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Abnormal gray and white matter volume in delusional infestation

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ABSTRACT

Little is known about the neural basis of delusional infestation (DI), the delusional belief to be infested with pathogens. Case series and the response to anti-dopaminergic medication indicate disruptions in dopaminergic neurotransmission in the striatum (caudate, putamen), but did not allow for population-based inference. Here, we report the first whole-brain structural neuroimaging study to investigate gray and white matter abnormalities in DI compared to controls. In this study, we used structural magnetic resonance imaging and voxel-based morphometry to investigate gray and white matter volume in 16 DI patients and 16 matched healthy controls. Lower gray matter volume in DI patients compared to controls was found in left medial, lateral and right superior frontal cortices, left anterior cingulate cortex, bilateral insula, left thalamus, right striatal areas and in lateral and medial temporal cortical regions ($p < 0.05$, cluster-corrected). Higher white matter volume in DI patients compared to controls was found in right middle cingulate, left frontal opercular and bilateral striatal regions ($p < 0.05$, cluster-corrected). This study shows that structural changes in prefrontal, temporal, insular, cingulate and striatal brain regions are associated with DI, supporting a neurobiological model of disrupted prefrontal control over somato-sensory representations.

1. Introduction

Delusional infestation (DI), also known as delusional parasitosis or Ekbom's syndrome, is characterized by a patient's fixed belief that one's skin or other parts of the body or one's immediate environment are infested with small living or inanimate pathogens, against all medical evidence for this (Freudenmann and Lepping, 2009; Freudenmann et al., 2012). Most patients also suffer from abnormal bodily sensations such as itching or biting on or below the skin that they wrongly explain with an infestation. In other words, somatic delusions and tactile hallucinations overlap and these two core features of DI may have the same neurobiology (Baker et al., 1995; Corlett et al., 2010). DI can occur as a primary monothematic delusional disorder or, more commonly, as a secondary delusion. In secondary DI, the delusion arises in the context of another major medical, neurological or psychiatric disorder that affects brain functioning (cerebro-vascular disease, stroke, tumors, dementia, delirium, major depression, schizophrenia) or is associated with the use of illicit or prescribed substances, usually with a dopaminergic mechanism of action (Flann et al., 2010; Freudenmann and Lepping, 2009; Huber et al., 2007; Kölle et al., 2010).

To date, little is known about the neural correlates of DI. Existing evidence does not allow for generalizations because of limitations such as obsolete neuroimaging methods or methods with poor spatial resolution, small samples and the lack of healthy control groups. First reports using skull X-ray (Skott, 1978), pneumencephalography ($n = 8$, reviewed by de Leon et al., 1992) and a single small computed cerebral tomography study ($n = 7$) suggested cortical or subcortical atrophy in some patients with DI (Schwitzer and Hinterhuber, 1983). Some case reports suggested frontal, temporo-parietal, striatal and thalamic dysfunction (reviewed by Freudenmann and Lepping, 2009; Freudenmann and Lepping, 2009). In the only case series to report structural brain magnetic resonance imaging (MRI) findings so far ($n = 9$), we observed lesions in the striatum (caudate, putamen), predominantly the left putamen, as the most common regional pathology in 4 out of 5 cases in the subgroup of "organic" DI, as well as cortical atrophy and subcortical white matter

Abbreviations: AP, anterior/posterior; CSF, cerebrospinal fluid; DARTEL, diffeomorphic anatomic registration through exponentiated lie algebra; DI, delusional infestation; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; FFE, fast field echo; FWHM, full width at half maximum; GMV, gray matter volume; FOV, field of view; MAP, maximum a posterior; MRI, magnetic resonance imaging; MNI, Montreal Neurological Institute; PVE, partial volume estimation; ROI, region of interest; SPM, statistical parametric mapping; TD, Talairach Daemon; TE, echo time; TIV, total intracranial volume; TR, repetition time; VBM, voxel-based morphometry; WFU, Wake Forest University; WMV, white matter volume.

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lesions of different severity as global pathologies; no brain pathology was found in the other cases (Huber et al., 2008). Recently, we reported the same pattern of brain lesions after increasing our sample to 17 cases (Huber et al., 2011) and found preliminary evidence for altered glucose metabolism, cerebral perfusion and gray matter volume in these regions together with dopaminergic dysfunction in the striatum in two independent cases (Freudenmann et al., 2010).

We have previously hypothesized that a dysfunctional fronto-striato-thalamo-parietal network could explain the two core symptoms of DI, i.e. frontal dysfunction explaining impaired judgment in delusions and dysfunctional processing in the dorsal striato-thalamo-parietal loop explaining abnormal somatic sensations (Freudenmann and Lepping, 2009). Here, we report the first whole-brain MRI study to investigate gray and white matter changes in patients with DI compared to controls. We applied voxel-based morphometry (VBM), a now widely employed automated analysis technique for structural MRI data (Ashburner and Friston, 2000; Tabrizi et al., 2009). VBM is a user-independent approach which allows an unbiased exploration of regional brain volume without the need to delineate or define specific regions of interest (ROIs), thus being useful for the investigation of potential volume changes across the whole brain. Given our hypotheses regarding potential neural correlates of DI (Freudenmann and Lepping, 2009), we predicted that DI patients would exhibit abnormal volume in frontal, striatal, thalamic and parietal regions.

2. Methods

2.1. Participants

Between 1998 and 2011 we saw 21 patients with DI in the Department of Psychiatry in the General Hospital Bruneck, in the German speaking part of Italy. In three cases an MRI scan was not possible to conduct (reasons for the 3 patients respectively: cardiac pacemaker, no consent given, transport impossible to arrange), leaving eighteen eligible for a structural MRI brain scan (see below). Two patients had to be excluded from this study because larger brain lesions made VBM analysis impossible because of an inaccurate segmentation.

The patient sample consisted of 16 cases of DI. Nine were females (56%). The mean age was 74.1 years. The mean disease duration was 7.9 years (±9.6). All diagnoses were made according to DSM-IV-TR based on a detailed clinical history and supporting clinical findings by the same psychiatrist (M.H.). We diagnosed primary DI meeting criteria for delusional disorder somatic type (DSM-IV-TR) in 6 cases and DI secondary to psychotic depression in three cases. Seven cases had an organic psychotic disorder manifesting as DI (such as subcortical vascular encephalopathy, hyperthyroidism etc.). All patients met criteria of DI as defined by Freudenmann and Lepping (2009). None of the patients met criteria for dementia (Mini Mental State Test sum score >26/30). All patients were right-handed (as identified by their dominant writing hand). Further details about the DI cases, such as demographic characteristics, psychiatric and somatic comorbidity, duration of illness and medication are shown in Table 1, supplementary data.

The control sample was a group of healthy volunteers matched (one by one) for gender, age and handedness (writing hand). Eligible subjects were determined with the help of the local electronic hospital patient information system and then contacted by phone. They were only considered when they had no psychiatric or neurological history or severe medical illness, as derived from the digital patient files. All volunteers underwent a psychiatric evaluation and did not show signs of cognitive impairment. An initial set of eighteen controls underwent the same structural MRI brain scan as the patients (see below), but for matching purposes only those sixteen that corresponded to the demographics of the remaining sixteen patients were further included in this study.

The study and the study protocol were reviewed and approved by the local responsible authority (Health District Bruneck, South Tyrol, Italy). Patients and controls gave written informed consent after the study had been fully explained. None of them received any payment for taking part in this study.

2.2. Structural neuroimaging and data analysis

Structural data were acquired in the Department of Radiology at the General Hospital Bruneck, South Tyrol, Italy, using an MRI system at 1.0 T (Philips INTERA, Release 11, Best, The Netherlands). The MRI parameters of the 3D T1 gradient echo recalled (fast field echo, FFE) sequence were as follows: TE = 6.9 ms; TR = 25 ms; FOV = 230 mm [AP], 172 mm [RL]; resolution = 0.9 mm^3; number of slices = 170.

After visually checking for data artifacts a VBM analysis was computed using Christian Gaser's VBM toolbox (VBM8, http://dbm.neuro.uni-jena.de/vbm8/) running within the Statistical Parametric Mapping software package version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The segmentation algorithm used by this toolbox is based on an adaptive "Maximum A Posterior" (MAP) technique. This approach does not require a priori information about tissue probabilities, i.e. the tissue probability maps are used for spatial normalization only (Rajapakse et al., 1997). During the MAP estimation local parameter variations are modeled as varying spatial functions, thus accounting for intensity inhomogeneity and other local intensity variations. During the data segmentation step, each participant's original T1 image was spatially normalized and segmented into gray and white matter and cerebrospinal fluid (CSF) based on MAP estimation. This segmentation procedure is then followed by partial volume estimation (PVE) (Tohka et al., 2004), data denoising based on a spatially adaptive non-local means filter (Manjon et al., 2010) and the application of Markov Random Fields (Rajapakse et al., 1997). The SPM8 toolbox also integrates a Diffeomorphic Anatomic Registration through Exponentiated Lie (DARTEL) algebra normalization (Ashburner, 2007). Using DARTEL, deformations are produced by exponentiation of a velocity field thus ensuring that the Jacobian determinants always remain positive. This precondition guarantees that the transformations are inversely consistent through generating both forward and inverse transformations from the same flow field (Ashburner, 2007). After data preprocessing, the modulated normalized gray and white matter (GM/WM) segments were smoothed using an 8 mm Full Width at Half Maximum (FWHM) Gaussian kernel prior to between-group analyses at the 2nd level. Due to the various somatic comorbidities within the patient sample, we performed an additional data quality check to ensure sample homogeneity prior to calculating 2nd level analyses. This procedure was performed using the function "check sample homogeneity using covariance", as implemented in the VBM8 toolbox. For both GMV and WMV segments, the relative boxplots did not reveal images beyond two standard deviations.

2.3. Statistical analysis

Between-group comparisons were computed using t-tests treating age, gender and total intracranial volume (TIV as the sum of GM, WM and CSF as derived from the segmentation process) as nuisance variables. Separate analyses were calculated to test for GM and WM volume differences (GMV/WMV) between the groups using an absolute threshold of 0.1. Between-group differences were assessed using a significance threshold of $p < 0.001$ (uncorrected at the voxel level, $p < 0.05$ corrected for spatial extent). To further reduce potential effects of tissue overlap occurring at tissue border regions, between-group comparisons for WMV were additionally constrained to this tissue type. In these analyses, we used an explicit WM mask based on the Talairach Daemon "Tissue Type" database (Lancaster et al., 1997), as provided by the Wake Forest University (WFU) PickAtlas toolbox (Version 3.0.4, http://fmri.wfubmc.edu/software/PickAtlas).

In addition, correlation analyses within the patient group were calculated to investigate the relationship between disease duration and brain volume differences relative to controls. These analyses