
<td>257</td>
<td>-2 -2 -66</td>
<td>20</td>
<td>4.93</td>
</tr>
<tr>
<td>Parietal and limbic lobe, p-recuneus and cingulate gyrus</td>
<td>R</td>
<td>31</td>
<td>554</td>
<td>6 -40 40</td>
<td>40</td>
<td>4.61</td>
</tr>
<tr>
<td>Medial frontal cortex</td>
<td>L</td>
<td>8</td>
<td>9</td>
<td>256</td>
<td>-46 -20 18</td>
<td>36</td>
</tr>
<tr>
<td>Superior temporal gyrus/angular gyrus</td>
<td>L</td>
<td>38</td>
<td>171</td>
<td>-48 -18 -26</td>
<td>26</td>
<td>4.15</td>
</tr>
<tr>
<td>Parietal lobe, precuneus</td>
<td>R</td>
<td>7</td>
<td>119</td>
<td>30 -66 40</td>
<td>40</td>
<td>4.18</td>
</tr>
<tr>
<td>Temporal lobe, middle temporal gyrus</td>
<td>R</td>
<td>21</td>
<td>120</td>
<td>62 0 -8</td>
<td>8</td>
<td>4.37</td>
</tr>
</tbody>
</table>

Table 3 displays significant differences between Gilles de la Tourette syndrome (GTS) and FMD patients during the tapping task across all participants (t-test, FDR corrected for multiple comparisons). DLPFC = dorsolateral prefrontal cortex.

**Figure 2** Results of tapping task

Figure 2A Main effects of the tapping task across all participants (ANOVA, FDR corrected for multiple comparisons), showing displays the voluntary motor circuit, primarily consisting of the contralateral (left) primary motor cortex, SMA and ipsilateral (and contralateral to a lesser extent) cerebellum. R= right hemisphere (images are displayed in "neurological" convention).

Figure 2B Between group comparison of the tapping task FMD < GTS. Figure 2B displays decreased activity in bilateral parietal cortex (Brodmann area (BA) 7 and 31) in FMD compared to Tourette (shown in blue/green).
Figure 3 shows the consistent directionality of the between group comparison FMD < GTS during the tapping task. Note that FMD patients consistently show decreased and GTS patients increased activations of this areas during finger tapping. The x axis lists the patients and control groups. The y-axis displays the parameter contrast estimate (value range: -1 to 1, expressed in arbitrary units, with 90% confidence interval). Significant differences were found in the peak activations [in brackets on y-axis] in the left dorso-lateral prefrontal cortex (DLPFC), left and right parietal cortex (BA7 and 31) between FMD and GTS patients groups.

FUNCTIONAL CONNECTIVITY (PPI)

Functional connectivity analysis by means of PPI of the peak activation in the primary motor cortex across all subjects (FMD, GTS and control subjects, ANOVA) revealed six significant clusters. See Table 4 and Figure 4A for details.

The first cluster encompassed the left postcentral somatosensory gyrus (p<0.001) which showed marked decreased connectivity in control subjects compared to increased connectivity in FMD and GTS. The second cluster consisted of the left paracentral lobe (Brodmann area 4A) and superior parietal lobe (Brodmann area 5m, p<0.001) with increased connectivity in FMD and GTS compared to decreased connectivity in control subjects. The next cluster consisted of the left posterior cingulate (Brodmann area 21,23, p<0.001) with increased connectivity in FMD and GTS relative to control subjects. The fourth cluster contained the left parahippocampal gyrus (p<0.001) with increased connectivity in FMD, compared to GTS and control subjects. The fifth cluster consisted of the left putamen and left amygdala (p=0.004) with increased connectivity in FMD relative to decreased activity in GTS and control subjects. The last cluster comprised the left middle temporal gyrus (p=0.001) with increased connectivity in FMD relative to decreased connectivity in GTS and control subjects. The directionality of the connectivity in healthy control subjects is considered normal and the direction of the connectivity of FMD and GTS patients compared to healthy control subjects is listed separately in Table 4.

Pair-wise between group comparison revealed one significant cluster in the FMD > GTS patients comparison. The cluster encompassed the left hippocampus and parahippocampal gyrus (cluster extent 248, p<0.001) which showed marked decreased connectivity in control subjects relative to the increased connectivity in FMD and GTS (see Figure 4B).
FUNCTIONAL CONNECTIVITY (PPI)

Functional connectivity analysis by means of PPI of the peak activation in the primary motor cortex across all subjects (FMD, GTS and control subjects, ANOVA) revealed six significant clusters. See Table 4 and Figure 4A for details.

The first cluster encompassed the left postcentral somatosensory gyrus \((p<0.001)\) which showed marked decreased connectivity in control subjects compared to increased connectivity in FMD and GTS. The second cluster consisted of the left paracentral lobe (Brodmann area 4A) and superior parietal lobe (Brodmann area 5m, \(p<0.001\)) with increased connectivity in FMD and GTS compared to decreased connectivity in control subjects. The next cluster consisted of the left posterior cingulate (Brodmann area 21,23, \(p<0.001\)) with increased connectivity in FMD and GTS relative to control subjects. The fourth cluster contained the left parahippocampal gyrus \((p<0.001)\) with increased connectivity in FMD, compared to GTS and control subjects. The fifth cluster consisted of the left putamen and left amygdala \((p=0.004)\) with increased connectivity in FMD relative to decreased activity in GTS and control subjects. The last cluster comprised the left middle temporal gyrus \((p=0.001)\) with increased connectivity in FMD relative to decreased connectivity in GTS and control subjects. The directionality of the connectivity in healthy control subjects is considered normal and the direction of the connectivity of FMD and GTS patients compared to healthy control subjects is listed separately in Table 4.

Pair-wise between group comparison revealed one significant cluster in the FMD > GTS patients comparison. The cluster encompassed the left hippocampus and parahippocampal gyrus (cluster extent 248, \(p<0.001\)) which showed marked decreased connectivity in control subjects relative to the increased connectivity in FMD and GTS (see Figure 4B).
Table 4 Results of functional connectivity analysis

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Area</th>
<th>Side</th>
<th>BA</th>
<th>p value (FDR)</th>
<th>Ke</th>
<th>Peak</th>
<th>Coordinates</th>
<th>Connectivity value</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Primary somatosensory cortex</td>
<td>L</td>
<td>3B, 4P</td>
<td>&lt;0.001</td>
<td>479</td>
<td>5.20</td>
<td>-44 -22 50</td>
<td>0.73 -0.21 -0.21</td>
<td>↑ =</td>
</tr>
<tr>
<td>2</td>
<td>Primary motor cortex</td>
<td>L</td>
<td>4A</td>
<td>0.004</td>
<td>257</td>
<td>4.34</td>
<td>-10 -28 70</td>
<td>0.23 0.32 -0.31</td>
<td>↑ ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>5m</td>
<td>0.004</td>
<td>257</td>
<td>3.26</td>
<td>-8 -38 54</td>
<td>0.23 0.32 -0.31</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>3</td>
<td>Midcingulate cortex</td>
<td>L</td>
<td>31/ 23</td>
<td>&lt;0.001</td>
<td>734</td>
<td>4.32</td>
<td>-10 -36 34</td>
<td>0.31 0.20 -0.30</td>
<td>↑ ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Hippocampus, parahippocampal</td>
<td>L</td>
<td>-</td>
<td>0.001</td>
<td>336</td>
<td>4.19</td>
<td>-10 -30 -20</td>
<td>0.84 0.20 -0.43</td>
<td>↑↑ ↑</td>
</tr>
<tr>
<td>5</td>
<td>Putamen</td>
<td>L</td>
<td>-</td>
<td>0.05</td>
<td>136</td>
<td>3.74</td>
<td>-28 6 2</td>
<td>0.37 -0.19 -0.32</td>
<td>↑↑ ↑</td>
</tr>
<tr>
<td></td>
<td>Amygdala</td>
<td>L</td>
<td>-</td>
<td>0.05</td>
<td>136</td>
<td>3.43</td>
<td>-26 -8 -6</td>
<td>0.37 -0.19 -0.32</td>
<td>↑↑ ↑</td>
</tr>
<tr>
<td>6</td>
<td>Middle temporal gyrus</td>
<td>L</td>
<td>21</td>
<td>0.010</td>
<td>212</td>
<td>3.57</td>
<td>-44 -28 -4</td>
<td>0.60 -0.18 -0.14</td>
<td>↑ =</td>
</tr>
</tbody>
</table>

Table 4 displays the results of the functional connectivity analysis across all participants (ANOVA, FDR corrected for multiple comparisons). Connectivity values (beta estimates) are listed per diagnostic group. In the last columns the direction of connectivity (increased or decreased) is depicted for FMD and GTS patients as compared to the connectivity value of the healthy control subjects (assumed to be normal connectivity value). FMD = functional movement disorder; L = left, R = right, BA = Brodmann area, ↑ indicates increased functional connectivity, ↓ indicates decreased, = similar functional connectivity to controls, - means not applicable. Ke = cluster extent.
**Figure 4** Functional connectivity results

Figure 4A shows the increased connectivity of the left putamen and amygdala (one cluster, left panel), posterior cingulate cortex and parahippocampal gyrus (middle panel) and somatosensory cortex (upper right panel) with the primary motor cortex in FMD patients compared to GTS patients and controls (ANOVA). Figure 4B shows the between group comparison FMD > GTS patients. It shows the increased connectivity of left hippocampus and parahippocampal gyrus to the primary motor cortex in FMD compared to GTS. Images are displayed in "neurological" convention (right side of image is right hemisphere).

**Figure 5**

Figure 5 shows the significant difference in the contrast estimate (y-axis, value range: -1 to 1, expressed in arbitrary units, with 90% confidence interval) of ANOVA analysis of the peak activation (coordinate in brackets) on y-axis) of the left amygdala in FMD patients compared to GTS patients and controls (x-axis).
Chapter 7

DISCUSSION
We investigated the pathophysiological mechanism underlying FMD by examining the common difficulty FMD patients have in executing an explicit voluntary movement using simultaneous EMG with functional MRI. The main finding of our study is the significantly increased functional connectivity between the primary motor cortex and the limbic circuit (hippocampus, parahippocampal and mid- and posterior cingulate gyrus and amygdala) in FMD patients compared to GTS patients and healthy controls. This increased limbic-motor connectivity suggests that voluntary movements that are performed in an explicit “attentional-full” context and by implication the functional jerky movements occur in the presence of increased connectivity to limbic areas. Interestingly, during finger tapping we found lower activation of the bilateral parietal cortex (Brodmann areas 31 and 7) and left DLPFC (Brodmann area 9) in FMD relative to in GTS patients. Our findings suggest that perceptual integration within the parietal lobe is decreased during finger tapping in FMD patients.

FUNCTIONAL CONNECTIVITY
The main finding of the connectivity analysis in FMD patients is the increased functional connectivity of the primary motor cortex with the limbic circuit (amygdala, hippocampus, parahippocampal and cingulate gyrus) in the left hemisphere compared to GTS and healthy controls. Increased connectivity of the limbic areas with motor cortex areas suggests an enhanced association between the two, i.e. either the movements produce heightened limbic activity or the reverse. This is in line with previous imaging studies that found increased connectivity between the right amygdala and SMA using an emotional instead of motor paradigm (looking at emotional (fearful) faces).(31) Our study by means of a motor task therefore provides additional evidence that increased functional coupling between the voluntary motor circuit and the limbic region is more widespread (more limbic structures appear to be involved) and is increased during performance of a difficult motor task. Alternatively, the increased limbic-motor connectivity could be due to the anxiety of the FMD patients, either general anxiety in FMD patients, or anxiety induced by execution of a difficult finger tapping task.

In addition we found increases in functional connectivity between the primary motor cortex and the primary somatosensory areas, the superior parietal lobe, midcingulate and posterior cingulate cortex in both GTS and FMD patients compared to controls. The increased connectivity between the primary motor cortex and somatosensory cortex implicates increased sensorimotor integration in both patient groups. Despite the similar increased sensorimotor integration, FMD patients still perceive a lesser degree of agency over the movements, suggesting altered involvement of additional neural networks in FMD.

DECREASED PARIETAL PERCEPTUAL INTEGRATION
During finger tapping FMD patients showed decreased activation of the bilateral parietal cortex (Brodmann areas 31 and 7) relative to GTS patients. We failed to observe significantly
decreased parietal activation compared to control subjects (although a trend is seen in Figure 3), possibly due to the relatively small FMD sample size. The parietal decreased activation compared to GTS patients may however reflect the pathophysiology of FMD. The parietal areas are known as the perceptual integrator and the generation of the sense of agency. In this cohort we found significantly less agency and control in FMD compared to GTS (SAPF questionnaire, p= 0.028 and p=0.007). We postulate that the decreased sense of agency relates to the decrease in parietal activation. This assumption is supported by the findings of a recent resting state fMRI study in patients with FMD that found decreased functional connectivity between the right parietal cortex and bilateral sensorimotor regions.(32) Moreover, the decreased parietal activation in FMD relative to GTS is in agreement with the hypothesis of Edwards and colleagues who postulated that the perceptual integrator in FMD is influenced by abnormal expectations and beliefs about movements (a.k.a. abnormal Bayesian priors, for a full description see (20)). While clearly in need of replication, our finding underlines the importance in the role of the bilateral parietal lobe in the neural network underlying FMD (Figure 6, in blue).

The decreased activation of the parietal praxis area (Brodmann area 7) during finger tapping in the FMD patients suggests an alternative explanation, namely that FMD patients suffer from ‘functional apraxia', i.e. a functional deficit in praxis. Our findings of decreased activation of the parietal areas 7 and 31 are in line with the imaging studies in apraxia patients.(33) Moreover, in FMD patients relative to GTS patients we found decreased activation of the medial frontal cortex and DLPFC. The medial frontal cortex is also known to be impaired in apraxia.(33) In line with our findings, decreased functional connectivity of the bilateral DLPFC and SMA was found in functional tremor.(37) Instead, the DLPFC has been consistently found to be increased in activation in several studies on functional sensorimotor dysfunction (both motor paralysis and somatosensory) and fixed dystonia, even though experimental paradigms varied (see reviews (34, 35) and (36)). The increased activation of the DLPFC has been explained in various ways, including impairments in motor intention or disruption of motor execution.(36) Other explanations are that hyperactive self-monitoring or limbic processing interferes with motor execution in the DLPFC. (34,35,37) Thus, the decreased activation in the left DLPFC found in our study could be a hallmark of hyperkinetic FMD as opposed to the increased activation of the DLPFC in hypokinetic functional disorders (fixed dystonia, paralysis).

Reconsidering the clinical observation that FMD patients have difficulty to finger tap in light of the findings of our imaging study as ‘functional apraxia', resemblance with apraxia is also clinically apparent. Ideomotor apraxia is defined as the impaired performance of skilled motor acts despite intact sensory, motor, and language function.(33) Patients with ideomotor apraxia and patients with FMD both show temporal and spatial errors affecting timing, sequencing, amplitude, configuration, and limb position in space.(4,33) FMD and apraxia patients both have increased visual attention to the tapping limb and decreased
tapping speed. Patients with ideomotor apraxia appear to use their limb as an object, and this bears resemblances to the perceived lack of self-agency of FMD patients. In analogy to FMD, patients with apraxia are often able to perform the same acts without difficulty in their daily lives. This phenomenon has been called the "voluntary-automatic dissociation". Importantly, the clinical interpretation of the difficulty to execute a voluntary motor task as functional apraxia could lead to different therapeutic strategies in FMD patients. Recent studies have demonstrated the significant benefits of physiotherapy of FMD. Based upon our imaging results, we suggest future studies and physiotherapists to approach FMD patients in a similar fashion as apraxia patients and adjust therapy to overcome the abnormal self-directed attention and the voluntary-automatic dissociation.

Our findings of altered activation of bilateral parietal cortex differ from previous fMRI studies, which demonstrated isolated decreased functioning of the right temporal-parietal junction. The more extended parietal impairment as found in our study and the involvement of BA 7 and 31 (praxis areas) instead of the temporo-parietal junction might be explained by the fact that in the current study patients executed a difficult motor task. During execution of the tapping task, we found no differences between groups in the voluntary motor circuits. This network primarily involves the primary sensory and primary motor cortex, as well as premotor cortex and SMA contralateral to the moving hand and both the ipsilateral and (to lesser extent) the contralateral cerebellum. Our findings imply that FMD patients are able to employ the voluntary motor circuit normally in order to finger tap, although the tapping frequency is decreased.

**INSIGHTS IN FMD PATHOPHYSIOLOGY**

Neurobiological models of FMD propose three pathophysiological mechanisms: 1) an abnormal sense of self-agency, 2) abnormal focus of attention (self-directed attention) and 3) abnormal prior beliefs and expectation of movements. Support for all three pathophysiological mechanisms has been provided by functional Magnetic Resonance Imaging (fMRI) studies. However, none of these studies explain why patients with FMD experience difficulty with the executing of a voluntary motor task and experience a decreased sense of agency while performing these tasks. Combining the results of the fMRI tapping task analysis and functional connectivity analysis we postulate the following pathophysiological model of FMD with hyperkinetic jerks (summarized in Figure 6). An increased limbic emotional drive to move (Figure 6) enables the jerky movements to occur via employment of the voluntary motor network (pre-SMA, SMA and primary motor cortex). This is reflected in the presence of the Bereitschaftspotential prior to the jerky movements, which is known to be generated by these structures. Our findings suggest that there is a continuous drive or readiness in FMD patients to move, resulting in hyperkinetic jerky movement. The DLPFC is decreased in activity, which may influence the ability of FMD patients to decide to move. The parietal perceptual integrator is less active in FMD. This could be due to the continuous feedforward signal that the parietal perceptual integrator
receives from the limbic areas. If this hypothesis is true, the decreased parietal activation is a secondary phenomenon and would normalise in case the increased limbic drive to move subsides with treatment. Alternatively, it could also be that the decreased parietal perceptual integration is primarily involved in FMD. In support of primary involvement is the fact that physiotherapy aimed at increasing ownership and control of movements is proven effective in FMD. Our findings therefore, call for new clinical and neuroimaging studies of praxis and agency in FMD patients.

**Figure 6** Insights pathophysiology of FMD based on imaging results

Figure 6 The findings of our study in FMD patients integrated in the conceptual framework for the generation of normal volitional movement as shown in Figure 1. During execution of the finger tapping task, decreased activation of the parietal cortices and dorso-lateral prefrontal cortex (DLPFC) is found (depicted in blue). We postulate that this implies decreased perceptual integration. In addition, in patients with FMD, the functional connectivity analysis showed that the drive to move originating in the limbic areas (in red) has increased functional connectivity with the primary motor cortex. The employment of the voluntary motor circuit appears normal in FMD compared to control subjects and GTS, because we did not find differences in the voluntary motor system (pre-SMA, mesial motor areas, and SMA), except for the DLPFC.
STRENGTHS AND LIMITATIONS OF THE STUDY
A limitation of our study is the relatively small sample size due to the exclusion of participants with excessive head motion. Even though during previously published EEG-EMG recordings we screened both FMD and GTS patients on head movements induced by their jerky movements and only included those with few head movement in the consecutive fMRI study, some patients still induced too much movement artefact with their movements. (12) Nevertheless, the sample size in our study is comparable to previous neuroimaging studies in FMD, in which the majority had similar small sample sizes. (31,32,36,37,41,46) These small sample sizes illustrate that it is obviously difficult to scan FMD patients, in particular jerky hyperkinetic movement disorders, with a motion artefact sensitive imaging technique such as fMRI. The occurrence of the movements induced by FMD or tics were not separately analysed, and occurred both during execution of the task and rest condition. Even though the sample size of the current study was rather small, we still found significant differences implicating a strong difference between FMD patients and GTS patients during finger tapping. However, a larger sample size might have resulted in significant differences of the parietal decreased activation compared to healthy control subjects, as the contrast estimates in Figure 3 show a consistent trend between FMD and healthy control subjects. The current study might have been underpowered in this respect. A major strength of our study is the inclusion of patients with FMD and GTS with similar movements. Patients were matched on the phenomenology of their movement disorder (jerks of trunk, arms, legs) and this resulted in a homogenous population of patients. In the current study GTS patients served as a hyperkinetic control sample. We replicated previous findings that GTS patients were able to finger tap normally and no difference were found in the underlying motor network upon fMRI task analysis. (14-19) Thus, we postulate that GTS patients are able to overrule or suppress tic generation during finger tapping. A possible explanation is the longer disease duration in GTS compared to FMD patients or the increased sense of control over the movements experienced by GTS patients. Thus, the main findings of our study therefore do appear to be specific for FMD patients.

In conclusion, we demonstrate for the first time increased connectivity between the limbic circuit and the primary motor cortex in FMD patients while executing a difficult voluntary motor task. Our finding provides evidence for an increased limbic and emotional drive to move, which might ultimately result in the hyperkinetic jerky movements in FMD. Moreover, we report decreased bilateral parietal integration of voluntary executed movement in FMD, which may explain the decreased sense of self-agency in FMD patients.

ACKNOWLEDGEMENTS
We thank Debbie de Boer and Eelke Brouwers for assistance during scanning.
A limitation of our study is the relatively small sample size due to the exclusion of
Nevertheless, the sample size in our study is comparable to previous neuroimaging studies
recordings we screened both FMD and GTS patients on head movements induced by their
We thank Debbie de Boer and Eelke Brouwers for assistance during scanning.
estimates in Figure 3 show a consistent trend between FMD and healthy control subjec ts.
parietal decreased activation compared to healthy control subjects, as the contrast
tapping. However, a larger sample size might have resulted in significant differences of the
implicating a strong difference between FMD patients and GTS patients during finger
analysed, and occurred both during execution of the task and rest condition. Even though
hyperkinetic movement disorders, with a motion artefact sensitive imaging technique such

In conclusion, we demonstrate for the first time increased connectivity between the limbic
circuit and the primary motor cortex in FMD patients while executing a difficult voluntary
therefore do appear to be specific for FMD patients.
longer disease duration in GTS compared to FMD patients or the increased sense of control
over the movements experien ced by GTS patients. Thus, the main findings of our study
move, which might ultimately result in the hyperkinetic jerky movements in FMD. Moreover,

ACKNOWLEDGEMENTS

REFERENCES
1. Stone J, Carson A, Duncan R, et al. Who is referred to neurology clinics?--the diagnoses made
2. Edwards MJ, Bhatia KP. Functional (psychogenic) movement disorders: merging mind and
Movement Disorders 2011;26:2575-2576.
sense of intention preceding voluntary movement in patients with psychogenic tremor.
9. Van der Salm SM, Cath DC, van Rootselaar AF, Koelman JH, de Haan RJ, Tijssen MA, Meynen
G. Clinician and patient perceptions of free will in movement disorders: Mind the gap.
Journal of Neurology, Neurosurgery and Psychiatry 2017 [In press].
jerky movement disorders: importance of evaluating non-credible cognitive performance
11. Van der Salm SM, de Haan RJ, Cath DC, van Rootselaar AF, Tijssen MA. The eye of the
beholder: inter-rater agreement among experts on psychogenic jerky movement disorders.
12. Van der Salm SM, Tijssen MA, Koelman JH, van Rootselaar AF. The bereitschaftspotential in
jerky movement disorders. Journal of neurology, neurosurgery, and psychiatry
2012;83:1162-1167.
13. Van der Salm SM, van Rootselaar AF, Cath DC, de Haan RJ, Koelman JH, Tijssen MA. Clinical
decision-making in functional and hyperkinetic movement disorders. Neurology. 2017
10;88:118-123.
15. Debes NM, Hansen A, Skov L, Larsson H. A functional magnetic resonance imaging study of a
large clinical cohort of children with Tourette syndrome. Journal of Child Neurology
2011;26:560-569.
syndrome and voluntary movement: a functional MRI study. Psychiatry Research
motor network recruitment during finger tapping in boys with Tourette syndrome. Human
Brain Mapping 2012;33:666-675.
18. Roessner V, Wittfthro M, August JM, Rothenberger A, Baudewig J, Dechent P. Finger tapping-
related activation differences in treatment-naive pediatric Tourette syndrome: a comparison
of the preferred and nonpreferred hand. Journal of Child Psychology and Psychiatry
Chapter 7