A feasibility study for somatomotor cortical mapping in Tourette syndrome using neuronavigated transcranial magnetic stimulation

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1. Abstract

Tourette syndrome (TS) is a hyperkinetic movement disorder characterised by the occurrence of chronic motor and vocal tics, and is associated with alterations in the balance of excitatory and inhibitory signalling within key brain networks; in particular the cortical-striatal-thalamic-cortical (CSTC) brain circuits that are implicated in movement selection and habit learning. Converging evidence indicates abnormal brain network function in TS may be largely due to the impaired operation of GABA signalling within the striatum and within cortical motor areas, leading to the occurrence of tics. TS has been linked to a heightened sensitivity to somatic stimulation and altered processing of somatosensory information, and there is evidence to indicate that alterations in GABAergic function is likely to contribute to altered somatomotor function. Based upon this evidence, we hypothesised that the specificity of somatomotor representations in primary motor cortex would likely be reduced in individuals with TS. To test this, we used a rapid acquisition method together with neuronavigated transcranial magnetic stimulation (nTMS) to measure the cortical representation of a several different muscles in a group of young adults with TS and a matched group of typically developing individuals.

2. Introduction

Tourette syndrome (TS) is a common neurological disorder of childhood onset that is characterised by the occurrence of vocal and motor tics and has been associated with alterations in the balance of excitatory and inhibitory signalling within key brain networks (Leckman, 2002). Specifically, TS has been linked to: dysfunction within cortical-striatal-thalamic-cortical brain circuits that are implicated in movement selection and habit learning (Albin & Mink, 2006); impaired operation of GABA (inhibitory) signalling within the striatum and within cortical motor areas (Albin & Mink, 2006; Gilbert et al., 2004; Kalanithi et al., 2005; Lerner et al., 2012; Orth, Münchau, & Rothwell, 2008; Orth & Rothwell, 2009); and hyper-excitability of limbic and motor regions of the brain that may contribute to the occurrence of tics (Heise et al., 2010; Vaccarino, Kataoka, Yuko, & Lennington, 2013).

There is mounting evidence that TS may be associated with the altered processing of somatosensory information, including altered interoception (Tinaz, Malone, Hallett, & Horovitz, 2015). First, the majority (~90%) of individuals with TS report that their tics are often preceded by 'premonitory sensory phenomena' (S. C. Cohen, Leckman, & Bloch, 2013) that are described as uncomfortable bodily sensations that occur prior to the execution of a tic and are experienced as a strong urge for motor discharge (hereafter referred to as premonitory urges

[PU]). Individuals who experience PU often report that: these experiences are more *bothersome* than their tics; that expressing their tics give them *relief from*, and temporarily *abolishes*, their PU; and that they *would not exhibit tics if they did not experience PU* (Cavanna, Black, Hallett, & Voon, 2017). For this reason, it has been proposed that PU should be considered as the driving force behind the occurrence of tics, and that tics are a learnt response to the experience of PU (Cavanna et al., 2017). PU are of clinical importance because they form the core component of behavioural therapies that are currently used in the treatment of tic disorders (S. C. Cohen et al., 2013).

Second, it has been suggested that PU may arise in part from heightened sensitivity to somatic stimulation (Belluscio, Jin, Watters, Lee, & Hallett, 2011; Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011). Consistent with this proposal, individuals with TS also often report heightened sensitivity to external sensory stimuli, such as irritation due to clothing fabrics, that causes great distress (Belluscio et al., 2011; A. J. Cohen & Leckman, 1992). Few studies have quantified the sensory thresholds empirically, but all show that in contrast to self-reports, patients with TS do not present with altered sensory thresholds (Belluscio et al., 2011; Schunke et al., 2016). Belluscio and colleagues (2011) hypothesised that the feeling of increased sensitivity in the periphery must arise within the CNS. However, no study has attempted to contextualise this observation, notwithstanding the high prevalence of self-reported hypersensitivity in TS (Belluscio et al., 2011; A. J. Cohen & Leckman, 1992).

There are now multiple lines of evidence to indicate that TS is associated with altered GABA function (e.g., Albin & Mink, 2006; Gilbert et al., 2004; Kalanithi et al., 2005; Lerner et al., 2012; Orth et al., 2008; Orth & Rothwell, 2009; Vaccarino et al., 2013), and that GABAergic signalling may play a key role in determining the precise neurophysiological response to somatic stimulation. For example, Kolasinski and colleagues (2017) recently demonstrated that increased GABA concentration, measured within primary somatosensory (S1) using magnetic resonance spectroscopy, was associated with more selective cortical tuning function, and with enhanced somatosensory perception. Furthermore, Puts and colleagues (Puts et al., 2015) have demonstrated previously that GABA concentrations within the sensorimotor cortex are significantly reduced in children with TS relative to typically developing controls (although see Draper et al., 2014 for a contradictory finding) and reported that tactile detection and adaptation is impaired in children with TS (cf., Belluscio et al., 2011; Schunke et al., 2016) consistent with reduced GABA signalling. Based upon these findings we hypothesise that the cortical tuning of somatomotor representations, as measured using transcranial magnetic stimulation, are likely to be less selective in individuals with TS. Importantly for our investigation, the primary motor (M1) and the S1 cortices show highly organised reciprocal connections with one another and both regions show increased activation

during overt movements of the hand (Darian-Smith, Darian-Smith, Burman, & Ratcliffe, 1993; Porro et al., 1996). This theoretical justification has been used in several studies where cued motor task is employed to elicit activity in and locate the outline of digit representations in the S1 (Kolasinski et al., 2017; Kolasinski, Makin, Jbabdi, et al., 2016; Kolasinski, Makin, Logan, et al., 2016). Furthermore, manipulation of the digit representations in the S1 causes greater motor confusion while using the affected digits and this was due to increased overlap of those particular digits in the S1 (Kolasinski, Makin, Logan, et al., 2016). Based on this information, reduced spatial specificity of particular somatomotor maps in M1 should show correspondence with the corresponding maps in the S1.

Transcranial Magnetic Stimulation (TMS) can be used to construct and make inferences about the gross somatotopy of the motor homunculus (Siebner & Rothwell, 2003). Using TMS, it is possible to locate and outline the intrinsic cortical muscle representations (Wassermann, McShane, Hallett, & Cohen, 1992; Wilson, Thickbroom, & Mastaglia, 1993). These measures are termed motor maps – defined as the area of the motor cortex eliciting motor evoked potentials (MEPs) in targeted muscles following a systematic stimulation of a predefined area of the cortex at a constant intensity (Hamdy et al., 1998). Motor maps are therefore considered to be related to the origin and spatial distribution of pyramidal tract neurones (Di Lazzaro, Ziemann, & Lemon, 2008; Rothwell, Thompson, Day, Boyd, & Marsden, 1991), representing corticospinal excitability of the stimulated muscle, and are reliably related to the known somatotopy of the sensorimotor cortex in humans (Wassermann et al., 1992; Wilson et al., 1993). Stimulation at a constant intensity with short inter-stimulation interval results in a progressive increase of MEPs, indicating that pyramidal tract neurones are added through synaptic recruitment (Monfils, Plautz, & Kleim, 2005). As such, spread of synaptic recruitment across localised groups of pyramidal tract neurones shapes the spatial characteristics of the somatomotor maps (Monfils et al., 2005). Furthermore, development of more refined movement execution and increased manual dexterity results in somatomotor maps of greater spatial specificity (Nudo, Milliken, Jenkins, & Merzenich, 1996; Reitz & Müller, 1998), which is also related to the stimulation intensity needed to elicit MEPs in young children and adolescents (Eyre, Miller, Clowry, Conway, & Watts, 2000).

Until recently, motor mapping studies employing TMS have been limited by long acquisition protocols, which are discouraged in clinical populations. van de Ruit and colleagues (2015) proposed a rapid acquisition method of collecting cortical motor maps, termed ‘pseudorandom walk method’, coupled with neuronavigated TMS (nTMS), where MEPs are sampled *randomly* across the areas of interest. Offline, the maps are constructed by synchronising the MEPs with coordinate location of the stimulating TMS coil, combined

with an interpolation approach (van de Ruit et al., 2015). In two recent studies, this method has been compared with the more traditional grid-based methods (van de Ruit & Grey, 2016; van de Ruit et al., 2015). From these studies, two important findings are reported: (1) only the time spent collecting maps differs between techniques, while both accuracy and reliability are unaltered; and (2) different stimulation intensities affected the size of the motor maps obtained, while the shape and location of the targeted muscle remained the same. As such, the pseudorandom walk method can be considered more suitable for use in patient populations, particularly those involving children or young adults. Another important issue is the use of neuronavigation (i.e., an image-guided frameless stereotaxy), which allows easy amalgamation of anatomical and functional information when coupled with cortical somatomotor mapping. Studies have shown that when coupled with cortical somatomotor mapping, nTMS improves the quality of MEPs, as well as allowing for better estimation of the location and angle of the TMS coil over the region of interest (Julkunen et al., 2009; Ruohonen & Karhu, 2010).

The primary objective of this study was to explore the efficacy and feasibility of using the rapid acquisition nTMS method to investigate the spatial extent of the cortical motor maps in a group of young adults with TS relative to a matched group of typically developing individuals. Furthermore, this feasibility study is thought to be a steppingstone in a wider investigation into the relationship between brain structure, GABAergic function and sensory acuity in patients with TS. Four characteristics of each motor map were computed: the centre-of-gravity (COG); the Euclidean distance (EDs) between maps; the variability of the area activated within a given motor map; and the overlap between areas. As noted above, we hypothesised that, based upon prior reports of altered GABA function within somatomotor regions in TS and given the role played by GABA signalling in determining the cortical tuning function of somatomotor representations, that individuals with TS should exhibit one or more of the following relative to matched controls: reduced EDs between motor maps; increased variability of individual motor maps; an increased overlap between different motor maps.

3. Methods

3.1. Participants

We recruited 16 patients with a confirmed diagnosis of TS (see Table 1 for participant characteristics) and 14 typically developing healthy volunteers for this study. Six patients were medicated at the time of testing and none was seeking alternative therapeutic intervention (e.g., CBIT). Three patients had confirmed or suspected comorbidities (i.e., OCD and attention deficit disorder [ADD]). Participants were excluded from participation if they had any contraindication to undergo TMS such as having metallic objects in their head.

This study was reviewed and approved by the Nottingham Healthcare foundation trust and the Nottingham Research Ethics committee 1 [Nottingham REC 1]. Written informed consent was acquired from all participants and where appropriate from their parents/caregivers. No part of our study procedures or study analyses were pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Finally, due to the conditions of our ethical approval, we are unable to archive individual EMG recordings and stimulation coordinates, clinical biographical data or analysis code under public domains because the data and code contain information that could identify patients. For this reason, EMG recordings and stimulation coordinates, clinical biographical data or analysis code cannot be shared with anyone outside of the research team identified in our ethical approval. There are no other conditions.

Table 1. Group characteristics.

	TS	*CS*	*Test statistic*	*P-value*
N	16	14		
Age [± SD]	20.4 [± 7.1]	17.43 [± 3.9]	1.66	0.11
Sex [M/F]	11/5	10/4	0.03	0.87
WASI [± SD]	109.6 [± 11.8]	118.85 [± 9.3]	2.3	**0.03***
Motor threshold [± SD]	49.6 [± 11.3]	43.9 [± 13.5]	1.58	0.13
PUTS /36 [± SD]	22.94 [± 6.4]	-	-	-
Yale motor tics /25 [± SD]	12.8 [± 3.5]	-	-	-
Yale vocal tics /25 [± SD]	8.2 [± 5.1]	-	-	-
YGTSS /100 [± SD]	34.6 [± 14.5]	-	-	-

Current symptoms of TS were assessed using the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989) and the Premonitory Urge for Tics Scale (PUTS; Woods, Piacentini, Himle, & Chang, 2005). IQ was assessed using two subtests (Matrix reasoning and vocabulary) of the Wechsler's Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

3.2. Cortical mapping

All participants completed the nTMS cortical motor mapping procedure outlined below. Electromyography (EMG) was recorded using disposable electrodes (24 mm outer ring, 1.6 mm diameter of conductive gel area, 6 mm electrode size) placed on muscles located on the right side of the body. The muscles targeted were: first dorsal interosseous ([FDI] hand); deltoid (shoulder); orbicularis oris ([O. Oris] lips); orbicularis oculi ([O. Oculi] eyes); and masseter (jaw). All of the muscle representations targeted in this study are associated with body areas linked to the occurrence of tics and the experience of PU in TS (Ganos et al., 2012; Kwak, Dat Vuong, & Jankovic, 2003; Schunke et al., 2016). nTMS was performed using a Magstim-bistim system, a 70 mm figure-of-eight magnetic coil, coupled with a BrainSight neuronavigation system (Rogue Research Inc., Montreal, Quebec, Canada).

During each study session, 150 TMS pulses were delivered to pseudorandom locations (ISI = 6 s) within a 40 cm^2 virtual grid superimposed on the MRI scan using the BrainSight neuronavigation software. The virtual grid encompassed the left precentral gyrus, partially overlapping with the left postcentral gyrus and premotor cortices. Coordinates in 3D space were simultaneously recorded and downloaded from the neuronavigation system (in MNI space) after the study session and stored offline.

Resting motor threshold (rMT) was determined independently for each participant from the FDI muscle only, and was defined as the TMS stimulation intensity (as % of maximum stimulator output [MSO]) necessary to evoke a peak-to-peak motor-evoked potential [MEP] amplitude of between 50-100 μV in 5 out of 10 trials (Rossi et al., 2009).

During the motor mapping procedure, TMS was delivered at 200% of rMT, up to a maximum limit of 80% MSO (to ensure participant comfort – all but 5 participants were capped at 80% MSO; 3 in TS group). The coil was held with the handle pointing posterior at a 45° angle and the current flow was in a posterior-anterior direction. When applicable, individual anatomical MRI images (available for 60% of participants) were uploaded to the neuronavigation system to locate an approximate position of the left sensorimotor cortex.

3.3. Data analysis

The EMG signal was amplified, bandpass filtered (10-2000 Hz, with 2000 Hz sampling rate) and digitalised using Brain Amp ExG and BrainVision Recorder (Brain Products GmbH). MEPs were time locked and extracted from each muscle separately via a specific time frame, based upon known latencies of each muscle (Inoue, Tani, Taniguchi, & Yamamoto, 2003; Kallioniemi, Pitkänen, Säisänen, & Julkunen, 2015; Säisänen et al., 2015) using an in-house written Matlab program (R2014a, The MathWorks). MEPs were rejected if noise levels in the

recording exceeded 50 μV before stimulation (if noise levels in one channel exceeded our noise level threshold, all channels were excluded for that particular trial), or were contaminated by obvious artefacts, and then synchronised to the 3D coordinates before being standardised using a z-transformation. This transformation was done to render the data more normally distributed and it also allowed us to threshold each motor map at $z \geq 1$ to exclude any spurious MEPs which were unlikely to be related to muscle contractions, which would otherwise skew the maps.

Following pre-processing of the MEPs and motor maps were constructed as follows: (i) 3D coordinates located on the scalp were converted to cortex coordinates via a transformation matrix using coil coordinates (given as direction of cosines) as trajectories; (ii) 2D maps were generated by fitting a rectangular plane to the cloud of the 3D coordinates by way of a fitting function where the X coordinates are dependent on the Y and Z coordinates (Eberly, 2017). Conversion of the coordinates is achieved using change of basis which transforms one coordinate system to another, perpendicular to the predefined plane. This is a key step in mapping the original X Y Z coordinates to a plane; (iii) a bounding box is fitted to the plane after finding the central point. The plane is then rotated to align with the respective x- and y-axes via a rotation matrix through the angle θ; and (iv) full cortical motor maps are constructed of the targeted muscle representations using a triangular linear interpolation ('Gridfit' toolbox, D'Errico, 2005). This motor map was an 80x80 pixel map, where each pixel is appointed an approximated MEP based on the nearest MEP datapoint.

The COG for each map was computed as detailed in van de Ruit, et al. (2015), where COG is the mean position in a map, based on the weighted mean intensity of each pixel in a map. EDs, which can be indicative of spatial re-organisation (Elbert et al., 1994), were computed as the distance between a pair of COGs in 2D space. ED is a robust measure since studies have reported good between-session reliability and less variability than equivalent measures derived from fMRI activation (Weiss et al., 2013). A 95% confidence interval ellipse, using the largest and smallest eigenvalues which were computed based on the covariance matrix of the data, was then fitted to each motor map. This results in an approximation of the *area* covered by each cortical muscle representation with respect to the maps' minor and major axes and captures the variability of the approximated MEPs. Finally, we calculated the overlap between the *area* occupied by each muscle representation in the motor maps using the Dice similarity coefficient (Dice, 1945). The Dice similarity coefficient is a spatial overlap index and varies from 0 (no overlap between motor representations) to 1 (complete overlap).

3.4. Statistical analysis

Shapiro-Wilks tests were used to assess normality. Parametric independent-sample t-tests were used to quantify group differences on continuous variables. Differences between groups on map parameters (COG, ED, area and Dice coefficient) was also assessed using independent-sample t-tests. Group differences in means were calculated using a repeated sampling technique with 1000 permutations without replacement; random allocation of data into groups, assuming data was missing completely at random. The p-value was calculated as the percentage of simulations where the simulated t-statistic was more extreme than the observed t-statistic. Relationship between map characteristics and clinical measures was determined using Pearson correlation coefficient. For categorical variables a chi-square test was used. Variables of interest were corrected for age and sex prior to statistical comparison. Statistical significance was noted at $p < 0.05$. We controlled for the error of multiple comparisons (false positive correction) using the false discovery rate (FDR) with the criterion set a 0.05. Statistical analysis was carried out in Matlab and SPSS v22.

4. Results

Mapping of cortical representations was successfully accomplished in all participants without any significant adverse events. Out of all participants initially enrolled, one had to be excluded due to a neuronavigation tracking error. This participant was part of the control group.

4.1. Sample characteristics

Normality tests showed that age ($W = 0.92$), rMT ($W = 0.90$) and IQ ($W = 0.93$) were not normally distributed (all $p < 0.05$). Boxplot are provided in Figure 1 and reveal that one participant in the TS group is an outlier due to his age. This participant was, however, retained in the analysis to maintain statistical power. T-tests showed that both groups were of comparable age ($t(27) = 1.76$, $p = 0.09$ – regardless of whether the outlier was removed or retained) and had similar resting motor thresholds ($t(27) = 1.51$, $p = 0.14$). We found, however, a statistical difference in IQ scores ($t(26) = -2.31$, $p = 0.03$), where patients with TS scored significantly lower in relation to controls (see Table 1 for group characteristics). However, it should be noted that both groups exhibited above-average mean IQ scores. Finally, the distribution of males and females in the two groups was comparable ($\chi^2 = 0.026$, $p > 0.05$).

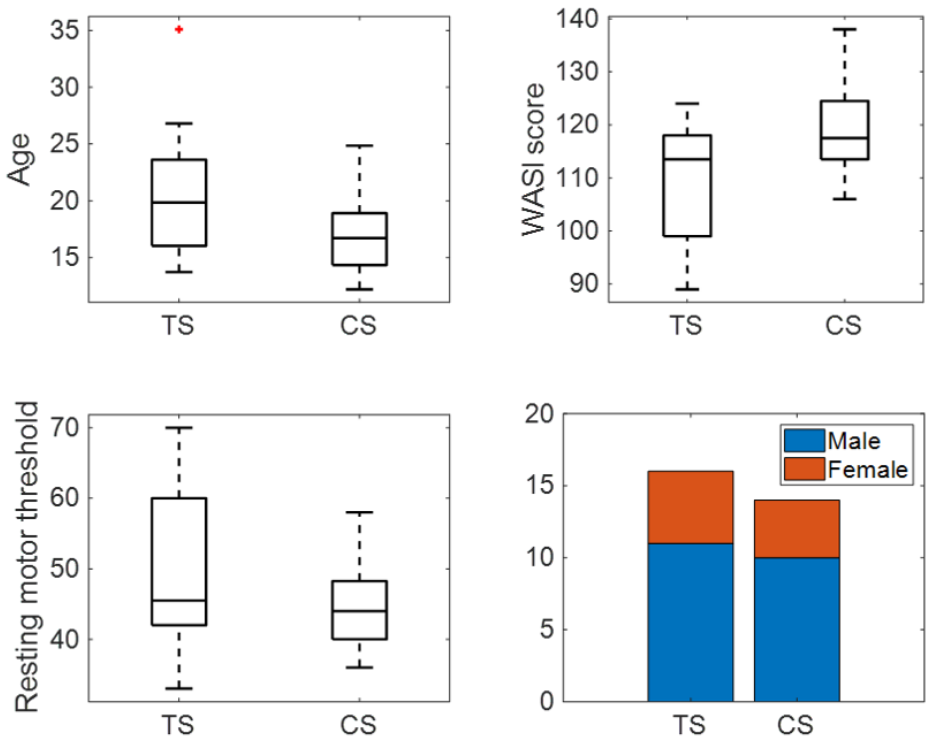

Figure 1. Boxplots demonstrating median and inter-quartile ranges for demographic variables used in the study. Note that WASI score was not collected from one participant in the CS group due to a mistake.

4.2. Somatomotor maps

Cortical motor mapping of facial muscles is difficult, mainly due to these muscles having a much higher motor threshold. Consequently, mapping of targeted muscle representations in our study was not always achieved. In the TS group only, recordings (i.e., number of participants) from the deltoid (6%), O. Oris (19%), masseter (19%) and O. Oculi (6%) had to be excluded from further analysis due to multiple discrete peaks in the map. Some recordings were also discarded due to electrode malfunction. Approximately 1% and 1.4% of trials were excluded due to excessive noise in the EMG recordings before stimulation in the TS and CS groups, respectively ($t(27) = 2.05$, $p = 0.4$).

Table 2. Summary statistics for the anterior-posterior (A-P) and lateral-medial (L-M) centre-of-gravity (COG) for each muscle representation. The table displays mean [± 1 SD]. Values are given as mm from the central point. P values are uncorrected.

	A-P COG				L-M COG			
Muscle	***TS***	***CS***	***DF***	***p***	***TS***	***CS***	***DF***	***p***
FDI	-2.40 (±3.40)	0.30 (±2.94)	27	*0.04*	-6.55 (±5.46)	-4.14 (±3.14)	27	0.20
Deltoid[a]	-4.37 (±3.91)	-3.72 (±3.76)	26	0.48	-9.22 (±6.66)	-10.32 (±2.75)	26	0.24
O. Oris[b]	6.95 (±3.90)	8.73 (±3.76)	24	0.23	7.78 (±5.48)	9.63 (±4.0)	24	0.18
Masseter[b]	6.69 (±4.22)	10.14 (±5.51)	24	0.11	9.22 (±5.18)	8.90 (±7.60)	24	0.64
O. Oculi[c]	5.39 (±3.87)	5.14 (±5.04)	26	0.83	7.01 (±4.74)	3.43 (±8.94)	26	0.84

Note for TS group only: [a]mean based on N = 15, [b]mean based on N = 13, [c]mean based on N= 14. Abbreviations: DF = degrees of freedom. A-P: Anterior-posterior. L-M: lateral-medial.

Statistical comparison of COGs between the two groups showed that the FDI representation was shifted more medially in the TS group (p = 0.04 uncorrected, see Table 2). No other differences in COG were observed. Figure 2 presents the group average COGs in for motor map. The figure interestingly, and reassuringly, demonstrates the that well-known somatotopy of the sensorimotor cortex (Penfield & Jasper, 1954) is evident for both the CS and TS groups.

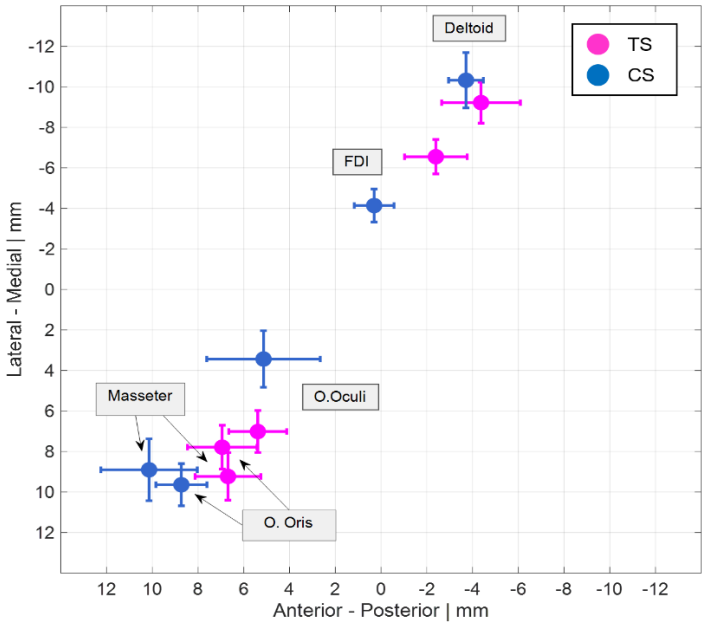

Figure 2. Location of targeted motor representations generated by the nTMS mapping procedure. The figure displays the COG of each representations. Filled circles (blue and magenta) represent group averages and errorbars are SEM.

Segregation in motor maps was assessed using Euclidean distances, computed between a pair of COGs. As detailed in Table 3, analysis of EDs yielded no statistically significant between-group differences for any pair of muscles (all $p > 0.05$).

Table 3. Summary statistics for the Euclidean distances between COGs (in mm). The table displays mean [±1 SD].

Pair	TS	CS	DF	p
FDI & Deltoid	9.48 (±4.58)	7.92 (±2.37)	26	0.23
FDI & O. Oris	19.05 (±9.99)	17.01 (±5.77)	24	0.61
FDI & Masseter	20.07 (±10.00)	15.32 (±7.38)	24	0.23
FDI & O. Oculi	16.59 (±8.93)	12.12 (±4.97)	26	0.26
Deltoid & O. Oris	23.06 (±12.76)	24.35 (±4.25)	23	0.45
Deltoid & Masseter	24.18 (±12.83)	22.54 (±6.53)	23	0.99
Deltoid & O. Oculi	21.00 (±11.64)	17.58 (±7.12)	25	0.71
O. Oculi & Masseter	3.19 (±2.43)	5.13 (±4.99)	23	0.45
O. Oculi & O. Oris	7.75 (±6.96)	9.09 (±8.14)	24	0.92
Masseter & O. Oris	6.59 (±6.20)	8.31 (±4.28)	24	0.83

Figure 3 illustrates a representative example of all motor maps measured in this study from an individual participant in the TS group. Detailed in Table 4 are the results of comparison of motor areas, which shows significantly reduced area of the FDI representation in the TS group relative to the control group ($p < 0.05$, significant following multiple comparison correction). No other comparisons exhibited statistically significant results.

Table 4. Summary statistics for the variable area (within the 95% CI ellipse) for each muscle representation. The table displays mean [± 1 SD] while values represent mm^2.

Muscle	*TS*	*CS*	*DF*	*p*
FDI	228.82 (± 122.8)	349.49 (± 94.9)	27	**0.002***
Deltoid	183.48 (± 123.3)	151.56 (± 71.5)	25	0.96
O. Oris	221.29 (± 179.2)	311.67 (± 210.7)	24	0.48
Masseter	208.78 (± 145.6)	373.9 (± 242.2)	25	0.21
O. Oculi	337.59 (± 275.6)	405.32 (± 277.2)	26	0.84

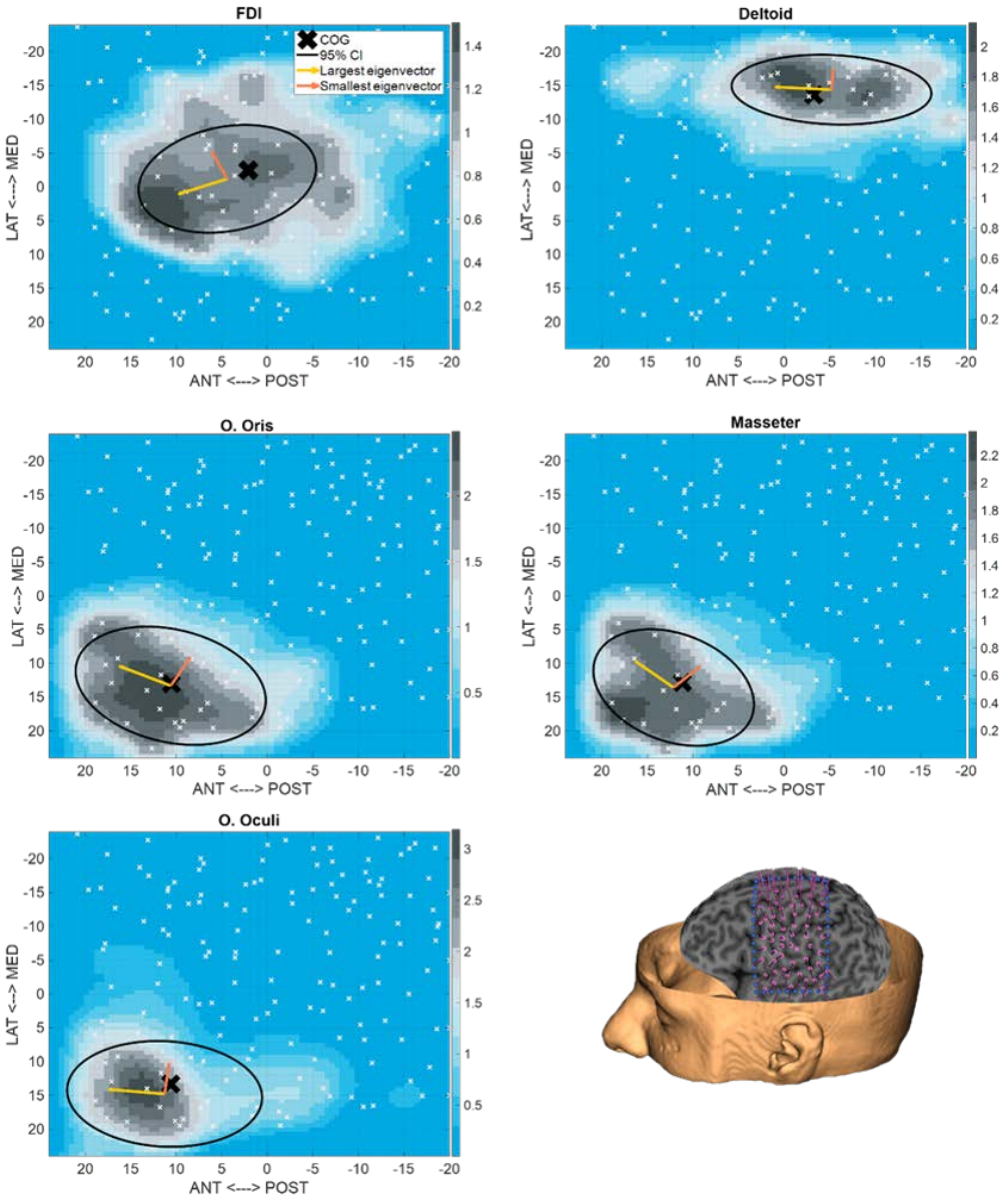

Figure 3. Example of somatomotor maps from a representative participant in the TS group. The images depict a 2D contour plot with the transformed coordinate system on the x- and y-axes (in mm) and normalised MEP amplitude on the z-axis. Colorbar depicts intensity of the z-transformed MEPs. In each map, the blue colour represents MEPs falling below the z-score threshold criteria, while white-light grey-dark colours represent increasing amplitude of MEPs. COG is represented by a black cross (X). Yellow and orange arrows indicate the eigenvectors of the covariance matrix of the data, whereas the length of the arrows corresponds to the eigenvalues. Smaller crosses: transformed location of triggered TMS coordinates. The x-axis represents the anterior-posterior position and y-axis the lateral-medial position. The image in the bottom left corner is an example of the superimposed grid (blue square), encompassing the sensorimotor cortex in a subject.

Finally, we computed the Dice similarity coefficient, measuring the 'overlap' of the area of two motor representations. Note that we only computed the overlap for a subset of the motor representations measured, since we believed there would be little or no overlap between, for example, upper limbs and facial representations. Results from this analysis are depicted in

Figure 5 and shows comparable Dice coefficient between the two groups (all comparisons p > 0.05).

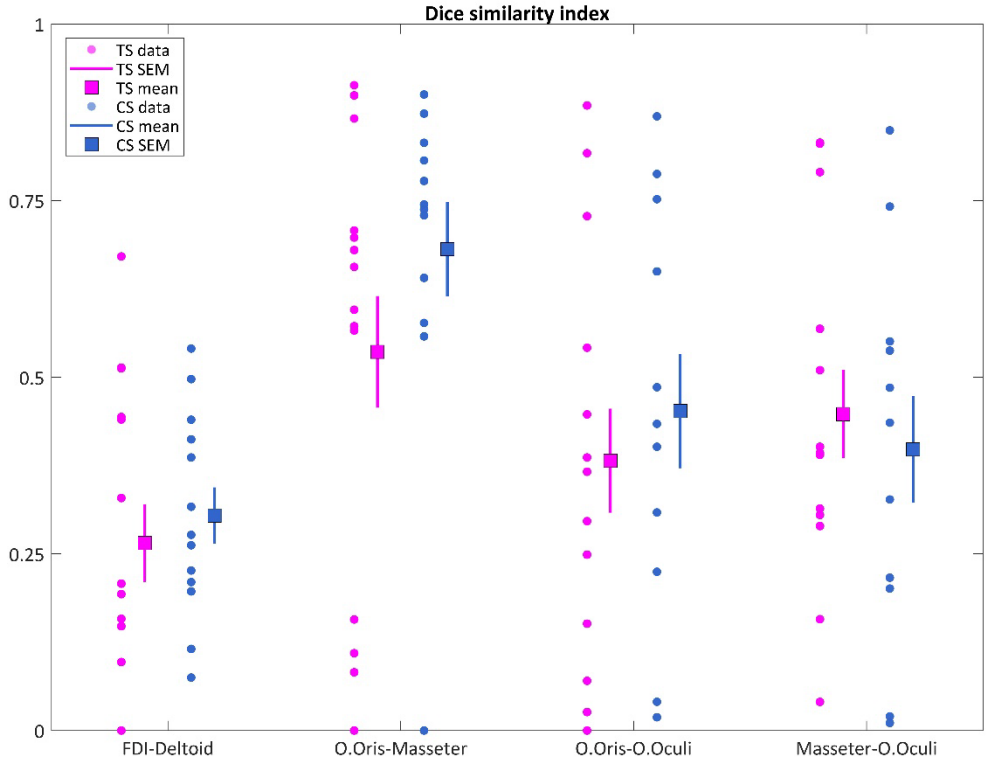

Figure 4. Comparison of the Dice similarity coefficient for 4 pairs of motor representations. Patients are denoted in magenta and controls in blue (individual datapoints). Squares indicate means while error bars represent the standard error of the mean.

4.3. Premonitory urge severity is related to distance between hand and facial cortical muscle representations

We also conducted a series of correlation analyses between motor map characteristics, corrected for age and sex, and clinical measured collected from participants in the TS group only. We present the results in Figure 5, which shows no significant relationship between map characteristics and tic scores. By contrast, the Euclidean distance between the FDI and O. Oris (r = -0.67, p = 0.012), FDI and masseter (r = -0.78, p = 0.002), and FDI and O. Oculi (r = -.69, p = 0.005) were all significantly and negatively correlated with PUTS scores (p < 0.05, corrected for multiple comparisons). Furthermore, at an uncorrected threshold, we observed a strong, positive correlation between area of the FDI cortical muscle representation and PUTS scores (r = 0.60, p = 0.01).

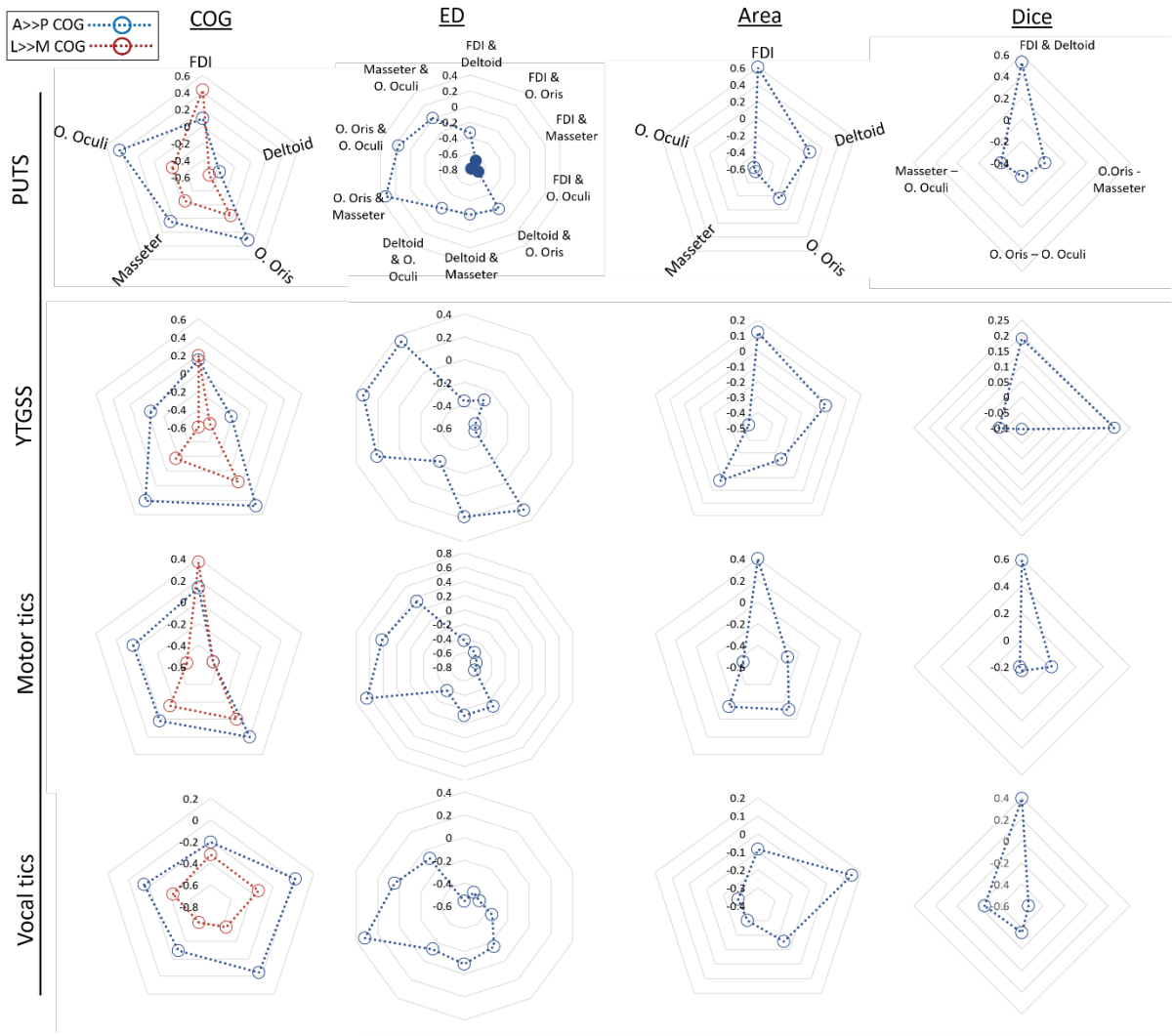

Figure 5. The figure displays results of the correlation analysis between map parameters and clinical variables measured in the study from the TS group. Filled circles indicate statistical significance following correction for multiple comparison.

5. Discussion

The primary aim of this study was to demonstrate the efficacy and feasibility of using the rapid-acquisition method (van de Ruit et al., 2015) together with the use of neuronavigated TMS to identify and characterise the cortical motor representations of multiple targeted muscles in individuals with TS. In the current study we successfully demonstrated that we could localise, identify, and quantify at least 5 different muscles in a group of young adults with TS. An example of the motor maps from one representative subject was presented in Figure 3 and demonstrates the quality of the data that can be achieved using this method in this population. This level of data quality was consistently produced for all participants, with the exception of few facial motor maps. Most importantly, the protocol was well tolerated, even by the youngest participant (12.2 years), and only one participant reported an adverse effect following the study (a slight headache) as measured with a standard questionnaire completed

24 hours post study session. As such, we have provided a clear method for how one might conduct further studies using this approach in the future.

An additional but secondary aim of this study was investigating whether the cortical motor maps in our TS group differed from those of a matched control group of typically developing individuals. We had hypothesised, as a consequence of the widespread changes in GABAergic function previously reported in TS (Albin & Mink, 2006; Gilbert et al., 2004; Kalanithi et al., 2005; Lerner et al., 2012; Orth et al., 2008; Orth & Rothwell, 2009; Vaccarino et al., 2013) and the putative role of GABA signalling in shaping the cortical tuning function of somatosensory representations (Kolasinski et al., 2017), that we would expect to see altered motor maps in TS characterised by reduced Euclidian distances between motor maps, increased variability (area) of individual motor maps, and increased overlap between adjacent motor maps. General support for this hypothesis comes in part from prior studies of focal hand dystonia [FHD], a neurological condition that is characterised by co-contraction of hand muscles leading to un-coordinated movements and abnormal postures, that shares many similarities with TS. For instance, FHD has, like TS, been linked to impaired physiological inhibition and GABAergic deficits (Gallea et al., 2018; Sohn & Hallett, 2004), including reduced GABA-A binding within the sensorimotor cortex (Gallea et al., 2018) and reduced short interval intracortical inhibition within the M1, which have been linked to changes in somatotopic representation in FHD (Beck et al., 2008). Importantly, one of the key findings in FHD has been the demonstration of overlapping motor maps for individual digits characterised by a reduction in the centre-of-gravity between digit representations for the affected hand (Elbert et al., 1998).

In the current study we examined this hypothesis by computing a number of spatial metrics that can be used to describe the motor map for each targeted muscle and then testing these for between-group differences. The measures were: the centre-of-gravity for each of the targeted muscles; the separation (Euclidian distance) between the centres-of-gravity for pairs of muscle maps; and the spatial extent (95% confidence ellipses) of each muscle map. In general, and in clear contrast to our predictions, we found very few between-group differences for the location of each muscle map, the separation between muscle maps, or their spatial extent. The only exception to this was that we found that: (a) the mean centre-of-gravity for the FDI muscle in the TS group was located more medially than that measured for the control group; and (b) the mean extent (95% confidence ellipse) of the FDI muscle map was significantly *reduced* for the TS group compared to the controls. Neither of these finding provide strong support for our general hypothesis that impaired physiological inhibition and altered GABAergic signalling within the sensorimotor cortex would lead to alterations in the

cortical motor maps characterised by a reduction the spatial precision and separation of individual motor maps in TS.

As noted above, while the shape and location of the targeted motor map is not thought to be influenced by stimulation intensity, the size of the motor maps obtained using TMS has been shown to be dependent upon the intensity of stimulation (van de Ruit & Grey, 2016), so could the lack of any observed differences in the motor maps be due to differing intensities of TMS used in the patient group? The individual motor thresholds measured (from the FDI muscle only) in this study, and used to determine the magnitude of the stimulation delivered to individual participants, did not differ between the groups. The finding that motor thresholds (commonly measured from the FDI or abductor digiti minimi) are within the normal range has been demonstrated previously in adults with TS, and has been cited as evidence that the neural populations recruited by TMS at threshold are in the same state in both samples (Orth, 2009). However, in this study stimulation was delivered substantially above threshold (i.e., 200% of MT or a limit of 80% of MSO) and it could be argued that previous studies have demonstrated that the motor 'gain' function elicited by TMS (i.e., when calculating a TMS recruitment curve) is reduced in TS, particularly as stimulation intensity increases (Draper et al., 2014; Pépés, Draper, Jackson, & Jackson, 2016). Therefore, while TMS-induced MEP amplitudes may be comparable between groups when TMS is delivered at motor threshold or slightly above threshold they may be significantly reduced relative to controls at higher levels of stimulation intensity. This issue will be discussed further when considering the limitations of this study and how future studies might address this issue.

While we did not observe between-group differences in the location, separation, or extent of the motor maps, we did nevertheless find that these measurements were associated with clinical measurements in the TS group. Specifically, we observed that the distance between the centre-of-gravity for hand (FDI) muscle and the centres-of-gravity for the facial muscles (i.e., O. Oris, O. Oculi, and masseter) were each significantly negatively correlated (minimum $r = -.67$) with the intensity of the premonitory urge phenomena reported by the patients, such that a reduced distance between the hand and facial muscles was associated with an increase in premonitory urges. Conversely, the extent (area) of the FDI muscle in the TS group was positively correlated with premonitory urge scores, indicating that an increase in the area of the FDI muscle representation is associated with an increase in premonitory urge phenomena. Furthermore, inspection of Figure 5 clearly indicates that while an increased area of the FDI muscle is associated with increased premonitory urges, it is a decrease in the area of the facial muscles (e.g., O. Oculi, and masseter) that is associated with increased premonitory urges ($\sim r = -.6$). These findings are consistent with the clinical picture for TS in which facial tics are by far the most prevalent form of motor tic (S. C. Cohen et al., 2013) and

suggest that further studies are required to investigate further whether motor maps are altered in TS and/or whether any alterations can explain the somatosensory phenomena associated with TS.

As noted above, our hypotheses were based upon prior reports indicating that maintaining the spatial specificity of cortical motor representations is governed by GABA and GABAergic interneurons (Feldman & Brecht, 2005; Griffen & Maffei, 2014; Jacobs & Donoghue, 1991; Kolasinski et al., 2017) and that aberrant GABAergic mechanisms have been demonstrated in TS (see Rapanelli, Frick, & Pittenger, 2017). We also drew parallels between TS and focal hand dystonia [FHD] in predicting how motor maps might be altered as a consequence of impaired physiological inhibition. However, contrary to findings observed in patients with FHD, we found little evidence of spatial reorganisation of somatomotor maps in TS. Thus, it is worth re-assessing the validity of our hypotheses with respect to TS.

First, several previous studies have directly examined somatosensory function in individuals with TS and have reported that while individuals with TS often report heightened sensitivity to external sensory stimuli (Belluscio et al., 2011; A. J. Cohen & Leckman, 1992) their somatosensory thresholds are within the normal range, indicating that the acuity of their somatosensory cortex is unimpaired (e.g., Belluscio et al., 2011; Schunke et al., 2016). Second, brain imaging studies that have sought to localise the neural antecedents of tics and the neural correlates of premonitory urges in TS have typically identified brain areas such as the insular and medial frontal cortices as the likely generators of the urge-to-tic (e.g., Bohlhalter et al., 2006; Jackson et al., 2011; Neuner et al., 2014). Together these findings might suggest that any alterations in somatosensory processing that may give rise to altered heightened sensitivity to somatic stimulation in TS or lead to the experience of premonitory urges in TS, need not necessarily involve any alteration in the representation of somatic or motor maps within primary somatomotor cortex.

Limitations of this study

The primary aim of this study was to demonstrate the feasibility of using neuronavigated TMS together with the rapid-acquisition method (van de Ruit et al., 2015) to identify and characterise the cortical motor maps for multiple targeted muscles in individuals with TS. The results of this study have clearly demonstrated the feasibility of this approach and its potential but have highlighted some issues that should be considered in subsequent studies. First, even when using the rapid-acquisition method (van de Ruit et al., 2015), the time taken to adequately quantify multiple muscles is considerable. In the current study the time taken to complete the study was close to two hours, which is not really ideal for testing children or young adults with TS, who may find it uncomfortable to remain still for long periods. A limitation

of the current study was that, in order to reduce the overall time of the study, we based our stimulation parameters on each individual's resting motor threshold measured with reference to the FDI (hand) muscle. We submit that it would have been preferable to have determined separate motor thresholds for each muscle and used these to determine the desired stimulation output for each muscle. In this way we could determine that the TMS stimulation at each muscle was sufficient to generate a MEP of 1mV or similar. In a similar vein, given that area, but not the size or location, of the motor maps is dependent upon the intensity of stimulation, it should be borne in mind that the specific results of this study of TS (but not the feasibility of this approach or its potential) might vary with substantially different stimulation parameters.

Differences in the age of the two groups is substantial, particularly when the oldest participant (part of the TS group) is included. To guard against the influence of age we entered age as a covariate in all comparisons. Also, we were unable to identify or obtain anatomical MRI scans for some participants (significantly fewer scans were available for the TS group). We do not view this as a major limitation however since the somatomotor maps are based on the averaging of EMG responses to TMS delivered to different scalp locations, which are then averaged across participants for statistical comparison. There is amble published evidence demonstrating that anatomical locus of the TMS-defined motor 'hotspot (e.g., for the FDI muscle) exhibits considerable individual variability. Ahdab et al., (2016) showed that in less than 50% of their sample did the TMS-defined motor 'hotspot' correspond to the 'hand knob' region of the central sulcus, which is often assumed to be the anatomical location of the FDI muscle. In the remaining individuals the TMS-defined motor 'hotspot' was located outside of the primary motor cortex, most often over the precentral or middle frontal gyrus. By contrast, other published studies have demonstrated that while there is considerable inter-subject variability in the anatomical location of the TMS-defined motor 'hotspot', there is nonetheless very good intra-observer reliability in determining the location of this motor 'hotspot' (e.g., Weiss et al., 2013). In our analysis, irrespective of whether individual anatomical scan or a template was used, the projection of the maps was in standard MNI space and not in individual native space. In our study we do not attempt to provide any concrete conclusions regarding differences in cortical topography between groups but rather we emphasise that the primary aim of this study was to develop an effective protocol to study somatomotor maps in this population.

Finally, one further potential limitation of this study concerns the patient sample size. Although the sample size used for this study is larger than for most previous studies investigating TMS-induced physiological alterations in TS, and more than adequate to reliably and accurately quantify MEPs from each of the muscles targeted in this study, it would have

been advantageous nonetheless to have investigated this issue in a larger sample of patients. This is particularly apparent with respect to investigating the relationship between the location, separation and area of motor maps and clinical measures of tic severity and premonitory urges in TS.

In conclusion, we note the feasibility of employing the rapid acquisition nTMS method in studying the somatotopic arrangement of the somatomotor cortex in a sample of patients. Even though we demonstrate limited differences in the characteristics of the motor representations measured in this study, we believe this to have important implications for future studies who wish to study cortical motor representations in patients with TS in relation to increased sensory responsiveness.

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