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Testing a Neurobiological Model of Depersonalization Disorder Using Repetitive Transcranial Magnetic Stimulation

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ABSTRACT

Background: Depersonalization disorder (DPD) includes changes in subjective experiencing of self, encompassing emotional numbing. Functional magnetic resonance imaging (fMRI) has pointed to ventrolateral prefrontal cortex (VLPFC) inhibition of insula as a neurocognitive correlate of the disorder.
Objective: We hypothesized that inhibition to right VLPFC using repetitive transcranial magnetic stimulation (rTMS) would lead to increased arousal and reduced symptoms.
Methods: Patients with medication-resistant DSM-IV DPD ($N = 17$) and controls ($N = 20$) were randomized to receive one session of right-sided rTMS to VLPFC or temporo-parietal junction (TPJ). 1Hz rTMS was guided using neuronavigation and delivered for 15 min. Co-primary outcomes were: (a) maximum skin conductance capacity, and (b) reduction in depersonalization symptoms (Cambridge Depersonalisation Scale (CDS) [state version]). Secondary outcomes included spontaneous fluctuations (SFs) and event-related skin conductance responses.
Results: In patients with DPD, rTMS to VLPFC led to increased electrodermal capacity, namely maximum skin conductance deflections. Patients but not controls also showed increased SFs post rTMS. Patients who had either VLPFC or TPJ rTMS showed a similar significant reduction in symptoms. Event-related electrodermal activity did not change.
Conclusions: A single session of right-sided rTMS to VLPFC (but not TPJ) significantly increased physiological arousal capacity supporting our model regarding the relevance of increased VLPFC activity to emotional numbing in DPD. rTMS to both sites led to reduced depersonalization scores but since this was independent of physiological arousal, this may be a non-specific effect. TMS is a potential therapeutic option for DPD; modulation of VLPFC, if replicated, is a plausible mechanism.

Introduction

Depersonalization disorder (DPD) is a psychiatric syndrome characterized by persistent and distressing feelings of unreality and alterations in a person's sense of self [1] as defined in DSM-IV-TR [2]. It is found in many cultures [3] and the condition affects around 1% of the population [4]. It often begins in adolescence and has a tendency for chronicity [5,6]. Depersonalization is frequently a transient phenomenon in states of fatigue or fear [7] and can appear as a symptom of other psychiatric disorders including panic disorder [8]. Secondary forms are also well described in patients with neurological conditions, such as temporal lobe epilepsy [9] and following substance misuse [10,11]. A variety of pharmacological treatments have been tried [12] but most fail to show substantial benefits [13]. A cognitive behavioral model has been developed [14] but has not been subjected to a randomized controlled trial [15].

A neurobiological model of DPD has also been proposed [16], hypothesizing dysfunctionally increased fronto-insula/limbic inhibitory regulation. This model is consistent with neurological case studies [17] and has been refined by neuroimaging research using fMRI [18,19], which has demonstrated reduced insula, limbic

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and visual association cortical activation in response to emotive pictures, and increased VLPFC activation. Psychophysiological studies using skin conductance response (SCR) measures [20] have found reduced autonomic responses in patients with DPD to unpleasant, emotive stimuli, in comparison to those with anxiety disorders and to healthy controls [21]. Work combining fMRI and SCR has shown a correlation between dorsolateral and ventral prefrontal and 'limbic' activation in response to emotional faces in DPD [22,23] which is consistent with the functional (reciprocal) interaction seen between VLPFC and insula in healthy volunteers [24], and patients with anxiety states [25]. Finally, preliminary work [26] shows that reduced right VLPFC (and increased insula) activation on fMRI corresponds to symptomatic improvement in DPD patients treated with lamotrigine [27]. This body of work appears to point to a mechanism for the emotional numbing frequently experienced by DPD suffers and may even relate to a core abnormal experiencing of the sense of self [28].

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, is well established both as a research tool and therapeutic intervention in a range of psychiatric disorder [29]. Of relevance to DPD, rTMS has been used to examine the role of the prefrontal cortex in emotional regulation. A single session of rTMS to the right DLPFC induced impairments in participants' ability to inhibit negative emotion processing in a facial evaluation task [30]. Other studies found that low frequency (inhibitory) rTMS to the right DLPFC in healthy participants could induce risk-taking behavior on a gambling paradigm [31] and reduce participants' willingness to reject unfair offers on 'the ultimatum game' [32,33]. High frequency (excitatory) rTMS to the left DLPFC can reduce food craving [34], cigarette smoking [35] and cocaine craving [36] compared to sham TMS. These studies indicate that rTMS can modulate behavior and motivational states by enhancing or attenuating inhibitory prefrontal mechanisms.

There have been two single case reports, and one trial reporting the usage of TMS in DPD. The first was a woman with co-morbid DPD and major depression (MDD) [37] whose single photon emission computed tomography (SPECT) scan showed right frontal hyperactivity, which was the target of 1Hz rTMS. It was reported that her self-awareness increased and depersonalization symptoms decreased. In a second case study, a 24 year-old male with comorbid DPD and MDD who had not responded to pharmacotherapy also received an SPECT scan [38]. The scan showed hypoperfusion bi-temporally and in the left frontoparietal region. rTMS was delivered to the left DLPFC, and a 28% reduction in symptoms was reported after 6 sessions. Finally, a trial in twelve DPD patients reported that half responded to temporal parietal junction (TPJ) TMS after three weeks of treatment [39]. The TPJ region was chosen due to its relevance in out of body experiences (OBEs), researched previously using TMS [40,41]. Five out of the six responders showed a 68% reduction in symptoms after a total of six weeks treatment. Unfortunately, none of these studies utilized either sham or active control conditions, so it is not possible to exclude placebo effects. In addition there was no offline-testing of behavioral or physiological markers.

The overall aims of this research were to firstly use low frequency TMS stimulation to test a neurobiological model of DPD, whereby the VLPFC was the target site of stimulation, the TPJ taking the role as active control site of stimulation, and secondly compare the potential therapeutic utility of these two sites of stimulation for future controlled clinical trials in DPD. We chose VLPFC rather than DLPFC because of the balance of evidence pointing to the former in DPD reviewed above, and its role in regulation of abnormal states of anxiety and arousal [25] despite the greater experience of TMS delivered to the DLPFC, and the likelihood that DLPFC as well as ventral and indeed medial frontal regions are also involved in emotion modulation [42].

We sought to test the hypothesis that low frequency (inhibitory) rTMS to the right VLPFC in patients with DPD would cause increases in autonomic arousal (SCRs) and decreases is symptoms of DPD.

Methods and materials

Ethical approval

NHS Research Ethics Review System, London, approved this research in accordance with the declaration of Helsinki. All participants gave written informed consent.

Participants

There were $N = 43$ participants in total: 22 had a primary diagnosis of DPD (DSM-IV TR) based on a detailed interview by the clinic psychiatrist. Patients were recruited through the Depersonalization Unit Clinic, a specialist outpatients service based at the Maudsley Hospital, South London. There were 21 healthy controls; these were staff and students of King's College London and local residents who responded to adverts for volunteers.

Inclusion criteria for cases: a current primary diagnosis of DPD and scores >70 on the Cambridge Depersonalization Scale [43]. All were unresponsive to at least one medication, although the majority had failed to respond to several and had been ill for at least 2 years. Patients taking medications could participate in the trial if their medication did not have safety contraindications with rTMS [44] and if they had been on a stable dose for at least two weeks.

Table 1
Baseline characteristics of all participants, DPD patients and controls – separated according to allocation to TMS condition.

	Patients with DPD ($N = 17$)		Healthy controls ($N = 20$)	
	VLPFC ($N = 8$)	TPJ ($N = 9$)	VLPFC ($N = 11$)	TPJ ($N = 9$)
Age, mean (SD)	34.9 (5.2)	39.3 (14.6)	30.1 (4.4)	28.3 (7.0)
Gender	7 male	6 male	5 male	3 male
Taking psychotropic medication	3	5	0	0
Duration of DPD (years)	15.1 (9.7)	12.4 (16.7)	–	–
Age of DPD onset	16.7 (5.9)	22.3 (15.3)	–	–
CDS trait total	133.9 (29.4)	119.2 (33.7)	7.6 (9.6)	20.3 (21.8)
DES	30.1 (13.4)	30.0 (14.2)	4.3 (2.0)	12.0 (12.3)
BAI	40.6 (12.9)	36.4 (14.0)	2.3 (1.9)	6.7 (9.4)
BDI	22.4 (12.7)	14.0 (7.9)	4.5 (3.5)	12.0 (10.1)
Resting motor threshold	56.4 (4.5)	52.7 (2.8)	52.5 (6.2)	51.3 (2.2)
Baseline SCR (μsiemens)	0.5 (0.8)	0.6 (0.5)	0.8 (0.9)	0.7 (0.4)
Baseline SCL (μsiemens)	3.2 (1.6)	4.0 (2.3)	3.2 (2.0)	3.4 (1.4)

DPD, depersonalization disorder; VLPFC, ventrolateral prefrontal cortex; TPJ, temporo-parietal junction; DES, Dissociative Experiences Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; SCR, skin conductance response; SCL, skin conductance level.

Exclusion criteria were inability to provide informed consent, personal history of severe headaches, a current or historical neurological diagnosis, a personal or family history of seizures or epilepsy, any medical condition involving a loss of consciousness, or the violation of MRI safety contraindications including metal in the body. Participants were screened using the CDS; controls were excluded if they scored >70.

One patient did not attend her MRI scan due to anxiety and so was not able to continue participation. A further five participants ($N = 4$ with DPD) were excluded from analyses; one patient's MRI scan revealed marked cortical atrophy of unknown cause; another could not complete all measures due to technical equipment problems and 3 were because of other protocol violations.

Assessments

Socio-demographic variables were recorded on all subjects. As noted, all subjects completed the CDS, a self-assessment instrument with good reliability and validity, which has state and trait versions. A score of 70 (out of a possible maximum 290, trait version) has a sensitivity of 75.5% and specificity of 87.2% as a clinical cut-off [43]. The CDS has a 'state' version (CDS-S) adapts 22 of the 29 items, which lend themselves to a 'here and now' rating, and uses the mean score expressed as a percentage. The scale has high reliability and has been shown to be sensitive to symptom change [15]. Other scales included the Beck Depression Inventory [45] and Beck Anxiety Inventory [46] and the Dissociative Experiences Scale [47]. All subjects underwent a full psychiatric assessment and duration of illness and treatment history was recorded (Table 1).

Participants were pseudorandomized to receive either VLPFC or TPJ TMS stimulation with the constraint of ensuring approximately equal numbers in each given the relatively small sample size. They were blind to the study hypotheses and predicted effects of the two stimulation sites. Researchers were not blind to site allocation. Since TPJ could also be therapeutically beneficial for patients but through an unrelated mechanism to that under investigation, it was considered ideal from both an ethical and methodological point of view as an active control [48].

Procedures

A structural MRI was obtained for all participants prior to TMS. MRI data were acquired on a GE 1.5 T HDx system (General Electric, Milwaukee, WI, USA) at the Institute of Psychiatry, London. Localizer and calibration scans were followed by 2D T2-weighted Fast Spin Echo and FLAIR (Fluid Attenuated Inversion Recovery) scans. A 3D T1-weighted Inversion Recovery prepared Spoiled Gradient Echo (IR-SPGR) scan was then collected with the following parameters: TE = 5 ms; TR = 12 ms; TI = 300 ms; excitation flip angle = 18°; matrix size 320 × 224 × 220 over a 288 × 202 × 198 field of view, giving an isotropic 0.9 mm voxel size over the whole brain. Images were converted to DICOM format for use within BrainSight-v2 neuronavigation software program. Neuronavigation has been demonstrated to improve the accuracy of positioning a TMS coil [49]. BrainSight ensures that TMS stimulation can only be delivered when the target site is positioned using the frameless stereotaxy.

Skin conductance

Two silver-chloride electrodes 0.5 cm in diameter were attached to the participants' non-dominant hand at the distal phalanges as per previous research [21]. The SC4 module (Contact Precision Instruments) was used to record skin conductance, attached to a laptop, recording SC signals at 100 mS intervals. Water-soluble electrolyte jelly was used as an electrolyte as per recommended guidelines [50]. These readings were synchronized with a picture presentation.

Stimulus presentation

An initial set of pictures was shown from the International Affective Picture System (IAPS) [51] in color on a laptop 1 m from the participant prior to rTMS and then the other set, again following rTMS. The two sets, A or B were matched for normative ratings of valence and arousal; participants were randomized to receive either set A or set B of the pictures first. After being asked to sit comfortably for 1 min, and then take a deep sigh (which reliably produces a large SCR), sixteen neutral, non-arousing pictures admixed with and sixteen aversive, emotionally-arousing pictures were shown. Each picture was shown for 2 s, after which the self-assessment manikin (SAM) [52] was shown for 13 s. The SAM uses a cartoon-like dummy, which depicts different states from 1 (feel most aroused) to 9 (feel nothing). Participants were requested to look at the picture, and when the SAM appeared to call out verbally the number on the scale which best fitted "how emotionally provoked [they] felt by the picture." SCRs were recording whilst participants looked at the SAM; this period included a 1–4 s post-IAPS image window for event-related SCRs with the remainder allowing recording of spontaneous fluctuations (please see below).

rTMS

Resting motor threshold (MT) in M1, defined as the lowest intensity of TMS which yielded motor-evoked potentials (MEPs) of at least 50 μV in 5 out of 10 trials using an MEP pod, was determined from electromyographic (EMG) activity in the abductor pollicis brevis using surface electrodes. Co-registration of the participant

Table 2
Maximum capacity for skin conductance response.

TIME POINT	Depersonalization disorder ($N = 17$)			Healthy controls ($N = 20$)		
	VLPFC ($N = 8$)	TPJ ($N = 9$)	Total ($N = 17$)	VLPFC ($N = 11$)	TPJ ($N = 9$)	Total ($N = 20$)
Pre TMS	4.66 (2.93)	5.39 (2.82)	5.05 (2.81)	4.89 (3.33)	4.58 (2.10)	4.75 (2.78)
Post TMS	6.37 (4.37)	5.19 (3.03)	5.74 (3.65)	4.97 (3.80)	7.05 (3.99)	5.91 (3.93)

Statistical analysis					
Main effects	ANOVA	Post-hoc	Significant interactions		
rTMS	$F[1,33] = 7.25$; $P = 0.01$	Pre < post	rTMS* Site of stimulation	$F[1,33] = 8.19$; $P < 0.01$	DPD patients who receive VLPFC rTMS show increases in Max. SCR post rTMS $t = -2.15$, df = 7, $P < 0.05$ Controls who receive TPJ rTMS show increases in Max. SCR post rTMS $t = -2.14$, df = 8, $P = 0.05$
Subject type	$F[1,33] = 0.0$; $P = 0.98$	NS	Subject type*		

DPD, depersonalization disorder; VLPFC, ventrolateral prefrontal cortex; TPJ, temporo-parietal junction; rTMS, repetitive transcranial magnetic stimulation; SCR, skin conductance response.

with their MRI scan and BrainSight version 2 (Rogue Research, Montreal) [53], and coil calibration were performed. 'Target sites' for stimulation using the Simple Point method were set prior to the participant's arrival by entering their Talairach coordinates as per their group allocation. The VLPFC coordinates (Right VLPFC $x = 35$, $y = 25$, $z = -7$) were selected to correspond to Brodmann Area (BA) 47 which was found to be active in only patients with a diagnosis of DPD in response to aversive scenes in an fMRI task [18]. The TPJ coordinates (Right TPJ $x = 63$, $y = 37$, $z = 20$) were selected as per previous research using neuronavigation, which studied OBEs and self-processing [40] and TMS stimulation of the right TPJ [41]. The coil was held tangential to the scalp of the head with the handle pointing back away from midline at 45°. Participants then received 15 min rTMS delivered at 1Hz and 110% MT to either the right VLPFC or right TPJ, as per their group allocation using a Magstim RMA6802, 3014-00 Rapid^2 Dual PSU figure-of-eight coil (Magstim Co. Ltd., UK) – i.e. 900 pulses. Following TMS, outcome measures were completed plus a side-effects checklist, and all participants were debriefed and offered a nominal cash sum for their time and expenses. Finally a semi-structured telephone interview was conducted 24 h later.

Main outcome measures

In this study, the minimum amplitude of SCRs and SFs measured was 0.04 μS. We recorded three types of electrodermal measure for analysis:

(1) *Maximum amplitude of skin conductance deflections*; traditionally used as a key index of individual differences in capacity to generate autonomic activity [50], it measures the highest single deflection in skin conductance recorded across all epochs. We reasoned that increased arousal capacity is likely to coincide with increased reactivity in DPD. We defined the maximum skin conductance as the highest recorded amplitude during any 15 s epoch, during or after stimulus presentation.

(2) *Spontaneous fluctuations* (SFs); the number of skin conductance deflections in the absence of an identifiable eliciting stimulus – a general measure of autonomic reactivity [50]. SFs were recorded following each 2 s picture presentation and outside the 1–4 s event-related window (i.e. the first 1 s and last 9 s of each 15 s epoch).

(3) *Event-related SCRs*; electrodermal responses to an identifiable stimulus, including phasic increase in deflection amplitude and changes in latency of response from stimulus onset. The time window was defined as a latency of between 1 and 4 s following the 2 s IAPS picture presentation.

In addition, depersonalization symptoms were measured using the self-report state version of the CDS immediately after TMS. A symptom reduction of at least 25% was considered clinically significant and "responsive" to TMS as per previous research [39]. All outcome measures were recorded pre and post rTMS for comparison.

Statistical analyses

SPSS version 20 was used for statistical analyses. Analysis of variance (ANOVA) was used to compare post rTMS session outcome measures between those allocated to either VLPFC or TPJ stimulation groups, and in patients and controls. A series of $2 \times 2 \times 2$ mixed model repeated measures ANOVAs was performed for each of the dependent variables: with a within subjects factor: rTMS (pre- and post); and two between groups factors, 'participant group': 'DPD patients' or 'healthy controls' and 'site of stimulation': 'VLPFC' or 'TPJ.' Covariates of BDI, BAI and DES were not used because their variance was not equal across the independent variable [54] but were entered into a multiple regression as potential predictors of outcome. Paired or student's *t*-tests were used to explore interactions.

Results

Baseline characteristics of all participants are summarized in Table 1. There were no significant differences between participants randomized to either VLPFC or TPJ stimulation. Inspection does show that the DPD group was somewhat older and contained fewer females.

Measures of electrodermal activity

In terms of *maximum capacity for SC*, there was a main effect of rTMS ($F[1,33] = 7.3$; $P = 0.01$). Maximum SCRs were generally larger post rTMS. However, there was a significant interaction between

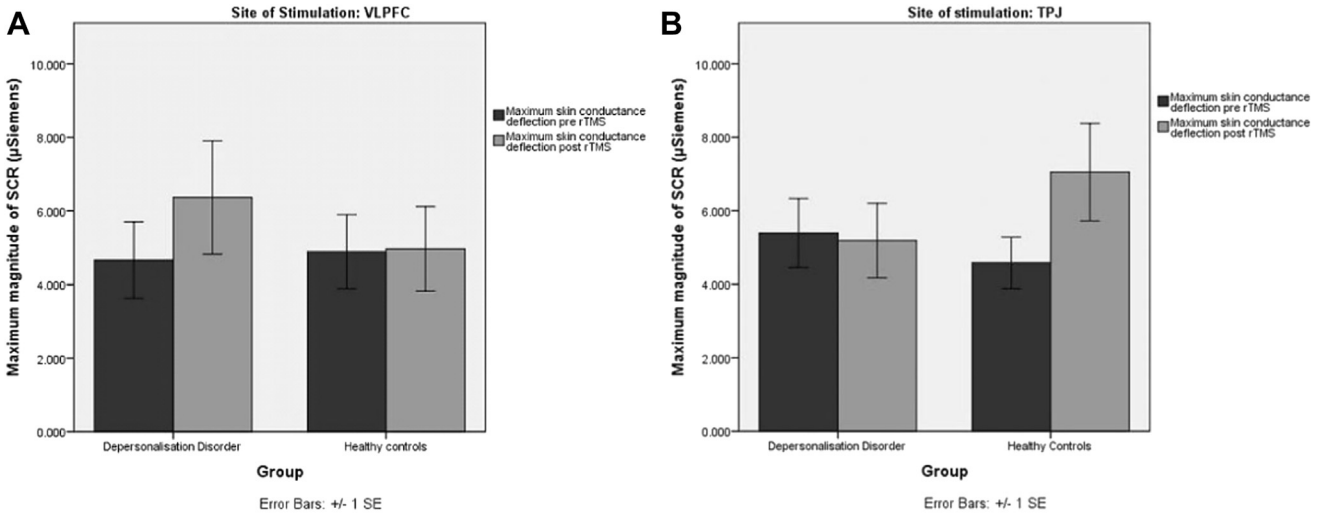

Figure 1. (A, B) Maximum skin conductance deflection of depersonalization disorder patients and healthy controls for both VLPFC and TPJ rTMS. DPD patients and controls. VLPFC, ventrolateral prefrontal cortex; TPJ, temporo-parietal junction; rTMS, repetitive transcranial magnetic stimulation; SE, standard error.

effects of rTMS, participant group, and site of stimulation (F [1,33] = 8.2; $P < 0.01$). Post hoc t-tests showed that patients with DPD who received VLPFC rTMS increased their maximum SCR post rTMS ($t = -2.2$, df = 7, $P < 0.05$) with controls showing no significant change (Table 2). TPJ rTMS given to DPD patients did not produce any appreciable change while, curiously, it did increase maximum SCR in controls ($t = -2.1$, df = 8, $P = 0.05$) (see Fig. 1A and B).

In terms of the number of SFs, there were no significant main effects. There was a significant interaction between effect of rTMS and participant group (F[1,33] = 7.3; $P = 0.01$; see Table 3; Fig. 2). From the figure it appears that the interaction reflects the patients' tendency to show an increase in SFs post rTMS (Paired t-tests: $t = -1.83$, df = 16, $P = 0.08$), while controls show a decrease ($t = 2.11$, df = 19, $P = 0.048$).

There was also a suggestion that the 2 sites of TMS may differ although the 3-way interaction between TMS, group and site was not significant. Nevertheless given our *a priori* interest in the effect of VLPFC on autonomic function in DPD we carried out paired t-tests which showed a trend increase in patients' SFs following VLPFC ($t = -2.11$, df = 7, $P = 0.07$) which was much weaker following TPJ stimulation ($P = 0.4$). In sum, rTMS appeared to increase SFs in patients rather than controls and there was a suggestion that this effect was stronger following VLPFC stimulation (see Fig. 2).

There were no significant differences post rTMS in event-related responses for cases and controls for measures including latency, and 'amplitude' uncorrected and corrected for electrodermal capability (maximum SC).

Subjective rating of depersonalization

As expected, there was a main effect of participant group (F [1,33] = 100.3; $P < 0.01$) with DPD patients scoring higher on the CDS-S than healthy controls: pre-TMS DPD (mean (SD) 42.0 (15.6) vs. controls mean 1.8 (2.7)). There was a main effect of rTMS (F [1,33] = 21.1; $P < 0.01$) but no effect of site of stimulation (F [1,33] = 0.1; $P = 0.70$). There was an interaction between the effect of rTMS and participant group (F[1,33] = 28.7; $P < 0.01$; Table 1; Fig. 3). Post hoc t tests ($t = 4.8$, df = 16, $P < 0.01$) found that patients with DPD showed a significant decrease in depersonalization symptoms post VLPFC rTMS (CDS-S score 31.3 (14.9)) and TPJ rTMS (CDS-S score 32.1 (17.6)), whereas healthy controls, marginally increased their depersonalization scores post VLPFC rTMS and TPJ rTMS ($t = -2.2$, df = 19, $P = 0.04$) (see Fig. 3A and B).

Adverse effects

All TMS participants completed the full session and no one chose to discontinue. One experienced a mild headache and another mild difficulties concentrating after rTMS. Three participants experienced "twitching or jerking" sensations and one felt "more present," experiences confined to right VLPFC stimulation. Two experienced 'drunk-like' feelings after right TPJ stimulation.

Multiple regression

All participants were included in the modeling since scales covered dimensions of psychopathology spanning healthy controls and DPD patient scores. Dependent variables were: maximum SC, SFs and CDS-S scores. Independent variables entered stepwise were: the CDS-Trait score, DES, BDI and BAI scores; gender and age. The results showed that none of the variables influenced maximum SC or SFs in response to rTMS. For the post rTMS CDS-S measure, baseline CDS, DES and BAI scores each contributed significantly to a total variance of 79% with β coefficients of 0.65, 0.46 and 0.22, respectively.

Discussion

The findings support our hypothesis that rTMS to the VLPFC increases autonomic activity in DPD patients. We found that patients with DPD produce a significant increase in the size of their maximum skin conductance response after rTMS but only in the VLPFC condition. Conversely, healthy controls show a different pattern of response, and only increase in their maximum SCRs after TPJ stimulation. We chose to record and analyze maximum SC deflection because it gives a measure of a person's capacity to respond autonomically to external or interoceptive stimuli, which has been found attenuated in DPD.

This finding in patients with DPD is suggestive of a disinhibitory effect of right VLPFC rTMS. Previous neuroimaging studies have shown hyperactivation in prefrontal areas in patients with DPD [18,22,23]. Such frontal activation is functionally related to lack of activation in emotion-generation related areas, e.g. the anterior insula [24], and increased frontal activity has been found to be inversely correlated with skin conductance responses [18].

It is not clear why healthy controls show a similar increase on maximum SCRs after TPJ stimulation. A previous study using low frequency rTMS on the right TPJ found a disruptive effect on the subjective sense of embodiment and the distinction between self and not-self, suggesting that the TPJ is actively involved in maintaining a coherent sense of one's body distinct from external non-corporeal objects [55].

Spontaneous SC fluctuations (SFs) are considered an overall index of skin conductance reactivity and it has been reported that patients with DPD who go into remission show an increase in SFs [20], akin to the tracings of anxiety patients. Post rTMS there was an increase in patients' SFs regardless of site while healthy controls tended to show fewer SFs, again, regardless of site. This might be

Table 3
Spontaneous fluctuations (SFs) in skin conductance.

Time point	Depersonalization disorder ($N = 17$)			Healthy controls ($N = 20$)		
	VLPFC ($N = 8$)	TPJ ($N = 9$)	Total ($N = 17$)	VLPFC ($N = 11$)	TPJ ($N = 9$)	Total ($N = 20$)
Pre TMS	2.45 (1.62)	2.20 (1.64)	2.32 (1.58)	2.65 (1.16)	3.28 (1.41)	2.93 (1.28)
Post TMS	3.08 (1.20)	2.59 (1.59)	2.82 (1.40)	2.16 (1.02)	2.94 (1.56)	2.51 (1.31)

Statistical analysis				
Main effects	ANOVA	Post-hoc	Significant interactions	
rTMS	NS	NS	rTMS* F[1,33] = 7.27; $P = 0.01$	DPD patients after VLPFC show trend to increase SFs post rTMS: (paired t-test)
Group	NS	NS	Group	$t = -2.11$, df = 7, $P = 0.07$; and after TPJ show no increase SFs post rTMS: $t = -0.85$, df = 8, $P = 0.42$

DPD, depersonalization disorder; VLPFC, ventrolateral prefrontal cortex; TPJ, temporo-parietal junction; rTMS, repetitive transcranial magnetic stimulation; SFs, spontaneous fluctuations; SCR, skin conductance response.

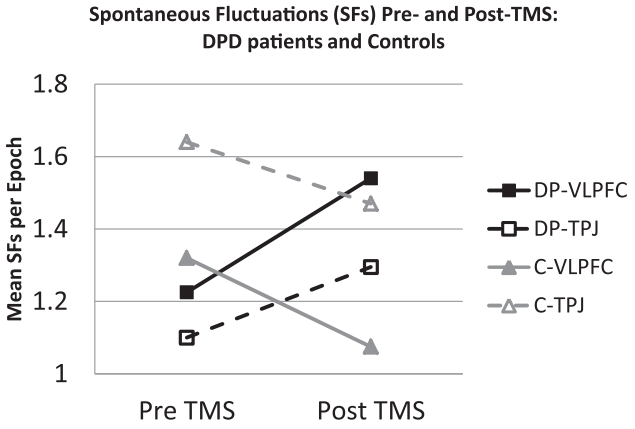

Figure 2. Spontaneous fluctuations (SFs) in skin conductance for both depersonalization disorder patients (DP) and healthy controls (C) receiving either VLPFC or TPJ TMS (transcranial magnetic stimulation). VLPFC, ventrolateral prefrontal cortex; TPJ, temporo-parietal junction.

interpreted as evidence of some non-specific arousal following rTMS, which could be beneficial in DPD patients although a modest trend was observed following post-hoc testing for a greater increase following VLPFC rTMS given to DPD patients, in line with our specific predictions.

We measured different parameters of skin conductance during each of the 15-s epochs inside the 1–4 s event-related window for IAPS pictures pre and post rTMS. No significant results were found for amplitude or for latency of SCR. One reason for the lack of change with event-related SCRs could be due to the problem of habituation to the emotional pictures contained in the IAPS – even though non-identical images were shown pre and post TMS. Few studies have explored the effect of prefrontal TMS on SCRs in general, but one study found that anterior frontal 1Hz rTMS reduced SCRs [56].

Our other main outcome measure was intensity of depersonalization symptoms on the CDS-State version pre and post rTMS. It was found that patients decreased in their scores post rTMS. Controls slightly increased in their scores but they were still way below clinical levels. These findings were irrespective of site of stimulation. The mean reduction in CDS-S scores was 28.8% (27.3 (17.5) and 30.1 (23.3) for VLPFC and TPJ, respectively, $P = 0.79$) and is noteworthy following just a single session of rTMS. Five of eight patients with DPD receiving a single session of right VLPFC stimulation would meet criteria for being a 'partial responder' i.e. showed a 25% reduction in CDS scores post rTMS. In the TPJ condition, results were similar; out of $N = 9$ patients with DPD, $N = 4$ would meet criteria for being a partial responder, and $N = 1$ would be classed as a full responder i.e. showed a 50% reduction in CDS scores post rTMS, according to criteria [39].

In the earliest trial [37], a patient was treated with 1Hz rTMS to the right prefrontal cortex. The next day, she reported dramatic improvement. Although her progress reportedly did not continue in the coming weeks, this is further evidence that after only 1 session significant improvements may be achieved. Another early trial [38], reported a patient with continuous DPD for seven years. Interestingly, 24 h after DLPFC rTMS, a 15% reduction in visual-analogue scales of DPD was reported. After six sessions, a 28% reduction in CDS scores was reported. In the case series [39], patients reported a 35% reduction in symptoms after receiving 3 weeks right-sided TPJ.

These results indicate that, based purely in terms of reduction on CDS-S scores alone, both VLPFC and TPJ stimulation may be beneficial to patients, working via different neurobiological mechanisms relevant to DPD. Patients with DPD sometimes complain of the feeling that their self and body are somehow disconnected and this is akin to feelings of disembodiment, which are provoked by physiological disruption to the TPJ [40,41] and hence could conceivably be ameliorated by rTMS. A recent secondary analysis [57] found that in those patients who benefitted from TPJ stimulation, symptoms of anomalous body experience, as rated from the CDS improved particularly, although emotional numbing also improved. Indeed we found that scores on the CDS state scale item that loads most heavily on emotional numbing ("I am not feeling any emotions at all"), fell following VLPFC but not TPJ stimulation. On the other hand, the item: "… I feel automatic and mechanical, as if I were a robot," fell somewhat more following TPJ stimulation than VLPFC.

Another possibility is that rTMS in both VLPFC and TPJ can affect autonomic arousal – directly or indirectly – as indexed by spontaneous fluctuations in electrodermal activity. Interestingly, ventral frontal cortex and TPJ are implicated in network which appears to be specialized in directing attention to salient stimuli [58], and this may even extend to social cognitive functions [59] which may be

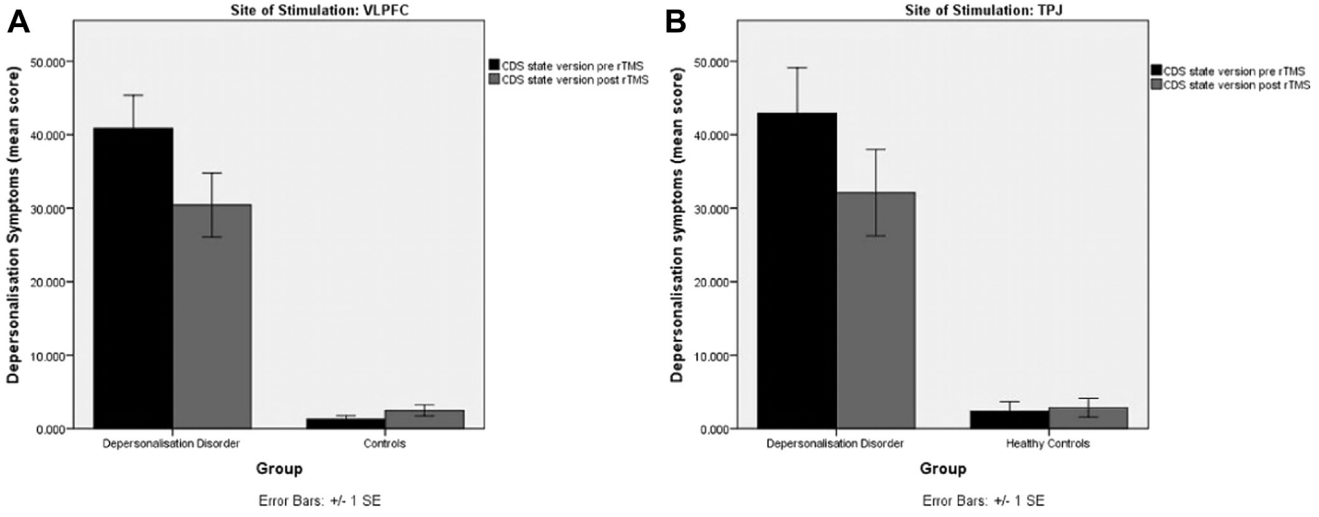

Figure 3. (A, B) Scores on the Cambridge Depersonalization Scale state version pre and post VLPFC and TPJ rTMS. DPD patients and controls. VLPFC, ventrolateral prefrontal cortex; TPJ, temporo-parietal junction.

disrupted in DPD. This might explain who TMS to the 2 sites may produce convergent effects. Subjective improvements such as symptom severity are susceptible to placebo effects. Patients may have high expectations of the treatment, which did not contain a sham condition. Improvement in CDS-S scores was influenced by baseline severity of depersonalization symptoms as well as broader anxiety and dissociative symptoms – according to the multiple regression analysis – which could be interpreted as regression to the mean. Nevertheless, it should be noted DPD are notoriously resistant to placebo effects in clinical trials [60].

We were concerned that VLPFC stimulation with rTMS would be poorly tolerated because of the inevitable muscular contraction around the eye. However, pilot work and post-experimental debriefing did not reveal this to be a problem, at least not at the frequencies used. Indeed therapeutic uses of VLPFC rTMS have been reported, such as for tinnitus [61]. Similarly, our findings were specific to right-sided stimulation – selected again based on previous empirical work but also to avoid potential disruption of language and verbal memory which might follow left side stimulation. Indeed both sites (VLPFC and TPJ) were in the right hemisphere hence we cannot comment on whether left hemisphere stimulation would have had the same therapeutic and physiological effects.

Differences found on key non-event related autonomic variables such as maximum SCRs by site of stimulation, indicates that distinct physiological perturbations were produced by TMS in DPD patients despite transynaptic effects which justifies stereotaxy-guided neuronavigation technology used to improve focality and consistency.

We considered alternative prefrontal sites for TMS stimulation. The DLPFC has been explored extensively in the clinical and non-clinical cognitive neuroscience literature, in part because its accessibility as well as its theoretical importance. As noted, the evidence is stronger for the role of VLPFC in DPD, due, we hypothesized, to its role in emotional control. Ventrolateral, orbitomedial and dorsolateral prefrontal regions each play a role in emotion–cognition interactions [42,62]. DLPFC seems particularly implicated in decision making which is emotionally biased, while more ventral regions modulate (and may inhibit) emotional response. Indeed source localization analyses of ERP data to an emotional go/no-go task [63] revealed right VLPFC activation in affective response inhibition whereas anterior cingulate activation was sensitive to emotional valence but not inhibition. Furthermore, low-frequency rTMS to the right DLPFC combined with H_2O^{15} positron emission tomography revealed regional cerebral blood flow increases under the stimulation site as well as ipsilateral ventrolateral PFC [64]. Similarly, rTMS to right DLPFC in conjunction with an attention task produced changes detected using fMRI in both ipsi- and contra-lateral VLPFC [65].

Limitations

Increasing the sample size would obviously be desirable to improve statistical power and permit sub-group analyses, although the current study is the first ever case–control comparison and builds on previous case reports and series. Naturally, the healthy controls were unlikely to be comparable with the cases in terms of general psychopathology although when this was considered in the multiple regression, it emerged that the effect of rTMS on the main objective outcome measure, maximum SCR, was not influenced by baseline psychopathology (although change in symptom scores was).

Besides the modest sample size, the other major limitation was the absence of a sham condition. Sham TMS is not however without technical and methodological difficulties [66] although technological advances have facilitated high quality controlled trials. Blinding is hard to maintain and the use of active coils held at 90° to the skull may in fact produce physiological effects. Future coils, which mimic real rTMS sufficiently to blind the participant are likely to be developed. In the absence of this, an alternative active control site could be considered such as occipital cortex, although this can interfere with visual stimuli and produce unwanted sensations.

Conclusion

A single session of right-sided 1Hz rTMS to VLPFC or TPJ stimulation significantly reduces depersonalization symptoms in patients. This procedures resulted in changes in non-event related electrodermal responses namely increased maximum SCR (VLPFC only) and increased SFs, whilst there was no change to event-related responses. Changes in symptoms might reflect physiologically driven improvements in DPD but placebo effects cannot be entirely excluded. These proof-of-concept findings, if replicated in a larger sample, should inform a randomized controlled clinical trial comparing multiples session rTMS at hypothesized therapeutic sites of stimulation (either VLPFC or TPJ) using low frequency neuronavigation-guided rTMS with sham stimulation.

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References

[1] Sierra M. The symptoms of depersonalization. In: Depersonalization: a new look at a neglected syndrome. Cambridge: Cambridge University Press; 2009. pp. 24–43.
[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press; 1994.
[3] Sierra M, Gomez J, Molina JJ, Luque R, Muñoz JF, David AS. Depersonalization in psychiatric patients: a transcultural study. J Nerv Ment Dis 2006;194:356–61.
[4] Hunter ECM, Sierra M, David AS. The epidemiology of depersonalization and derealisation: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2004;9:9–18.
[5] Baker D, Hunter E, Lawrence E, Medford N, Patel M, Senior C, et al. Depersonalisation disorder: clinical features of 204 cases. Br J Psychiatry 2003;182:428–33.
[6] Simeon D, Knutelska M, Nelson D, Guralnik O. Feeling unreal: a depersonalization disorder update of 117 cases. J Clin Psychiatry 2003;64:990–7.
[7] Sedman G. Depersonalization in a group of normal subjects. Br J Psychiatry 1966;112:907–12.
[8] Sierra M, Medford N, Wyatt G, David AS. Depersonalisation disorder and anxiety: a special relationship? Psychiatry Res 2012;197:123–7.
[9] Lambert MV, Sierra M, Phillips ML, David AS. The spectrum of organic depersonalization: a review plus four new cases. J Neuropsychiatry Clin Neurosci 2002;14:141–54.
[10] Medford N, Baker D, Hunter E, Sierra M, Lawrence E, Phillips ML, et al. Chronic depersonalization following illicit drug use: a controlled analysis of 40 cases. Addiction 2003;98:1731–6.
[11] Simeon D, Kozin D, Segal K, Lerch B. Is depersonalization disorder initiated by drug use any different? A survey of 394 adults. J Clin Psychiatry 2009;70:1358–64.
[12] Sierra M. Towards a pharmacology of depersonalization. In: Depersonalization: a new look at a neglected syndrome. Cambridge: Cambridge University Press; 2009. pp. 113–23.
[13] Sierra M, Phillips ML, Irvin G, Krystal J, David AS. A placebo-controlled cross-over trial of lamotrigine in depersonalization disorder. J Psychopharmacol 2003;17:103–5.
[14] Hunter EC, Phillips ML, Chalder T, Sierra M, David AS. Depersonalisation disorder: a cognitive-behavioural conceptualization. Behav Res Ther 2003;41:1451–67.
[15] Hunter EC, Baker D, Phillips ML, Sierra M, David AS. Cognitive-behaviour therapy for depersonalisation disorder: an open study. Behav Res Ther 2005;43:1121–30.
[16] Sierra M, Berrios GE. Depersonalization: neurobiological perspectives. Biol Psychiatry 1998;44:898–908.
[17] Sierra M, Lopera F, Lambert MV, Phillips ML, David AS. Separating depersonalization and derealisation: the relevance of the "lesion method". J Neurol, Neurosurg Psychiatry 2002;72:530–2.

[18] Phillips ML, Medford N, Senior C, Bullmore ET, Suckling J, Brammer MJ, et al. Depersonalization disorder: thinking without feeling. Psychiatry Res 2001;108:145–60.
[19] Medford N, Brierley B, Brammer M, Bullmore ET, David AS, Phillips ML. Emotional memory in depersonalization disorder: a functional MRI study. Psychiatry Res 2006;148:93–102.
[20] Lader MH, Wing L. Physiological measures, sedative drugs, and morbid anxiety. Maudsley Mongraphs No. 14. London: Oxford University Press; 1966. p. 179.
[21] Sierra M, Senior C, Dalton J, McDonough M, Bond A, Phillips ML, et al. Autonomic response in depersonalization disorder. Arch Gen Psychiatry 2002;59:833–8.
[22] Lemche E, Surgaladze SA, Giampetro VP, Anilkumar A, Brammer MJ, Sierra M, et al. Limbic and prefrontal responses to emotion face expressions in depersonalization. Neuroreport 2007;18:473–7.
[23] Lemche E, Anilkumar A, Giampetro VP, Surguladze S, Gasston D, Chitnis X, et al. Cerebral and autonomic responses to emotional facial expressions in depersonalization disorder. Br J Psychiatry 2008;193:222–8.
[24] Tabibnia G, Satpute AB, Liberman MD. The sunny side of fairness: preference for fairness activates reward circuitry (and disregarding unfairness activates self-control circuitry). Psychol Sci 2008;19:339–47.
[25] Bishop SJ. Trait anxiety and impoverished prefrontal control of attention. Nat Neurosci 2009;12(1):92–8.
[26] Medford N. Emotional and the unreal self: depersonalization disorder and de-affectualisation. Emotion Rev 2012;4(2):139–44.
[27] Sierra M, Phillips ML, Lambert MV, Senior C, David AS, Krystal JH. Lamotrigine in the treatment of depersonalization disorder. J Clin Psychiatry 2001;62:826–7.
[28] Sierra-Siegert M, David AS. Depersonalization: a selective impairment of self-awareness. Conscious Cogn 2011;20(1):99–108.
[29] Hallett M. Transcranial magnetic stimulation. Nature 2000;406:147–50.
[30] Leyman L, De Raedt R, Vanderhasselt MA, Baecken C. Influence of high-frequency repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex on the inhibition of emotional information in healthy volunteers. Psychol Med 2009;39:1019–28.
[31] Knoch D, Gianotti LR, Pascual-Leone A, Treyer V, Regards M, Hohmann M, et al. Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behaviour. J Neurosci 2006;26:6469–72.
[32] Knoch D, Pascual-Leone A, Meyer K, Treyer V, Fehr E. Diminishing reciprocal fairness by disrupting the right prefrontal cortex. Science 2006;314:829–32.
[33] Van't Wout M, Kahn RS, Sanfrey AG, Aleman A. Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex affects strategic decision-making. Neuroreport 2005;16:1849–52.
[34] Uher R, Yoganathan D, Mogg A, Eranti SV, Treasure J, Campbell IC, et al. Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. Biol Psychiatry 2005;58:840–2.
[35] Eichhammer P, Johann M, Kharraz A, Binder H, Pittrow D, Wodarz N, et al. High frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. J Clin Psychiatry 2003;64:951–3.
[36] Camprodon JA, Martinez-Raga J, Alonso-Alonso M, Shih MC, Pascual-Leone A. One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. Drug Alcohol Depend 2007;86:91–4.
[37] Keenan JP, Freund S, Pascual-Leone A. Repetitive transcranial magnetic stimulation and depersonalization disorder. A case study. Proc Abstr East Psychol Assoc 1999;70:78.
[38] Jiménez-Genchi AM. Repetitive transcranial magnetic stimulation improves depersonalization: a case report. CNS Spectr 2004;9:375–6.
[39] Mantovani A, Simeon D, Urban N, Bulow P, Allart A, Lisanby S. Temporo-parietal junction stimulation in the treatment of depersonalization disorder. Psychiatry Res 2011;186(1):138–40.
[40] Blanke O, Mohr C, Michel CM, Pascual-Leone A, Brugger P, Seeck M, et al. Linking out-of-body experience and self processing to mental own-body imagery at the temporoparietal junction. J Neurosci 2005;25:550–7.
[41] Blanke O, Ortigue S, Landis T, Seeck M. Inducing illusory own-body perceptions. Nature 2002;419:269–70.
[42] Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci 2005;9:242–9.
[43] Sierra M, Berrios GE. The Cambridge Depersonalisation Scale: a new instrument for the assessment of depersonalization. Psychiatry Res 2000;93:153–64.
[44] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. J Clin Neurophysiol 2009;120:2008–39.
[45] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
[46] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893–7.
[47] Bernstein E, Putnam F. Development, reliability, and validity of a dissociation scale. J Nerv Ment Dis 1986;174:727–35.
[48] Kerr C, Robinson A, Stevens A, Braunholtz D, Edwards S, Lilford R. Randomisation in trials: do potential trial participants understand it and find it acceptable? J Med Ethics 2004;30:8–84.
[49] Herwig U, Padberg F, Unger J, Spitzer M, Schönfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 2001;50:58–61.
[50] Dawson ME, Schell AM, Filion DL. The electrodermal system. In: Cacioppo JT, Tassinary LG, Berntson GG, editors. Handbook of psychophysiology. 2nd ed. Cambridge: Cambridge University Press; 2000. pp. 200–23.
[51] Lang PJ, Bradley MM, Cuthbert BN. International Affective Picture System (IAPS): affective ratings of pictures and instruction manual. Gainesville, FL: Center for Research in Psychophysiology; 1999. University of Florida.
[52] Bradley MM, Lang PJ. Affective norms for english words (ANEW): stimuli, instruction manual and affective ratings: Technical report C-1. Gainesville, FL: Center for Research in Psychophysiology; 1999. University of Florida.
[53] BrainSight 2. Neuronavigation System for TMS. www.rogue-research.com.
[54] Miller GA, Chapman JP. Misunderstanding analysis of covariance. J Abnorm Psychol 2001;110:40–8.
[55] Tsakiris M, Constantini M, Haggard P. The role of the right temporo-parietal junction in maintaining a coherent sense of one's body. Neuropsychologia 2008;46:3014–8.
[56] van Honk J, Schutter DJ, d'Alfonso A, Kessels RP, Postma A, de Haan EH. Repetitive transcranial magnetic stimulation at the frontopolar cortex reduces skin conductance but not heart rate: reduced ray matter excitability in orbitofrontal regions. Arch Gen Psychiatry 2001;58:973–4.
[57] Christopeit M, Simeon D, Urban N, Gowatsky J, Lisanby SH, Mantovani A. Effects of repetitive transcranial magnetic stimulation (rTMS) on specific symptom clusters in depersonalization disorder (DPD). Brain Stimul 2013. http://dx.doi.org/10.1016/j.brs.2013.07.006. pii: S1935-861X(13)00228-3.
[58] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–15.
[59] Saxe R. Uniquely human social cognition. Curr Opin Neurobiol 2006;16:235–9.
[60] Simeon D, Guralnik O, Schmeidler J, Knutelska M. Fluoxetine therapy in depersonalization disorder: randomized controlled trial. Br J Psychiatry 2004;185:31–6.
[61] Vanneste S, De Ridder D. The involvement of the left ventrolateral prefrontal cortex in tinnitus: a TMS study. Exp Brain Res 2012;221:345–50.
[62] Taylor SF, Liberzon. Neural correlates of emotion regulation in psychopathology. Trends Cogn Sci 2007;11:413–8.
[63] Chiu PH, Holmes AJ, Pizzagalli DA. Dissociable recruitment of rostral anterior cingulate and inferior frontal cortex in emotion response inhibition. Neuroimage 2008;42:988–97.
[64] Eisenegger C, Treyer V, Fehr E, Knoch D. Time-course of "off-line" prefrontal rTMS effects – a PET study. Neuroimage 2008;42:379–84.
[65] Rounis E, Klaas SE, Lee L, Siebner HR, Presenti A, Friston KJ, et al. Acute changes in fronto-parietal activity after repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in a cued reaction time task. J Neurosci 2006;26:9629–38.
[66] Broadbent HJ, van den Eynde F, Guillaume S, Hanif EL, Stahl D, David AS, et al. Blinding success of rTMS applied to the dorsolateral prefrontal cortex in randomized sham-controlled trials: a systematic review. World J Biol Psychiatry 2011;12:240–8.