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A structural MRI study of cortical thickness in depersonalisation disorder

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ABSTRACT

Depersonalisation disorder (DPD) is characterised by a sense of unreality about the self and the world. Research suggests altered autonomic responsivity and dysfunction in prefrontal and temporal lobe areas in this condition. We report the first structural magnetic resonance imaging study of 20 patients with DPD and 21 controls using the FreeSurfer analysis tool employing both region-of-interest and vertex-based methods. DPD patients showed significantly lower cortical thickness in the right middle temporal region according to both methods of analysis. The vertex-based method revealed additional differences in bilateral temporal lobes, inferior frontal regions, the right posterior cingulate, and increased thickness in the right gyrus rectus and left precuneus. Clinical severity scores were negatively correlated with cortical thickness in middle and right inferior frontal regions. In sum, grey matter changes in the frontal, temporal, and parietal lobes are associated with DPD. Further research is required to specify the functional significance of the findings and whether they are vulnerability or disease markers.

1. Introduction

Depersonalisation is a distressing impairment of self-awareness characterised by the following characteristics: a feeling of detachment from the body, subjective emotional numbing, and feelings of estrangement from personal memories and one's surroundings (Sierra et al., 2005). Depersonalisation disorder (DPD) is included in the classification systems of the DSM-5 (American Psychiatric Association, 2013) and the ICD-10 (World Health Organization, 1992). Psychophysiological and neuroimaging research has revealed distinct abnormalities which support the idea that the condition is firmly grounded in neurobiological mechanisms.

An impaired sense of self is arguably a central symptom cluster in depersonalisation disorder (Mohr and Blanke, 2005). Closely related to this are out-of-body experiences (OBEs) sometimes experienced by neurological patients (Blanke et al., 2004) and often associated with lesions in the temporo-parietal junction (TPJ). Blanke et al. (2005) subsequently showed, using electroencephalography (EEG), that OBEs produce TPJ activation in healthy volunteers while they imagine looking on themselves from the outside, as typically reported by neurological patients with autoscopy. Stein and Simeon (2009) suggested that aberrant temporal lobe activity could be a contributing factor in producing DPD symptoms. A transcranial magnetic stimulation (TMS) study by Mantovani et al. (2011) substantiated this line of evidence by demonstrating a significant reduction in depersonalisation and dissociation scores in 6 out of 12 participants through stimulation of the TPJ. In sum, there is increasing evidence for a link between altered cortical functioning in temporo-parietal areas and dysfunctional perception of their own body in patients with DPD.

More broadly, a fronto-limbic 'suppressive' mechanism has been proposed for depersonalisation whose ecological function may be to preserve coping behaviour from potentially disorganising levels of anxiety at times of extreme threat. For instance, functional magnetic resonance imaging (fMRI) studies have revealed that in comparison to controls, patients with DPD show hyperactive prefrontal areas (i.e. an enhanced blood oxygenation level dependent [BOLD] response) relevant in the regulation of emotional responses, together with under-activation (i.e. reduced response relative to controls) of limbic-related areas, such as the amygdala, hypothalamus (Lemche et al., 2007), and anterior insula (Phillips et al., 2001), relevant for experiencing emotion. It has also been found that patients with DPD show attenuation of autonomic sympathetic responses to arousing visual stimuli (Sierra et al.,

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2002a, 2006). Finally, there has been longstanding interest in the notion of depersonalisation that is secondary to clear-cut brain disorders, particularly those affecting the temporal lobes (Sierra et al., 2002b) (e.g. temporal lobe epilepsy [TLE]; Lambert et al., 2002). Despite the increasing evidence for a neurobiological underpinning of DPD, there have been no structural imaging studies of (primary) DPD to date, and it remains unknown whether the previously reported differences at a functional level in DPD are mediated by atypical brain structure.

We therefore carried out a structural neuroimaging study on a well-characterised sample to test the primary hypothesis that individuals with DPD have abnormalities in brain anatomy that differentiate them from healthy controls. As this is the first structural neuroimaging study in this condition, we formulated predictions based on the growing functional neuroimaging literature in the disorder (see above), and related disorders (e.g. anxiety). That is, previous functional neuroimaging research in DPD suggests involvement of prefrontal areas known to play a role in emotion regulation (Ochsner and Gross, 2005), or regions regulated by them. These include the anterior insula (Phillips et al., 2001; Medford et al., 2006) and other lateral (Simeon et al., 2000; Phillips and Sierra, 2003) and medial temporal lobe structures (Lemche et al., 2007). Temporal lobe involvement may also link with DPD in patients with TLE (Lambert et al., 2002). Also of possible relevance are magnetic resonance imaging (MRI) studies using vertex-based morphometrics which have reported abnormal brain structural changes in patients with anxiety disorders, centred on a network regulating fear and arousal (Blackmon et al., 2011; Kühn et al., 2011; Syal et al., 2012; Frick et al., 2013) that predominantly includes the amygdala and orbitofrontal cortex (OFC).

To test our hypothesis of atypical brain structure in DPD, we used a vertex-based approach, which allowed us to investigate brain anatomy at a high level of specificity based on different morphometric features, such as cortical thickness (CT) and regional cortical volume (CV).

2. Methods

2.1. Participants

A total of 42 participants consented to enter the study, which was part of a controlled trial of imaging-guided transcranial magnetic stimulation (Jay et al., 2014). Twenty-one patients referred to a Depersonalisation Disorders Clinic at the Maudsley Hospital, London were diagnosed with DPD according to ICD-10 criteria by an experienced psychiatrist (MS). All patients had established (>2 years) depersonalisation as their primary condition and scored above the clinical cut-off of 70 on the Cambridge Depersonalisation Scale (CDS; Sierra and Berrios, 2000). None had a primary diagnosis of panic disorder or generalised anxiety disorder. Twenty-one right-handed healthy controls were recruited from the local community who answered advertisements calling for volunteers, and were screened to ensure that they had neither a history nor a current experience of psychiatric illness, no on-going neurological disorder, and were not taking any psychotropic or other medication. One of the patients was excluded from the analysis based on marked cortical atrophy on inspection of the MR images. All participants were rated on the CDS and other psychopathology scales, including the Beck Depression (BDI; Beck and Ward, 1961) and Anxiety Inventories (BAI; Beck et al., 1988) and the Dissociative Experiences Scale (DES; Bernstein and Putnam, 1986). The project had ethical approval from the National Health Service (NHS) local research ethics committee.

2.2. MRI data acquisition

MRI data were acquired on a GE 1.5-T HDx system (General Electric, Milwaukee, WI, USA) at the Institute of Psychiatry, London. Localiser 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: echo time (TE)=5 ms; repetition time (TR)=12 ms; inversion time (TI)=300 ms; excitation flip angle=18°; matrix size $320\times224\times220$ over a $288\times202\times198$ field of view, giving an isotropic 0.9-mm voxel size over the whole brain. The manufacturer's eight k-channel head coil was used for signal reception, with the body coil being used for radio-frequency transmission.

2.3. Image processing

The FreeSurfer image analysis suite (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA) was used to derive representations of the cortical surface in each T1-weighted image. These fully automated and well-validated procedures have been outlined in detail elsewhere (Dale et al., 1999; Fischl et al., 1999, 2004; Fischl and Dale, 2000; Ségonne et al., 2004; Jovicich et al., 2006). In brief, a single filled white matter volume was generated for each hemisphere after intensity normalisation, the removal of extra-cerebral tissue using a 'skull stripping' algorithm, and image segmentation using a connected components algorithm. Then, a surface tessellation was generated for each white matter volume by fitting a deformable template. The grey matter and cerebrospinal fluid surfaces were also modelled using a similar process.

FreeSurfer software provides measures of cortical thickness (CT), surface area (SA) and cortical volume (CV). Given explicit models for the white/grey and grey/cerebrospinal fluid (CSF) surfaces, the measure of absolute CT at any given point on the white/grey matter surface was taken to be the closest distance from the grey/white boundary to the grey/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). Vertex-based estimates of SA were obtained as outlined by Winkler et al. (2012). Estimates of regional cortical volume were derived by multiplying CT and SA at each vertex on the cortical surface, or $CV=CT\times SA$. Thereby, CT, SA, and CV for the left and right hemisphere grey matter as well as a volumetric index for the left and right hemisphere white matter could be established. For the regional analysis of between-group differences in neuroanatomical measures, we used the cortical parcellation scheme proposed by Desikan et al. (2006). A list of all subcortical areas that were examined is provided in Supplementary materials 1. The current analyses are limited to CT and CV outcomes.

2.4. Statistical analyses

Participants' demographic data were analysed in SPSS v19 (IBM Corp., Armonk, NY, USA) using *t*-tests for continuous measures, and Fisher's exact tests for categorical variables. Due to the exploratory character of the study, MR data were analysed in two different ways. Between-group differences in neuroanatomical measures (CT and CV) were examined (a) using a region-of-interest (ROI) approach based on the neuroanatomical parcellation (Desikan et al., 2006), and (b) in a vertex-wise fashion (i.e. at all spatial locations on the cortical surface; see below for additional details). For the ROI analysis, we used a between-group analysis of variance (ANOVA) initially, subsequently covarying for age and gender (ANCOVA).

The authors' reasoning for the inclusion of age and gender as the main covariates rests on neuroimaging studies which have investigated the typical neurodevelopmental trajectory. The study of brain anatomy suggests that there are significant age-related differences in brain morphology (and cortical thickness, in particular) across the human life span (Giedd et al., 1999). For example, brain volume and cortical thickness reach their peak during early adulthood when the brain is fully matured, followed by a steady decline in brain volume/cortical thickness across adulthood (Shaw et al., 2006). Also, these studies show that males differ from females in their neurodevelopmental trajectory of brain maturation (Giedd et al., 1999). Accounting for these effects across various age groups and genders is in line with previous neuroimaging studies in other psychiatric conditions such as autism (Ecker et al., 2013).

The exploratory, spatially unbiased analysis was conducted using the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/) for Matlab (R2010b, The Mathworks, Massachusetts). Parameter estimates for CT, SA and CV and a main effect of group (G) were estimated by regression of a general linear model at each vertex *i* and subject *j*, and gender as categorical fixed effects factor as well as age and a total brain measure (B) as continuous covariates (i.e. mean CT, total SA, or total CV, respectively)

$$y_{ij}=\beta_0+\beta_1 G_j+\beta_4 Gender_j+\beta_3 Age_j+\beta_5 B_j+\varepsilon_{ij}$$

where ε is the residual error. Between-group differences were estimated from the fixed effect coefficient β_1 normalised by the corresponding standard error. Corrections for multiple comparisons across the whole brain were performed using random field theory-based (RFT) cluster analysis for non-isotropic images using $p<0.05$ (two-tailed) cluster significance threshold (Worsley et al., 1999). None of the clusters survived the correction for multiple comparisons. Hence, results are presented at an uncorrected vertex-threshold of $p<0.01$, which we believe to be warranted given the exploratory nature of this investigation.

Lastly, psychopathological–anatomical associations were explored in the whole sample using Pearson's correlation coefficients.

3. Results

3.1. Demographics

As expected, patients scored significantly higher on measures of depersonalisation (on the CDS and DES) as well as showing mild to moderate levels of anxiety and depression (on BAI and BDI; see Table 1). Fourteen patients were taking medication (mostly selective serotonin reuptake inhibitors and benzodiazepines) for such symptoms without significant relief of DPD. There were significant differences in age and gender distribution between patients and controls, $p < 0.05$ (two-tailed) which were therefore treated as potential confounders in subsequent analyses.

Table 1
Demographics and clinical measures.

	Controls ($n=21$) Numbers (%)	Patients ($n=20$) Numbers (%)	Statistics χ^2 (Sig.)
Gender (males)	9 (42.9%)	16 (80%)	5.93 ($p < 0.05$)
	Mean (S.D.)	Mean (S.D.)	t values (Sig.)
Age, years	27.2 (5.6)	35.75 (11.4)	3.09 ($p < 0.01$)
CDS (trait version)	16.7 (21.3)	130.5 (44.2)	10.58 ($p < 0.001$)
BAI	8.1 (7.9)	19.55 (14.0)	3.27 ($p=0.002$)
BDI	4.1 (4.5)	14.6 (8.1)	5.11 ($p < 0.001$)
DES	7.6 (9.0)	28.8 (15.0)	5.42 ($p < 0.001$)

Means and standard deviations for gender, age and various clinical measures obtained from the patient and control groups. Please note that one Beck Depression Inventory (24) score from the patient group and one Dissociation Experiences Scale (26) score from the control group are missing.

3.2. Structural MR data

3.2.1. ROI analysis based on parcellation

3.2.1.1. Between-group differences in total brain measures. Overall, there were no significant differences between individuals with DPD relative to controls in the total cortical volume, mean cortical thickness or total white matter volume within hemispheres. We also found no evidence of inhomogeneity of variance between the two groups in these measures as assessed by Levene's test. Left cortical volume (mm^3) was 259,991 controls vs. 261,981 patients; right cortical volume 260,679 controls vs. 263,004 patients. Left cortical thickness (mm) was 2.442 controls vs. 2.403 patients; right cortical thickness, 2.441 controls vs. 2.409 (all $p > 0.10$).

3.2.1.2. Between-group differences in regional morphometric measures based on the cortical parcellation scheme. Initially, we examined between-group differences in CT and CV for 78 regions across the cortical surface (Desikan et al., 2006; see Table 2).

All listed areas showed a tendency for reduced cortical thickness in DPD patients. However, only the middle temporal cortical area in the right hemisphere survived correction for age and gender (ANCOVA). In terms of cortical volume, no area survived the adjustment for confounders in either the left or the right hemisphere.

3.2.2. Exploratory vertex-wise analysis of CT

A more finely grained analysis of the structural MRI data based on cortical vertices was carried out. Table 3 presents all regions that achieve a p value below 0.01 and there are no less than 10 vertices, grouped according to the common cerebral lobes. Localisations are provided in terms of Brodmann area (BA) denominations as well as Talairach coordinates.

Table 2
Results of region-of-interest analyses.

Region	Controls	Patients	Statistics	
Thickness	($n=21$) Mean, S.D. (mm)	($n=20$) Mean, S.D. (mm)	F score	Sig. (unadjusted)
Left hemisphere:				
Caudal middle frontal	2.66 (0.14)	2.57 (0.08)	5.97	0.019
Inferior temporal	2.82 (0.17)	2.72 (0.14)	4.30	0.045
Posterior cingulate	2.73 (0.17)	2.61 (0.15)	5.43	0.025
Frontal pole	2.74 (0.22)	2.57 (0.20)	5.90	0.020
Right hemisphere:				
Middle temporal	2.95 (0.14)	2.87 (0.10)	4.51	**0.040***
Pars triangularis	2.55 (0.10)	2.46 (0.11)	7.12	0.011
Posterior cingulate	2.71 (0.19)	2.60 (0.15)	4.28	0.045
Frontal pole	2.64 (0.22)	2.48 (0.26)	4.67	0.037
Transverse temporal	2.44 (0.16)	2.52 (0.18)	2.24	0.142**
Volume	Mean, S.D. (mm^3)	Mean, S.D. (in mm^3)	F score	Sig. (unadjusted)
Cortical regions:				
Lingual gyrus (right)	6828 (833)	7450 (760)	6.20	0.017
Pericalcarine (right)	2606 (446)	2917 (466)	4.77	0.035
Subcortical regions:				
Pallidum (left)	1785 (199)	1676 (165)	3.62	0.064**
Third ventricle	818 (234)	967 (231)	4.23	0.047

Cortical areas (according to Desikan et al. (2006)), left pallidum and 3rd ventricle of significantly different thickness/volume between patients with depersonalisation disorder and controls in the left and right hemispheres. Unadjusted ANOVA comparing patients vs. controls.

* Survived ANCOVA for age and gender ($p=0.04$); highlighted in bold.

** Trend towards difference after ANCOVA for age and gender ($p=0.06$).

Table 3
Results of vertex-based analysis.

Lobe	#	Region	Hemisphere	BA	Talairach coordinates			*t* value	Size (mm^2)
					x	*y*	*z*		
Frontal	1	Rectal gyrus	Right	11	6	25	−28	2.857	23.49
	2	Rectal gyrus	Right	11	10	49	−25	2.799	21.43
	3	Superior frontal gyrus	Right	10	16	62	8	−3.337	214.83
	4	Superior frontal gyrus	Left	6	−19	10	52	−3.348	93.07
	5	Inferior frontal gyrus	Left	47	−50	28	−2	−3.608	200.44
Temporal	6	Middle temporal gyrus	Left	21	−56	−19	−6	2.650	7.14
	7	Inferior temporal gyrus	Left	20	−57	−27	−26	−3.048	128.80
	8	Inferior/middle temporal gyrus	Right	20/21	66	−13	−24	−3.279	188.74
Parietal	9	Postcentral gyrus	Right	3	39	−27	51	3.603	152.87
Occipital	10	Precuneus	Left	31	−22	−63	23	2.905	73.90
	11	Precuneus	Left	31	−6	−61	26	2.704	18.65
	12	Lingual gyrus	Left	19	−23	−62	5	−2.720	42.77
Sub-lobar	13	Claustrum	Left	n/a	−35	−12	11	−2.686	15.15
Limbic	14	Cingulate gyrus	Right	24	18	−15	38	−3.647	104.72

Results of vertex-based analysis showing areas of the both hemispheres with significantly different cortical thickness outcomes comparing controls and patients ($p < 0.01$). Negative *t*-values indicate regions with lower cortical thickness of patients compared with controls whereas positive *t*-values represent the reverse. Region labels according to Desikan et al. (2006). *Abbreviation*: BA=Brodmann area. The results include covariates for age and gender (as described above).

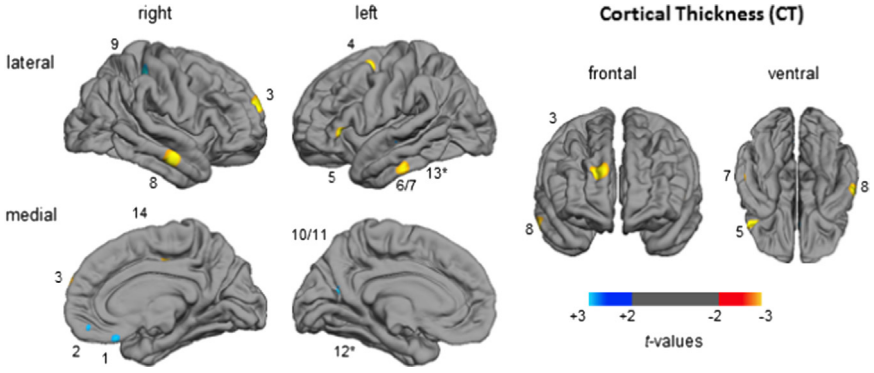

Fig. 1. FreeSurfer output showing lateral, medial, frontal, and ventral views of normalised, curved cortex with areas of significantly greater cortical thickness in controls > patients (red/yellow shades) and patients > controls (blue shades) according to their *t*-values with $p < 0.01$ (uncorrected, with age and gender as covariates in the model). Visible areas are numbered according to their order in Table 3. *Areas 12 (lingual gyrus) and 13 (claustrum) are obscured. Please see Supplementary material for a view of all areas of significant difference. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The results are summarised in Fig. 1. Blue shadings denote those areas that have a significantly greater cortical thickness ($p < 0.01$) in patients compared with controls while bright red/yellow shadings show those regions that have a significantly greater cortical thickness in controls compared with patients ($p < 0.01$).

3.2.2.1. Correlation analyses between measures of symptom severity and morphometric features. Further analyses across groups revealed some significant correlations between ROI-based cortical thickness and clinical measures. For the left hemisphere, there was a significant negative correlation (i.e. more symptoms, and reduced thickness) between CDS scores and cortical thickness in the caudal middle frontal area ($r = -0.336$, $p = 0.032$, $n = 41$). Significant negative correlations also emerged between the DES and the caudal middle frontal ($r = -0.371$, $p = 0.019$, $n = 40$) as well as the inferior temporal area ($r = -0.417$, $p = 0.007$, $n = 40$). For the right hemisphere, we found a significant negative correlation between the CDS and the pars triangularis near the inferior frontal gyrus ($r = -0.328$, $p = 0.036$, $n = 41$). There were also two significant negative correlations between the DES score and the pars triangularis ($r = -0.407$, $p = 0.009$, $n = 40$) and the frontal pole ($r = -0.350$, $p = 0.027$, $n = 40$). There were no significant correlations for the Beck Depression and Anxiety Inventories or for the volumes of subcortical areas identified using the above analyses.

4. Discussion

This is, to our knowledge, the first study to investigate the neuroanatomical substrates underlying DPD. Our expectations were shaped by earlier work on anxiety disorders and altered bodily perception, using the same methodology, which has pointed to the orbitofrontal cortex (OFC) and amygdala as potential areas of interest, although we were also interested to see whether a 'fronto-limbic' network might be implicated given neurophysiological findings in DPD. Finally, the possibility of links with the temporal lobes was considered likely, given the association between clinically evident temporal lobe abnormalities and symptoms of depersonalisation. We were guided by convergent findings from two image-analysis methodologies – region-based and vertex-based – which point to DPD-related changes in the temporal and prefrontal lobes.

Patients were found to have decreased cortical thickness, particularly in the right inferior/middle temporal gyrus, regardless of method. This finding is interesting in view of an established association between depersonalisation and both structural as well as functional abnormalities in temporal lobe areas (Ackner, 1954; Sierra and Berrios, 1998) in which, in addition to anxiety,

subjective alteration of the sense of self and passage of time are well recognised. A systematic review of cases reporting a relationship between brain pathology and depersonalisation concluded that temporal lobe lesions are overrepresented in 'organic' cases of depersonalisation (Lambert et al., 2002): in over 60 neuropsychiatric cases, 32 suffered from a focal brain pathology, which in 78% was circumscribed to the temporal lobe. Furthermore, the right middle temporal gyrus finding of reduced thickness is in keeping with the reduced [^{18}F]fluorodeoxyglucose uptake shown in a positron emission tomography (PET) study of DPD (Simeon et al., 2000). Interestingly, in our correlational analyses, thinning of the left inferior temporal gyrus, but not the right, was significantly correlated with DES scores.

Evidence of an association between depersonalisation and the temporal lobe has also been provided by studies exploring the frequent co-occurrence of depersonalisation and panic symptoms in both patients with temporal lobe epilepsy as well as in those with chronic depersonalisation (Roth and Harper, 1962; Toni et al., 1996). Locatelli et al. (1993) found temporal lobe EEG abnormalities in panic disorder patients with depersonalisation as compared with those without. Recently, an EEG study of patients with panic disorder found that, out of a comprehensive list of panic symptoms, depersonalisation was one of only three associated with EEG abnormalities over the temporal lobes. In fact, while depersonalisation was reported by nearly half of those with EEG abnormalities, it was present in only 7.5% of those with normal EEG findings (Hayashi et al., 2010).

In addition to our findings on temporal lobe areas, prefrontal areas were also observed to show case-control differences. To begin with, the gyrus rectus (Brodmann area 11), an area within the ventromedial prefrontal cortex (vmPFC) or OFC, was found to be thicker in patients than in controls. This region, centred posteriorly and inferiorly, is within the territory noted for its role in the inhibition of emotional responses to threatening and fearful stimuli (Hänsel and von Känel, 2008). Indeed, a recent study found a significant, direct correlation between thickness of the vmPFC and ability to extinguish emotional and autonomic responses (skin conductance responses, SCRs) to a previously aversive conditioned stimulus (Milad et al., 2005). The authors went on to suggest that differences in cortical thickness of this area might account for individual differences in the ability to modulate fear. In line with this, functional neuroimaging studies have found that a subgroup of PTSD patients who had depersonalisation-like experiences and attenuated autonomic responses during trauma recall (analogous to findings in DPD; Sierra et al., 2002a) showed increased activation in the vmPFC, together with decreased activation in limbic areas (Lanius et al., 2010). In this regard, we found two adjacent prefrontal regions with reduced thickness in DPD according to the unadjusted comparison with controls, namely the pars triangularis and the prefrontal pole, to show significant correlations with the typical DPD symptoms scored on the CDS and DES.

Given the clinical association between depersonalisation and panic disorder discussed above, it is worth noting that recent MRI studies in patients with panic disorder have also revealed decreased cortical thickness in both frontal and temporal regions (Lai and Wu, 2013, 2012). Such findings partially overlap with those of the present study, particularly in the left inferior frontal gyrus, in our patients using very similar imaging methods (Lai and Wu, 2013). It would seem, however, that in patients with panic disorder the affected areas are distributed somewhat differently, extending to the insula, posterior cingulate and amygdala (Lai and Wu, 2012).

Our finding of an area of increased cortical thickness within the right parietal cortex of patients deserves consideration given the aforementioned PET study which, along with areas of reduced uptake, also showed increases in the right parietal lobe which were positively correlated with depersonalisation symptoms (Simeon et al., 2000). Lesion and neuroimaging research has identified a network of parietal regions, which seems to play an important role in the generation of embodiment and agency (Frith et al., 2000; Farrer et al., 2007) and hence can be relevant to the experience of disembodiment in depersonalisation (Sierra and David, 2011). However, the TPJ region did not appear to be an area of either increased or reduced cortical thickness or volume, as might have been predicted from the OBE literature (Blanke et al., 2004).

The limitations of the study include the somewhat selective sample being taken from patients attending a specialist clinic who had agreed to participate in a trial of brain stimulation. Although it is known that DPD is highly comorbid with both lifetime and ongoing mood and anxiety disorders (Sierra, 2009), these were assessed as part of structured interviews by an experienced clinician and found not to be present. Hence, they may not be generalisable to other DPD patients and tended to be those with the most intractable symptoms. Partly as a result of this selection, significant age and gender differences emerged between the DPD and the healthy control group which we tried to counter by using these two variables as covariates in the analysis. However, after adjusting for these potential confounds, differences in the cortical thickness of the middle temporal lobe remained significant. Another possible confound, which it was not possible to adjust for in the analysis, was medication, since over half of the patient group was prescribed various medications, particularly antidepressants. However, we know of no evidence that such medications significantly affect brain volume.

None of the regions presented in Table 3 survived a cluster-level analysis using FreeSurfer, and although we used an adjusted significance threshold of $p < 0.01$ for these analyses, there was no further adjustment for multiple comparisons. We believe this to be justifiable for two reasons. Firstly, in an exploratory study such as this, there were several candidate regions worthy of consideration. Secondly, we have emphasised cortical regions where both area-wise vs. vector-wise comparisons revealed consistent results. Nonetheless, the current outcomes bear the risk of being false positives and therefore warrant replication.

In sum, our novel findings of structural brain changes in patients with depersonalisation disorder compared with controls in frontal, temporal and cingulate areas are meaningful given the complex phenomenology of the condition. They include areas of increased thickness in the orbitofrontal region, but mostly reduced thickness in superior and inferior frontal regions, the cingulate and middle and inferior temporal lobes. The regions highlighted in this study are compatible with problems of emotional regulation as well as subjective alterations in the sense of self and the world. It is hoped that the study will enhance the debate on depersonalisation research around the disorder's neural basis and provide fertile ground for future structural and functional investigations of DPD and related conditions.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.06.007.

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