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Non-invasive neuromodulation of the right temporoparietal junction using theta-burst stimulation in functional neurological disorder

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ABSTRACT

Background Disrupted sense of agency (SoA)—the sense of being the agent of one's own actions—has been demonstrated in patients with functional neurological disorder (FND), and a key area of the corresponding neuronal network is the right temporoparietal junction (rTPJ). Several functional MRI (fMRI) studies have found hypoactivation as well as hyperactivation of the rTPJ in FND. In a proof-of-concept study, we tested whether repetitive transcranial magnetic stimulation (rTMS) over the rTPJ could restore this aberrant activity.

Methods In a randomised, crossover, single-blinded, sham-controlled study design, theta-burst stimulation (tb-rTMS) was applied over the rTPJ in 23 patients with FND and 19 healthy controls (HC), with each participant undergoing three stimulatory visits (inhibitory continuous TBS (cTBS), excitatory intermittent TBS (iTBS) and sham). During fMRI, participants played a visuomotor task artificially reducing their SoA (manipulated agency, MA), repeated after each neurostimulation. We compared brain activity and behavioural SoA as primary outcomes before and after tb-rTMS and investigated the feasibility of tb-rTMS over the rTPJ in FND as secondary outcome.

Results At baseline, patients showed decreased accuracy in detecting reduced agency compared with controls ($p<0.001$), paralleled by lower brain activation in the rTPJ during MA ($p=0.037$, volume of interest). A region of interest analysis on the rTPJ showed no effect of the sham condition in FND or HC ($p=0.917$; $p=0.375$) but revealed a significant effect of stimulation protocol (*cTBS/iTBS*, $p=0.037$) in patients with FND, with the excitatory protocol increasing the blood-oxygen-level-dependent (BOLD) signal, whereas this effect was not found in HC. In neither group, a behavioural effect of tb-rTMS was observed.

Conclusion Aberrant processing of agency in FND was confirmed at baseline, reflected in behavioural outcome and reduced activity in the rTPJ. Tb-rTMS over this key region elicited neuronal changes in patients, paving ways for future studies exploring TMS as neurobiologically informed intervention to restore SoA in FND. We critically discuss methodological intricacies and outline further steps in this research line.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Functional neurological disorder (FND) has been associated with a disrupted sense of agency (SoA) and an aberrant activity and functional connectivity of the right temporoparietal junction (rTPJ) which delineates a key node in the agency network. Most of the previous studies investigated behaviour and brain activity separately or were limited to methods of correlative nature, while interventional studies aiming to elaborate on the potential to modulate abnormal rTPJ activity in order to restore SoA in FND are lacking.

WHAT THIS STUDY ADDS

⇒ By combining neurostimulation (theta-burst repetitive transcranial magnetic stimulation, tb-rTMS) and task-based neuroimaging (functional MRI), reduced accuracy in detecting low agency was found to be paralleled by decreased blood-oxygen-level-dependent (BOLD) signal in the rTPJ in patients with FND compared with healthy controls. Furthermore, tb-rTMS revealed a neuromodulatory potential on the rTPJ activity during the performance of the task paradigm.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The evidence of a neuromodulatory potential of the rTPJ as main node during cognitive processing of SoA in patients with FND sets the ground for future clinical trials. These data could serve as rationale and methodological precursor to design and conduct power analysis for a study protocol looking at clinical benefits in parallel to this neuromodulatory finding.

INTRODUCTION

Functional neurological disorder (FND) is a frequent disorder characterised by the presentation of a variety of neurological symptoms in the absence of an identifiable underlying neurological disease responsible for those symptoms.[1] A key characteristic is the experience of symptoms as being

produced involuntarily,[2] even though there is evidence that the pathways related to voluntary motor control are capable of normal functioning.[3] To explain this discordance between *perceived* control over the body and *observed* motor function, recent research has proposed a disrupted sense of agency (SoA)—the feeling of being the agent of one's own actions and their consequences—in FND.[4]

Several studies reported aberrant encoding of agency attribution in FND using proxies of SoA such as intentional binding,[2 5] sensory attenuation,[6] movement in virtual reality[4] or a visuomotor task.[7] Accordingly, neurobiological models have put forward a network disturbance as an explanation for impaired SoA.[8] Of particular interest is the right temporoparietal junction (rTPJ) as a multisensory association cortex that evaluates the concordance between the intention of a movement and the sensory feedback resulting from the executed movement.[9] In FND, abnormal activity and functional connectivity (FC) of the rTPJ have been found in resting-state imaging[10–13] but also in task-based functional MRI (fMRI) during involuntary or externally generated movements[3 4] and during recall of traumatic events.[14] Due to conflicting findings of hypoactivation or hyperactivation, deciphering the contribution of this region to FND pathophysiology remains challenging.

Non-invasive brain stimulation (NIBS) can facilitate or inhibit cortical excitability and allows to study specific directional effects on behaviour and neurophysiology. Transcranial magnetic stimulation (TMS) is a NIBS technique, generating a magnetic field which induces local electrical pulses in the brain tissue, altering cortical excitability.[15] Novel protocols of repetitive TMS (rTMS) called theta-burst stimulation (TBS; hereafter tb-rTMS) deliver high-frequency triplets and have been proven to elicit longer-lasting effects—intermittent delivery (iTBS) leads to excitation of cortical membranes, while continuous delivery (cTBS) has shown inhibitory effects.[16]

Although an increasing amount of empirical work on NIBS in FND has emerged recently, reports on rTMS protocols are scarce and constraint with heterogeneity in methods and outcome measures.[17 18] Only two studies investigated the potential of rTMS over the rTPJ: one case report on a single patient[19] and one case series of seven patients[20] with functional seizures reporting improved symptom severity after rTMS over the rTPJ.

Whereas NIBS has predominantly been used to improve symptom severity in FND,[17] we set out to assess the effect on the SoA's neural correlates. The rTPJ activity was previously found to be enhanced during an incongruence condition of an action-recognition task with manipulated visuomotor feedback in healthy controls (HC), and behavioural measures of SoA were successfully modulated by cTBS applied over this region.[21] Using the same task along with functional neuroimaging, we compared the processing of SoA betwee patients with FND and HC and investigated the effect and feasibility of tb-rTMS on the rTPJ in a proof-of-concept study. This aims at filling the gap on physiological evidence about a potential neuromodulatory effect of TMS in FND, prior to translating tb-rTMS protocols to clinical outcome measures.

We hypothesised that (1) patients show a reduced sensitivity in detecting an artificial manipulation of their agency and display rTPJ hypoactivation compared with HC. Targeting the rTPJ, we hypothesised that (2) tb-rTMS has a neuromodulatory effect that can be measured as blood-oxygen-level-dependent (BOLD) signal change in the rTPJ and alters participants' SoA (primary outcomes) while being well tolerated (secondary outcome).

MATERIALS AND METHODS

Patients with FND were recruited and measured at the neurology department at the University Hospital of Bern (Inselspital), Switzerland. The diagnosis was confirmed and enrolment performed by a board-certified neurologist based on the presence of positive signs.[22] Eligible symptom types included motor symptoms (abnormal movements and weakness, F44.4), functional seizures (F44.5) and mixed symptoms (F44.7), according to the International Classification of Diseases 10th Edition (ICD-10) nomenclature. Exclusion criteria were as follows: comorbid psychosis, major depression, bipolar affective disorder, epilepsy, alcohol or drug abuse and contraindication to MRI. Age-matched and sex-matched HC were included applying the same exclusion criteria. All participants provided written informed consent. The study was approved by the Ethics Committee of Canton Bern, Switzerland (2017–00997, DRKS00012992), and followed the guidelines of the Declaration of Helsinki.

Study design

A randomised, single-blinded, sham-controlled, neuronavigation-guided, crossover study was conducted, including three interventional visits (visits 1–3, figure 1) so that each participant received excitatory and inhibitory neurostimulation over the rTPJ as well as active sham stimulation over the vertex in random order. At each visit, participants performed the agency task during fMRI before and after the tb-rTMS protocol (run 1–6). Participants were unaware of the effects of the three protocols. The visits occurred with a 1-week interval.[23]

Clinical data

We assessed mood (Beck's Depression Inventory[24] and State-Trait Anxiety Inventory[25]) at each visit and patients' subjective symptom severity (SSS; visual analogue scale, 1–10) before and after each stimulation. Symptom duration was calculated from the onset of symptoms to the date of first visit.

Agency task and fMRI acquisition

The behavioural task performed during fMRI was based on Metcalfe and Greene[26] (figure 2) and had already been used to study SoA in HC[21 27] and patients,[28–30] including FND.[7]

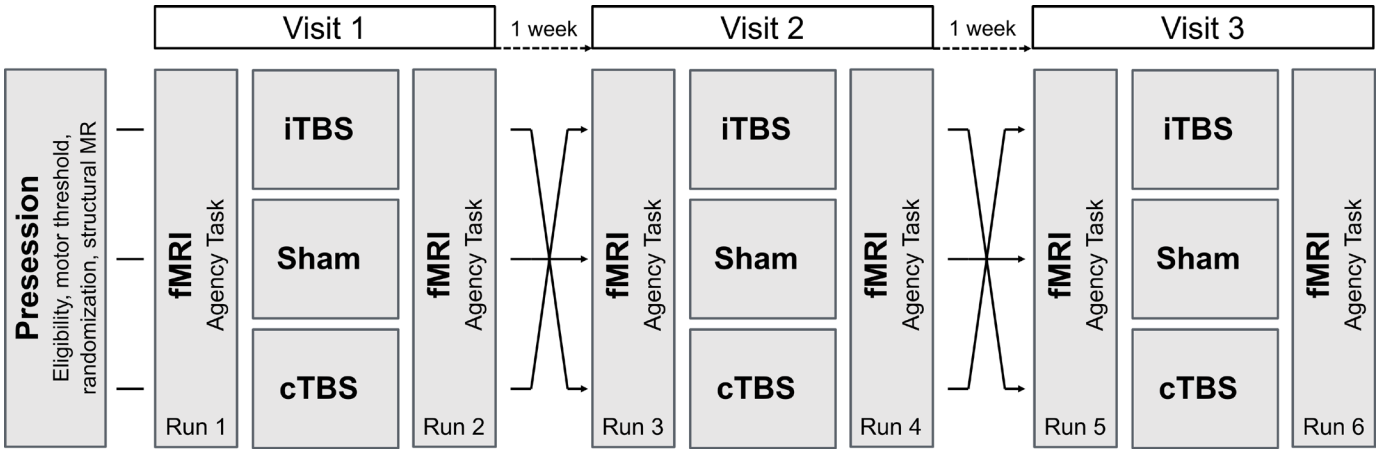

Figure 1 Study design: randomised, crossover, single-blinded trial with active control condition. Randomisation performed by dice roll. Data acquisition from October 2018 to November 2019. Recruitment terminated due to ceasing access to eligible patients. cTBS, continuous theta-burst stimulation; fMRI, functional MRI; iTBS, intermittent theta-burst stimulation.

The game phase contained two conditions: no manipulation of the cursor in *non-Turbulence* (*non-Turb*), whereas an artificial decrease of agency was implemented during *Turbulence* (*Turb*) by adding random noise (movement of the cursor to the opposite direction as intended or no cursor movement at all) to 25% of the participants' button clicks. Participants rated judgement of performance (*JoP*) and judgement of agency (*JoA*) on a Likert scale from −5 ('very poor') to +5 ('very high'). Each game phase was presented for 15 s, whereas the judgements relied on confirmation and thus were self-paced. Details on MRI acquisition are presented in online supplemental material A.

Transcranial magnetic stimulation

The three stimulation protocols are exposed in table 1. Details on neuronavigation for target localisation are available in online supplemental material C.

Analyses

Analyses of neuroimaging and behaviour (primary outcomes) were divided into *baseline* and *stimulation effect*. For *baseline*, data acquired in runs prior to neurostimulation (1/3/5) were pooled to study group characteristics irrespective of tb-rTMS. For the *stimulation effect*, data acquired in all runs (1–6) were included in the analyses to assess the effect of tb-rTMS.

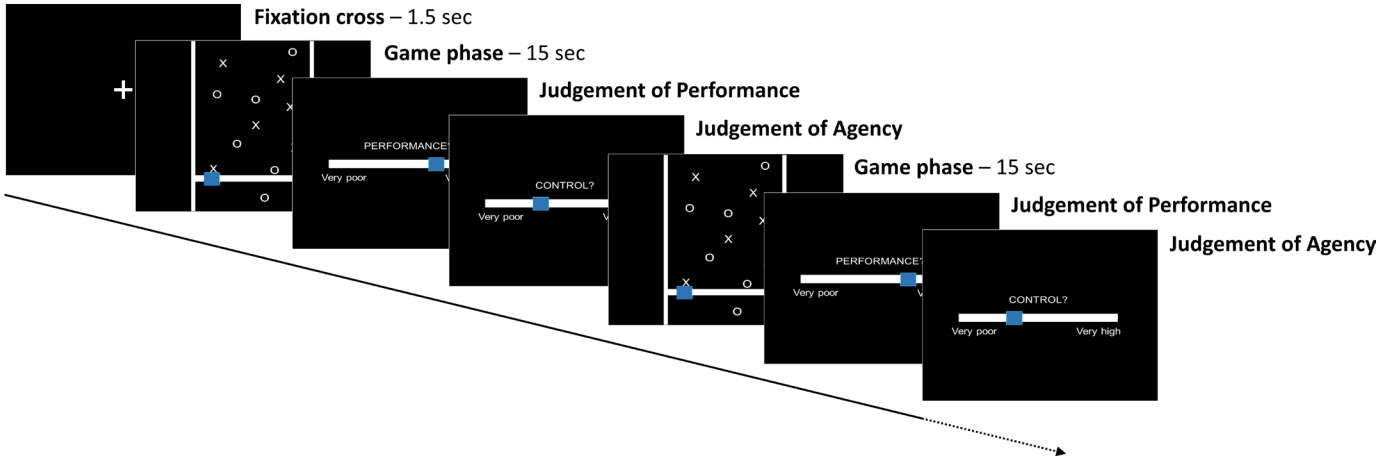

Figure 2 Behavioural paradigm during task-based functional MRI: agency task including two phases for each trial (game phase and judgement phase) with implemented manipulation of agency (non-Turb, Turb). Prior to each trial, participants were presented with a black screen with a white fixation cross for 1.5 s. The game phase consisted of a rectangular frame with an accentuated bar at the bottom on which a blue square served as a cursor that could be moved by the participants. In each trial, 12 targets (x) and non-targets (o) moved from the top of the screen to the bottom towards the bar. Participants were instructed to move the cursor in order to catch the targets while avoiding the non-targets. Touching a target with the cursor made the target turn green, while the non-targets turned red in response to being touched (visual feedback). During judgement phase, participants had to rate their performance (judgement of performance), as well as their feeling of control during the previous trial (judgement of agency) on a Likert scale. Each participant completed a total of 51 trials consisting of 24 trials for non-Turbulence (Turb), 18 trials for Turb and 9 trials of a pure visual condition in which no game was played, and participants were instructed to rest while observing the moving stimuli. Prior to data acquisition, a training session outside the scanner and a training session inside the scanner took place.

Table 1 tb-rTMS protocols: stimulation protocols were repeated after a break of 15 min[23]

	iTBS	cTBS	Sham
	Intermittent theta-burst stimulation	Continuous theta-burst stimulation	Continuous theta-burst stimulation
Target region*	rTPJ (MNI [62 -34 30][30])	rTPJ (MNI [62 -34 30][30])	Interhemispheric fissure
Expected effect	Increased cortical excitability of target region	Decreased cortical excitability of target region	No effect
Stimulation intensity†	80% of RMT	80% of RMT	80% of RMT
Total pulses	810	810	810
Number of triplets	270	270	270
Frequency of triplets	30 Hz	30 Hz	30 Hz
Frequency of triplet repetition	6 Hz (167 ms)	6 Hz (167 ms)	6 Hz (167 ms)
Repetition mode	Intermittent 8.33 s break after 10 triplets	Continuous	Continuous
Coil orientation	45° angle with the anterior part of the coil directing to the contralateral forehead	45° angle with the anterior part of the coil directing to the contralateral forehead	Orthogonal to the participant's forehead
Stimulation device and software	MagPro X100 device with MagPro software V.7.0, distributed by MagVenture, Farum, Denmark (in Switzerland by Neurolite Advanced Medical Solutions, Belp, CH), manufactured by Tonica Elektronik A/S, Farum, Denmark		
Stimulation coil	70 mm butterfly coil (MC-B70)		

*MNI = Montreal Neurological Institute, target coordinates based on Zito *et al*.[21]
†Stimulation intensity at 80% of resting motor threshold[23] assessed using the relative frequency method (see online supplemental material B).
cTBS, continuous theta-burst stimulation; iTBS, intermittent theta-burst stimulation; MNI, Montreal Neurological Institute; RMT, resting motor threshold; rTPJ, right temporoparietal junction.

Processing of behavioral data

Real performance (RP) was computed as $RP = \left(\frac{(Hit\ targets - Hit\ non-targets)}{total\ number\ stimuli\ (12)} \right)$. For JoP and JoA, the median for each condition was calculated.

fMRI analysis

SPM12 was used for image processing (https://www.fil.ion.ucl.ac.uk/spm/software/spm12). Preprocessing steps are detailed in online supplemental material D.

At the first level, a general linear model (GLM) for each subject's fMRI data was built containing the regressors for each game phase, each judgement phase and six motion regressors as block design. At the second level, we contrasted all non-Turb trials to all Turb trials ([non-Turb<Turb]) to build contrast maps representing *manipulated agency* (MA). One contrast map representing MA at *baseline* (runs 1/3/5) was created. Six contrast maps encoding MA in each run (1–6) were built to study the *stimulation effect*. The judgement phase was not considered in the second level analysis, as the duration of JoP (M=2.04 s, SD=0.80) and JoA (M=1.67 s, SD=0.63) was below the time of repetition.

rTPJ: volume of interest, region of interest

At baseline, a whole brain analysis was conducted as quality check to verify that the task activated the agency network (online supplemental figure 1 and online supplemental table 1 in online supplemental material E). As our main hypothesis focused on the role of the rTPJ, we selected a volume of interest (VOI) approach[31] which allows addressing structural and functional intersubject heterogeneity in localisation of rTPJ during tasks targeting the SoA.[32] Hence, centred around Montreal Neurological Institute (MNI),[30] a sphere of r=15 mm was placed on the contrast map representing MA. Within this sphere and for each subject separately, the coordinates of the peak activation were identified and used as centre coordinates for a sphere of r=10 mm (k_E=515 voxels), which was defined as the final region of interest (ROI) for the analysis and matched the cluster size of preceding studies (k_E=431).[21] To verify comparability of the regions between groups, a permutation test (1000 iterations) on the Euclidian distance between centre coordinates of individual ROI and seed coordinates was computed (t=−0.987, p=0.308). Additional ROI analyses were performed on further brain areas linked to the agency network; see online supplemental material H.

To study the stimulation effect, due to the technical impracticality of VOI (ie, resulting bias towards activity before stimulation), the rTPJ was defined as a sphere of r=10 mm centred around MNI.[30]

All abovementioned ROI masks were overlayed on the corresponding contrast map. Mean contrast estimates within the ROI were extracted and entered to statistical

analyses. We computed a delta score (Δ) by subtracting contrast estimates of poststimulation from those assessed in prestimulation.

Statistical analysis

Analyses were performed using MATLAB R2017b (V.9.3) and R studio (V.1.3.1093). In analyses including between-subject factors only, Pearson's χ^2 test or Wilcoxon rank-sum test was used on non-parametric data, while t-tests were applied on parametric data. In ROI analyses at baseline, nuisance regression was performed to correct for covariates of no interest (depression and trait anxiety). Testing the effect of each neurostimulation protocol on SSS, we applied false discovery rate (α=0.05) to correct for multiple comparisons.

In analyses including between-subject as well as within-subject variables, linear mixed-effect models were estimated allowing a random subject intercept. If included variables had >2 levels, an analysis of variance was applied to determine if the coefficients defined as fixed effects are equal to 0. Covariates of no interest (depression, trait anxiety and order of stimulation) were added to the models. For ROI analysis of the stimulation effect, the effect of sham stimulation was tested on contrast estimates (paired t-test), and Δ_{Vertex} was added to the abovementioned covariates of no interest, to exclude an indistinct effect deriving from time variations, environmental factors or placebo. To test veridical TMS-induced effects, the model inclusion was limited to real stimulation (cTBS, iTBS; delta scores) and patients to enhance the understanding of pathophysiological mechanisms while excluding bias due to potential ceiling effects in HC.

To test for associations between behavioural data and BOLD signal, Pearson's product moment correlation coefficient (PCC) was computed between absolute values (JoA and JoP) and mean contrast estimate within VOI at baseline. Investigating the stimulation effect on that association, PCC between absolute changes $(post - pre)$ or relative changes $\frac{(\text{post} - \text{pre})}{pre}$ (sensitive to ceiling or flooring effects) and change in mean contrast estimate within ROI was computed. In case of significance, association was tested in a GLM to correct for covariates of no interest (depression and trait anxiety).

RESULTS

Four patients were excluded due to incidental neuropathological finding in the MRI (n=1), lack of time (n=2) or without specification of reasons (n=1). Four HC were excluded due to non-applicability of TMS (n=1), lack of time (n=1), side effects of TMS (headache, n=1) or missing data during fMRI acquisition (n=1). The final sample consisted of 23 patients and 19 HC. No significant difference in age (t(39.69)=1.637, p=0.110) or gender distribution (χ^2(1, n=42)=0.019, p=0.890) between FND and HC was found. Demographic and clinical characteristics are reported in table 2.

SoA and rTPJ activity during MA at baseline

To test group characteristics before neurostimulation, subjective ratings of JoA and neuroimaging data (MA, contrast [non-Turb<Turb]), from all runs prior to tb-rTMS (1/3/5), were included.

SoA

At baseline, we detected a game mode and group interaction (β=−3.105, SE=0.306, p<0.001), showing that patients adapted their JoA significantly less compared to HC during Turb versus non-Turb (figure 3). A main effect of game mode was observed with both groups reporting lower JoA during Turb than that of no-Turb (β=−2.444, SE=0.186, p<0.001). Moreover, patients reported significantly lower JoA compared with that of HC during non-Turb (W=93.5, p=0.002).

Analyses of RP and JoP at baseline are detailed in online supplemental material F,G.

rTPJ activity during MA

The whole brain analysis is presented in online supplemental material E.

Mean contrast estimate extracted from individual VOI encoding MA ([non-Turb<Turb]) at baseline was compared between groups and showed a significant difference between FND and HC (t(40)=-1.831, p=0.037; figure 4), which survived correction for depression and trait anxiety (t(40)=-1.720, p=0.047).

The analysis of further brain areas linked to the agency network based on the parcellation of the automated anatomical labelling atlas 3 (AAL3) revealed group differences in the right middle frontal and right inferior frontal gyrus (online supplemental table 2).

Linking JoA to rTPJ activity

During MA, JoA was found to be positively correlated with the brain activity in the rTPJ (VOI) at baseline in patients (r=0.572, p=0.004; figure 4) but not controls (r=0.272, p=0.260). In a GLM corrected for depression and trait anxiety, the rTPJ activity was identified as a significant predictor for JoA during MA (β=0.632, SE=0.201, p=0.005). This association was not observed in JoP (r=0.011, p=0.960).

Neuromodulatory potential of tb-rTMS over rTPJ on SoA

To test the effect of tb-rTMS, subjective ratings of JoA and neuroimaging data (MA, contrast [non-Turb<Turb]), from all runs (1–6), were included.

Sense of agency

The model testing the stimulation effect on JoA confirmed a main effect of group (F(1, 40.95)=37.942, p<0.001) and a main effect of timepoint (F(1, 202.70)=4.136, p=0.043), indicating lower JoA in patients across all sessions and an increase of JoA due to intervention irrespective of stimulation protocol. Moreover, the model showed a significant interaction of group and timepoint (F(1, 195.76)=7.777, p=0.006): HC increased their rating from prestimulation to poststimulation runs to a larger extent compared with

Table 2 Participants' demographic and clinical characteristics at visit 1

Variable	Overall, n=42*	Group		P value†
		FND, n=23*	HC, n=19*	
Gender				0.9
Female	27 (64%)	15 (65%)	12 (63%)	
Male	15 (36%)	8 (35%)	7 (37%)	
Age (y)	36.8 (13.5)	39.8 (13.9)	33.2 (12.5)	0.11
Handedness§				>0.9
Right	39 (93%)	21 (91%)	18 (95%)	
Left	3 (7.1%)	2 (8.7%)	1 (5.3%)	
Symptom type‡		11 weaknesses, 3 seizures, 14 gait disorders, 1 dystonia, 7 tremors, 1 myoclonus	NA	
ICD-10 diagnosis		8 F44.4 2 F44.5 13 F44.7	NA	
Symptom duration (y)		4.21 (3.57)	NA	
Subjective symptom severity (SSS)		3.87 (3.14)	NA	
Beck's Depression Inventory		8.8 (8.6)	2.2 (3.4)	<0.001
Trait from State-Trait Anxiety Inventory		37.3 (11.5)	29.9 (11.8)	0.066

*n (%), mean (SD).
†Pearson's χ^2 test, Welch two-sample t-test, Wilcoxon rank-sum test.
‡Patients can present with more than one symptom type.
§Deviating this classification: one patient used left instead of dominant right hand during task due to symptoms.
FND, functional neurological disorder; HC, healthy controls; ICD-10, International Classification of Diseases 10th Edition; y, year.

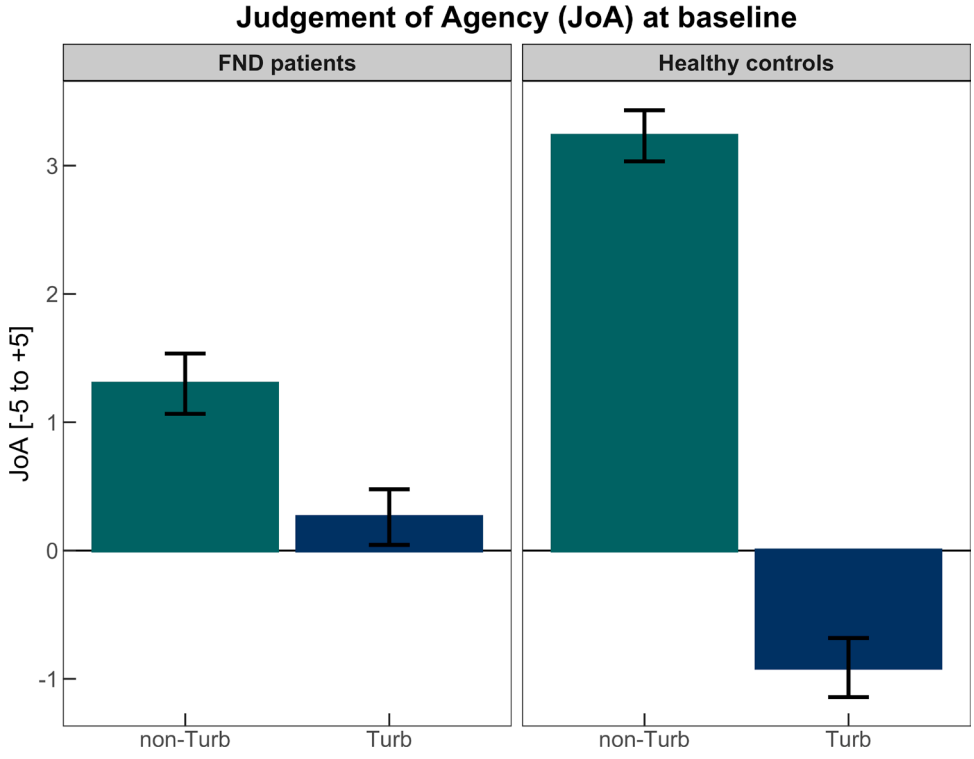

Figure 3 Judgement of agency at baseline (runs 1/3/5): subjective ratings displayed for patients with functional neurological disorder versus healthy controls, divided according to condition (non-Turb versus Turb). Error bars indicating SE. FND, functional neurological disorder; HC, healthy controls; JoA, judgement of agency; non-Turb, non-Turbulence.

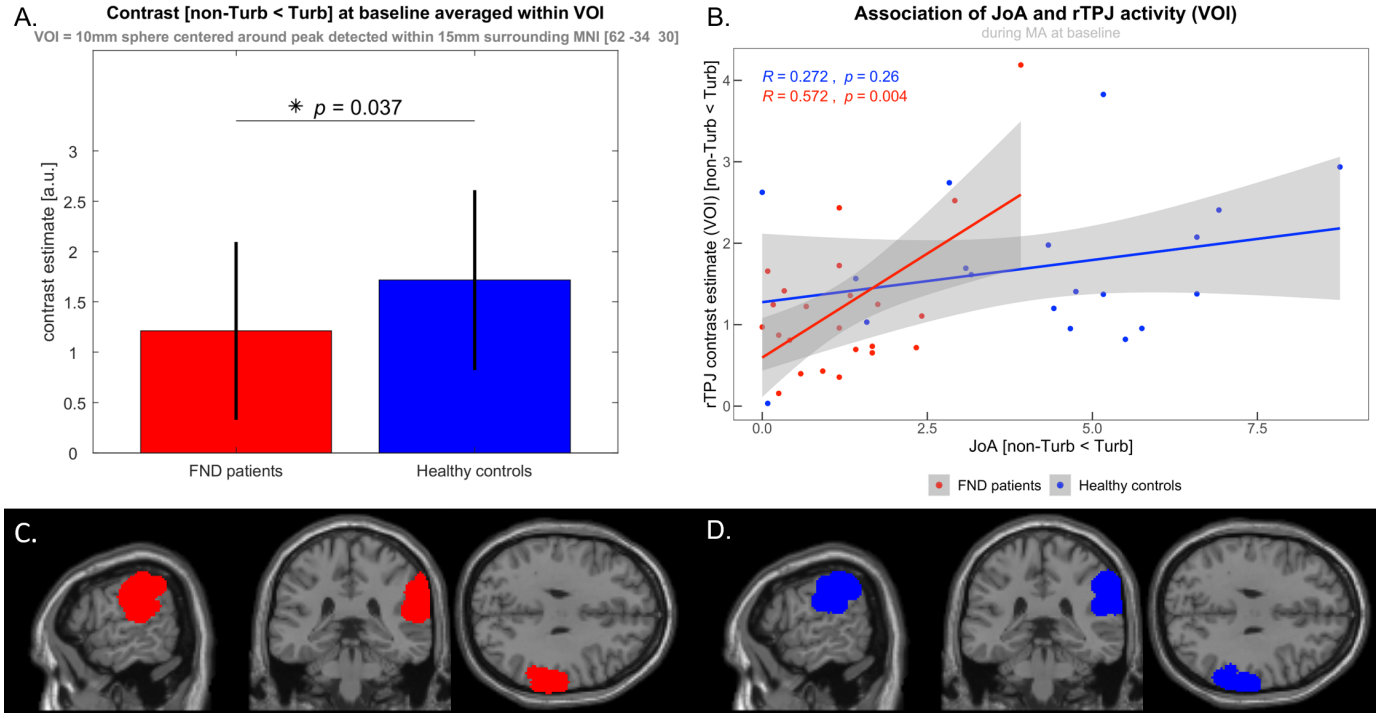

Figure 4 Activation of the right temporoparietal junction (rTPJ) during manipulated agency (MA) at baseline (runs 1/3/5), comparing patients with functional neurological disorder (FND) versus healthy controls (HC). (A) Mean contrast estimate extracted from individual volume of interest (VOI) (rTPJ) on contrast of MA ([non-Turb<Turb]). Comparing FND patients with HC in one-tailed two-sample t-test. Error bars indicating SD. (B) Association of judgement of agency (JoA) and rTPJ activity extracted from VOI during MA ([non-Turb<Turb]) at baseline. Regression graph for FND patients versus HC with corresponding Pearson's product moment correlation coefficient. (C) Summed binary VOI of patients (red). (D) Summed binary VOI for controls (blue). Presented as overlay on T1-weighted MRI of standardised brain. Centred at Montreal Neurological Institute.[30] Comparability of localisation statistically described in Methods section. FND, functional neurological disorder; HC, healthy controls; JoA, judgement of agency; MA, manipulated agency; MNI, Montreal Neurological Institute; rTPJ, right temporoparietal junction; Turb, Turbulence; VOI, volume of interest.

patients. No interaction of group, timepoint and stimulation was observed ($F(2, 195.76)=0.304$, p=0.738).

No effect of stimulation on RP or JoP was found (online supplemental material F,G).

rTPJ activity during MA

To control for a placebo effect, a two-tailed paired t-test on contrast estimate was used to test whether the rTPJ activity changed significantly due to sham stimulation, which was neither the case in patients ($t(22)=-0.106$, p=0.917) nor in HC ($t(18)=-0.909$, p=0.375). Therefore, we tested a model including real stimulation delta scores in patients only and found a significant effect of stimulation (cTBS and iTBS, $\beta=0.403$, $SE=0.187$, p=0.037), which survived correcting for depression, trait anxiety and order of stimulation ($\beta=0.403$, $SE=0.187$, p=0.037; figure 5, details in online supplemental table 3). Furthermore, by adding Δ_{Vertex} as covariate of no interest, the significant effect of stimulation remained even after accounting for a patient's indistinct sham response ($\beta=0.403$, $SE=0.186$, p=0.036). In HC, this effect was not observed (online supplemental table 4).

Linking JoA to rTPJ activity

The relationship between the change in rTPJ (ROI) activity due to stimulation and the change in JoA in FND was investigated. No association between JoA and brain activity was found (online supplemental material I).

Feasibility

In neither group, a severe adverse event (AE) was encountered, with the number of participants reporting AEs being comparable between groups (online supplemental table 5). Moreover, patients' ratings of SSS did not significantly change due to cTBS ($V=30$, p=0.603), iTBS ($V=32$, p=0.672) or sham stimulation ($V=21$, p=0.079).

DISCUSSION

The first study in the field of FND, combining fMRI and NIBS targeting the agency network, showed (1) a reduced JoA associated with hypoactivation of the rTPJ in FND compared with HC and (2) neuroimaging-based evidence for a neuromodulatory potential of tb-rTMS on the rTPJ in FND.

SoA in FN

The behavioural paradigm successfully captured the well-described distorted agency attribution in patients with FND.[2 4–7] Not only did patients report lower agency (JoA during non-Turb) than that of controls, they were also less able to acknowledge an external manipulation of their

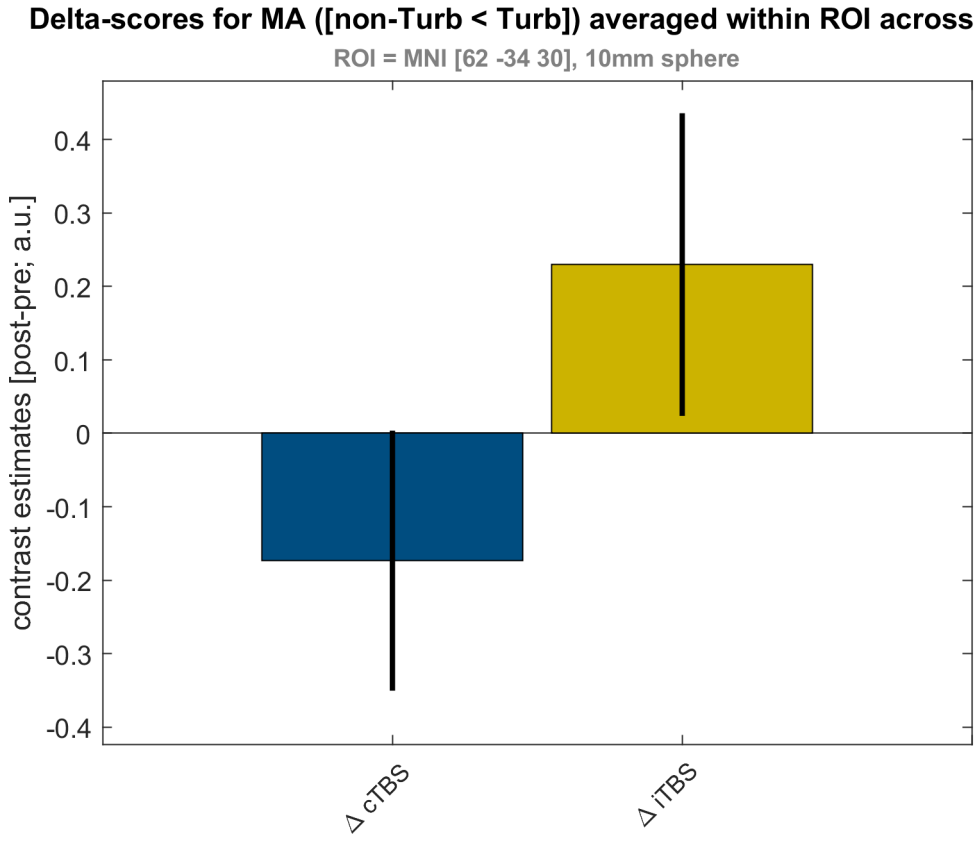

Figure 5 Neurophysiological modulation of repetitive transcranial magnetic stimulation on the right temporoparietal junction (rTPJ) activity during manipulated agency in patients with functional neurological disorder. Mean delta scores (Δ) extracted from region of interest (rTPJ) in patients including continuous theta-burst stimulation and intermittent theta-burst stimulation. Error bars indicating SD. FND, functional neurological disorder; cTBS, continuous theta-burst stimulation; iTBS, intermittent theta-burst stimulation; MA, manipulated agency; MNI, Montreal Neurological Institute; ROI, region of interest; Turb, Turbulence.

agency (interaction game mode and group), indicating an impairment in the inference of one's own intentions, motor commands and the resulting outcome.[9]

Neuroimaging findings confirmed the key role of the rTPJ during the agency task, in accordance with the previous literature agreeing on the experience of agency as the brain's default state, while disruption of agency leads to an activation of the agency network.[33] An increase of rTPJ activity during reduced agency (MA) was found across both groups, but patients had significantly less activity during MA compared with that of HC, supporting findings of hypoactivation in rTPJ in FND.[3 13]

An association between rTPJ activation and reported SoA (JoA) was found in patients with FND, suggesting the rTPJ being engaged as a resource for the metacognitive evaluation of explicit agency when a decrease of agency is experienced.[33] Notably, the rTPJ involvement was unique to the evaluation of agency (no correlation of rTPJ activity and JoP). HC did not show such an association, which might represent higher sensitivity to distortion detection, thus possibly reflecting a ceiling effect. In summary, we assume that the rTPJ might serve as neurophysiological correlate to the reported disturbance in SoA and potentially relates to the involuntariness of symptoms in FND.[3]

Neuromodulatory potential of tb-rTMS over rTPJ in FND

Investigating the stimulation effect on subjective JoA, we did not identify significant changes. In contrast to the pooled data at baseline, a limited number of trials were available to infer this complex effect, and we therefore assume a lack of power rather than a negative result. However, we observed an increase of JoA over time across both groups (effect of timepoint), suggesting a non-specific learning effect, which is more pronounced in HC (interaction group and timepoint). This may be of interest to future studies, implicating that SoA could be amenable to training.

Importantly, this study provides the first preliminary evidence for a neurophysiological modulation of the rTPJ during artificially reduced agency in FND. A significant effect on the BOLD signal was found with excitatory iTBS increasing the signal in the rTPJ and inhibitory cTBS eliciting a decrease. Testing the isolated effect of vertex stimulation (contrast estimates) confirmed the absence of a sham-induced change in the rTPJ, and accounting for Δ_{Vertex}, as proxy for non-specific, time-varying, repetition-related effects or placebo-associated changes as covariate of no interest, the significant difference of cTBS-elicited and iTBS-elicited modulations persisted in the main model, arguing against an exclusively placebo-based effect.

Regarding the lack of transfer from neurophysiological to behavioural modulation, it is conceivable that the rTPJ reflects a correlate of a non-conceptual, implicit feeling of agency based on action monitoring, whereas JoA reflects a metacognitive process of explicit agency claiming an integration of multimodal perception and cognitive sources, thus requiring (pre)frontal areas.[34 35] Hence, tb-rTMS over the rTPJ potentially altered the feeling of agency, whereas the stimulation of this region alone is not sufficient to alter the interplay of areas involved in the judgement of agency.

Despite the absence of a behavioural effect, our findings on changes in rTPJ activity after tb-rTMS contribute to the scientific debate, by reflecting genuine neurophysiological modulatory processes rather than unspecific placebo effects[36] and can thus add to the advances in inferring on therapeutic applicability.

Feasibility of tb-rTMS in FND

We report high feasibility and tolerability of tb-rTMS in patients with FND. The applied experimental intervention neither elicited substantial adverse effect nor a rise in SSS. rTMS over the rTPJ was successfully applied in two studies,[19 20] and one study applied iTBS in FND targeting a different area.[37] Considering the potential of TBS regarding long-term plasticity changes, the available reports of feasibility in FND provide valuable groundwork for future studies.

Limitations

Although the presented sample is relatively large in comparison with other rTMS studies in the field,[17 18] we acknowledge the sample size of 23 patients and 19 HC as a major limitation. This furthermore prevented us from performing subgroup analyses to determine whether specific symptom types would be more responsive to neuromodulation. An additional limitation constitutes the presence of depressive comorbidity in our patient cohort, which may influence the neuroimaging findings. Nonetheless, the results remained significant after correcting for mood scores, whereas psychiatric medication should be addressed in future studies. Finally, TBS protocols have a limitation in themselves as there is an ongoing debate on the precise neurochemical excitatory/inhibitory processes and observed interindividual and intraindividual variability.[38] We can hypothesise that similar variability is responsible for the negative results we obtained on behavioural scores of agency. Measuring the BOLD signal to assess target engagement strengthens our findings, whereas the variability especially in vertex stimulation calls for more attention in upcoming studies and careful selection of control protocols.

Outlook

The reported neuromodulatory potential sets grounds for future studies and clinical trials; however, many challenges need to be tackled to develop a neurobiologically informed treatment in FND, and the next steps entail to verify (1) a behavioural effect on agency and (2) a clinical effect on symptom severity. While the first step could be achieved by adapting the number of trials in the agency task and adjusting the sample size, achieving the second step would require adding objective symptom assessment and quality of life as outcome measures. Since the brain is organised in networks—as also the agency network—other hubs could be amenable to neurostimulation,[35] whereas modulation of connectivity between relevant nodes should be investigated in future studies, given the recent demonstration of FC modulation using iTBS in FND.[37] Moreover, advanced placebo delivery setups (eg, sham coils, spacer and sensory stimulation) and collecting a patient's hypothesis about received stimulation (active/passive) are advised to provide and verify masking while excluding external modulation. By elaborating on optimal and individualised stimulation intensity and location (eg, peak activation during task of interest) and refining the number of applications (considering a dose-dependent mechanism of rTMS[39]), tb-rTMS efficiency might be enhanced, while also other NIBS techniques (eg, rTMS, transcranial direct current stimulation) could be explored.

Lastly, patient characteristics as an indicator for stimulation efficacy and outcome success require attention in future studies (eg, symptom type, symptom duration and comorbidities). Brain-state dependencies[40] could be used to either evaluate eligibility for treatment (eg, resting-state FC) or to boost the treatment response by priming relevant brain circuits (eg, psychotherapy/physiotherapy, suggestion).

CONCLUSION

The current study confirmed impaired SoA in patients with FND, which is associated with a decreased rTPJ activation. Furthermore, as a proof-of-concept report, tb-rTMS over the rTPJ revealed the potential for modulating cortical activation, delineating an important step for future research refining a protocol being used in a clinical trial to test its efficacy on behaviour, symptoms and clinical outcome.

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REFERENCES

1 American Psychiatric Association. Diagnostic and statistical Manual of mental disorders. Arlington, VA, US2013. xliv, 947-xliv, p,
2 Edwards MJ, Moretto G, Schwingenschuh P, *et al*. Abnormal sense of intention preceding voluntary movement in patients with psychogenic tremor. *Neuropsychologia* 2011;49:2791–3.
3 Voon V, Gallea C, Hattori N, *et al*. The involuntary nature of conversion disorder. *Neurology* 2010;74:223–8.
4 Nahab FB, Kundu P, Maurer C, *et al*. Impaired sense of agency in functional movement disorders: an fMRI study. *PLoS One* 2017;12:e0172502.
5 Kranick SM, Moore JW, Yusuf N, *et al*. Action-effect binding is decreased in motor conversion disorder: implications for sense of agency. *Mov Disord* 2013;28:1110–6.
6 Pareés I, Brown H, Nuruki A, *et al*. Loss of sensory Attenuation in patients with functional (psychogenic) movement disorders. *Brain* 2014;137(Pt 11):2916–21.
7 Stager L, Morriss S, McKibben L, *et al*. Sense of control, selective attention and cognitive inhibition in pediatric functional seizures: A prospective case-control study. *Seizure* 2022;98:79–86.
8 Drane DL, Fani N, Hallett M, *et al*. A framework for understanding the pathophysiology of functional neurological disorder. *CNS Spectr* 2020;2020:1–7.
9 Blakemore SJ, Frith C. Self-awareness and action. *Curr Opin Neurobiol* 2003;13:219–24.
10 Weber S, Heim S, Richiardi J, *et al*. Multi-centre classification of functional neurological disorders based on resting-state functional Connectivity. *Neuroimage Clin* 2022;35:103090.
11 Wegrzyk J, Kebets V, Richiardi J, *et al*. Identifying motor functional neurological disorder using resting-state functional Connectivity. *Neuroimage Clin* 2018;17:163–8.
12 Maurer CW, LaFaver K, Ameli R, *et al*. Impaired self-agency in functional movement disorders: a resting-state fMRI study. *Neurology* 2016;87:564–70.
13 Baek K, Doñamayor N, Morris LS, *et al*. Impaired awareness of motor intention in functional neurological disorder: implications for voluntary and functional movement. *Psychol Med* 2017;47:1624–36.
14 Aybek S, Nicholson TR, Zelaya F, *et al*. Neural correlates of recall of life events in conversion disorder. *JAMA Psychiatry* 2014;71:52–60.
15 Hallett M. Transcranial magnetic stimulation: a primer. *Neuron* 2007;55:187–99.
16 Huang YZ, Edwards MJ, Rounis E, *et al*. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45:201–6.
17 Oriuwa C, Mollica A, Feinstein A, *et al*. Neuromodulation for the treatment of functional neurological disorder and somatic symptom disorder: a systematic review. *J Neurol Neurosurg Psychiatry* 2022;93:280–90.
18 Gonsalvez I, Spagnolo P, Dworetzky B, *et al*. Neurostimulation for the treatment of functional neurological disorder: A systematic review. *Epilepsy Behav Rep* 2021;16:100501.
19 Agarwal R, Garg S, Tikka SK, *et al*. Successful use of Theta burst stimulation (TBS) for treating psychogenic non epileptic seizures (PNES) in a pregnant woman. *Asian J Psychiatr* 2019;43:121–2.
20 Peterson KT, Kosior R, Meek BP, *et al*. Right Temporoparietal junction transcranial magnetic stimulation in the treatment of psychogenic Nonepileptic seizures: A case series. *Psychosomatics* 2018;59:601–6.
21 Zito GA, Anderegg LB, Apazoglou K, *et al*. Transcranial magnetic stimulation over the right Temporoparietal junction influences the sense of agency in healthy humans. *J Psychiatry Neurosci* 2020;45:271–8.
22 Stone J, LaFrance WC, Brown R, *et al*. Conversion disorder: current problems and potential solutions for DSM-5. *J Psychosom Res* 2011;71:369–76.
23 Nyffeler T, Wurtz P, Lüscher H-R, *et al*. Repetitive TMS over the human Oculomotor cortex: comparison of 1-Hz and Theta burst stimulation. *Neurosci Lett* 2006;409:57–60.
24 BECK AT, WARD CH, MENDELSON M, *et al*. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
25 Spielberger CD, Gorsuch RL, Lushene R, *et al*. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, 1983.
26 Metcalfe J, Greene MJ. Metacognition of agency. *J Exp Psychol Gen* 2007;136:184–99.
27 Miele DB, Wager TD, Mitchell JP, *et al*. Dissociating neural correlates of action monitoring and Metacognition of agency. *J Cogn Neurosci* 2011;23:3620–36.
28 Delorme C, Salvador A, Voon V, *et al*. Illusion of agency in patients with Gilles de la Tourette syndrome. *Cortex* 2016;77:132–40.
29 Zalla T, Miele D, Leboyer M, *et al*. Metacognition of agency and theory of mind in adults with high functioning autism. *Conscious Cogn* 2015;31:126–38.
30 Metcalfe J, Van Snellenberg JX, DeRosse P, *et al*. Judgements of agency in schizophrenia: an impairment in Autonoetic Metacognition. *Philos Trans R Soc Lond B Biol Sci* 2012;367:1391–400.
31 Tong Y, Chen Q, Nichols TE, *et al*. Seeking optimal region-of-interest (ROI) single-value summary measures for fMRI studies in imaging Genetics. *PLoS One* 2016;11:e0151391.
32 Zito GA, Wiest R, Aybek S. Neural correlates of sense of agency in motor control: A neuroimaging meta-analysis. *PLOS ONE* 2020;15:e0234321.
33 Haggard P. Sense of agency in the human brain. *Nat Rev Neurosci* 2017;18:196–207.
34 Moore JW, Fletcher PC. Sense of agency in health and disease: a review of cue integration approaches. *Conscious Cogn* 2012;21:59–68.
35 Malik RA, Galang CM, Finger E. The sense of agency for brain disorders: A comprehensive review and proposed framework. *Neurosci Biobehav Rev* 2022;139:104759.
36 Nicholson TRJ, Voon V. Transcranial magnetic stimulation and sedation as treatment for functional neurologic disorders. *Handb Clin Neurol* 2016;139:619–29.
37 Spagnolo PA, Parker J, Horovitz S, *et al*. Corticolimbic modulation via intermittent Theta burst stimulation as a novel treatment for functional movement disorder: A proof-of-concept study. *Brain Sci* 2021;11:791.
38 Boucher PO, Ozdemir RA, Momi D, *et al*. Sham-derived effects and the minimal reliability of Theta burst stimulation. *Sci Rep* 2021;11:21170.
39 Nettekoven C, Volz LJ, Kutscha M, *et al*. Dose-dependent effects of Theta burst rTMS on cortical excitability and resting-state Connectivity of the human motor system. *J Neurosci* 2014;34:6849–59.
40 Bergmann TO. Brain state-dependent brain stimulation. *Front Psychol* 2018;9:2108.