Progress in Neuro-Psychopharmacology & Biological Psychiatry 48 (2014) 112–116

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Source-based morphometry reveals distinct patterns of aberrant brain volume in delusional infestation

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ARTICLE INFO

Article history:
Received 20 August 2013
Received in revised form 26 September 2013
Accepted 27 September 2013
Available online 8 October 2013

Keywords:
Delusional infestation
Independent component analysis
Magnetic resonance imaging
Source-based morphometry

ABSTRACT

Little is known about the neural correlates of delusional infestation (DI), the delusional belief to be infested with pathogens. So far, evidence comes mainly from case reports and case series. We investigated brain morphology in 16 DI patients and 16 healthy controls using structural magnetic resonance imaging and a multivariate data analysis technique, i.e. source-based morphometry (SBM). In addition, we explored differences in brain structure in patient subgroups based on disease aetiology. SBM revealed two patterns exhibiting significantly ($p < 0.05$, Bonferroni-corrected) lower grey and higher white matter volume in DI patients compared to controls. Lower grey matter volume was found in medial prefrontal cortex, anterior cingulate cortex, medial temporal lobe structures (parahippocampus and hippocampus), sensorimotor cortices, bilateral insula and thalamus and inferior parietal regions. Higher white matter volume was found in medial and middle frontal and temporal cortices, left insula and lentiform nucleus. Grey matter volume was abnormal in both "psychiatric" (primary DI and DI associated with an affective disorder) and "organic" DI (DI due to a medical condition). In contrast, aberrant white matter volume was only confirmed for the "organic" DI patient subgroup. These results suggest prefrontal, temporal, parietal, insular, thalamic and striatal dysfunction underlying DI. Moreover, the data suggest that aetiologically distinct presentations of DI share similar patterns of abnormal grey matter volume, whereas aberrant white matter volume appears to be restricted to organic cases.

1. Introduction

Delusional infestation (DI) is characterised by a patient's fixed false belief that one's skin or other body parts or one's immediate environment is infested with pathogens (Freudenmann and Lepping, 2009; Freudenmann et al., 2012). DI can occur as a monothematic delusional disorder (primary DI), or within the context of a psychiatric or medical disorder affecting brain function such as cerebrovascular disease, stroke, tumours, dementia, substance misuse, schizophrenia or affective disorders (secondary DI; Freudenmann and Lepping, 2009; Huber et al., 2008). At present, little is known about the neural underpinnings of DI. Early case reports reviewed by our group highlighted frontal, temporoparietal, striatal and thalamic dysfunction associated with DI (Freudenmann and Lepping, 2009). Case series in patients investigated by means of structural brain magnetic resonance imaging (MRI) reported striatal lesions as common regional pathology in four out of five cases in a subgroup of secondary DI patients (Huber et al., 2008). The same patients also showed cortical atrophy and subcortical white matter lesions of different severity. However, no other abnormal findings were evident in the other cases of the sample (Huber et al., 2008).

We have previously hypothesised that abnormalities of a fronto-striato-thalamo-parietal network could explain core symptoms of DI. In short, the idea is that misinterpretations of normal or aberrant somatic sensations or beliefs arising de novo lead to errors of probabilistic reasoning (the improbable is preferred over the probable explanation) and the subsequent delusional belief that one's body must be infested

Abbreviations: ANOVA, analysis of variance; AP, anterior/posterior; 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; GMV, grey matter volume; FOV, field of view; GIFT, Group ICA for fMRI Toolbox; ICA, Independent Component Analysis; MAP, maximum a posterior; MRI, magnetic resonance imaging; PVE, partial volume estimation; SBM, source-based morphometry; TD, Talairach Daemon; TE, echo time; TIV, total intracranial volume; TR, repetition time; VBM, voxel-based morphometry; WMV, white matter volume.

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http://dx.doi.org/10.1016/j.pnpbp.2013.09.019

(Freudenmann and Lepping, 2009). The before mentioned brain areas are responsible for the analysis of sensory input and give meaning to these experiences. Consistent with our hypothesis, in the first controlled structural MRI study using whole-brain voxel-based-morphometry [VBM] (Ashburner and Friston, 2000), we have recently shown lower grey matter volume in medial and lateral frontal cortices, insula, thalamus, striatum and temporal cortical regions in an aetiologically mixed sample of sixteen DI patients. In patients we also observed higher white matter volume compared to controls, particularly in cingulate, frontal opercular and striatal regions (Wolf et al., 2013). However, structural variation in one brain region is likely to affect multiple brain areas even if it occurs in a remote location. The identification of such changes in structural networks, i.e. the relationship among multiple brain regions associated with a disorder, can therefore allow us to understand how altered interrelationships between regions can contribute to the disorder (Kasparek et al., 2010; Xu et al., 2009). To address this issue, we applied a novel multivariate statistical technique for structural MRI data, i.e. "source-based morphometry" [SBM] (Xu et al., 2009), to the structural imaging data set of DI patients and healthy controls that were included in our recent VBM study (Wolf et al., 2013). Similar to VBM, SBM does not rely on a priori definitions of regions of interest and allows an automated, user-independent investigation of brain structure. Unlike VBM, however, SBM takes advantage of Independent Component Analysis (ICA) to extract spatially independent patterns that occur in structural MRI data. Thus, in contrast to univariate voxel-by-voxel testing, SBM takes into account interrelationships between voxels to identify naturally grouped patterns of structural variation between populations. Importantly, the application of SBM to structural data in psychiatric patient samples has been shown to successfully identify distinct patterns of volume change (i.e. structural networks) which were not detected by VBM (Kasparek et al., 2010; Xu et al., 2009). Also, since in SBM group comparisons are based on component values, i.e. on "component loadings", this technique substantially reduces the severity of multiple comparisons which is particularly problematic in small samples analysed by means of mass-univariate methods.

In this report, we applied SBM to complement our previous VBM-findings in DI (Wolf et al., 2013) by providing a description of interrelationship differences between brain structures rather than describing regional changes which are better investigated using a VBM approach. Given the paucity of data addressing this issue we were especially interested in patient subgroup analyses. We investigated patient subgroups based on disease aetiology and explored potential differences in brain structure between "psychiatric" (i.e. primary DI and DI in the context of another metal disorder) and "organic" DI patients (i.e. DI due to a medical condition). We expected structural changes of both grey and white matter volume, particularly in medial frontal, insular, striatal and thalamic as well as parietal regions. Moreover, we expected that organic DI patients will exhibit more pronounced patterns of structural change.

2. Methods

2.1. Participants

The patient sample consisted of 16 cases of DI (Table 1a). Diagnoses were made according to DSM-IV-TR. We defined "psychiatric" DI meeting criteria for delusional disorder somatic type in six cases. Three cases showed DI in the context of psychotic depression. Seven "organic" DI cases had a medical condition with co-morbid DI. The first nine cases were pooled as "psychiatric", i.e. non-medical or non-organic cases, whereas the others were pooled as "organic" cases because they had a clear underlying medical pathology (Table 1b; further demographic and medical details are shown in Table 3, supplementary data). The control sample consisted of healthy volunteers matched for gender, age and handedness. Eligible subjects were determined using the local electronic hospital patient information system and then contacted by phone. They were included in the study if they had no psychiatric or neurological history or severe medical condition. The study protocol was reviewed and approved by the local responsible authority (Health District Bruneck, South Tyrol, Italy). All participants gave written informed consent after the study was fully explained.

2.2. Data acquisition

Data were acquired at the Department of Radiology at the General Hospital Bruneck, South Tyrol, Italy, using a 1.0 Tesla system (Philips INTERA, Best, The Netherlands). A 3D T1 gradient echo recalled (fast field echo) protocol was used (TE/TR = 6.9/25 ms; FOV = 230 mm [AP], 172 mm [RL]; number of slices/resolution = 170/0.9 mm^3).

2.3. Data preprocessing

Prior to SBM, data were preprocessed using the segmentation routines provided by 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). In brief, the segmentation algorithm implemented in VBM8 relies on an adaptive "Maximum A Posterior" (MAP) technique which does not require a priori information about tissue probabilities (Rajapakse et al., 1997). During the data segmentation step, individual T1 images were spatially normalised and segmented into grey and white matter and cerebrospinal fluid. This procedure was followed by partial volume estimation (Tohka et al., 2004), data denoising (Manjon et al., 2010), application of Markov Random

Table 1
Demographic and clinical data.

a. For controls and patients	Controls (n = 16)		Patients (n = 16)		p-Value
	Mean	sd	Mean	sd	
Age (years)	74.1	9.4	74.1	9.4	1[a]
Gender (M/F)	7/9		7/9		1[b]
Duration of DI symptom expression (years)	n.a.		7.9	9.6	
Total intracranial volume (ml)	1353.9	122.1	1340.8	129.0	0.77[a]
b. For the patient subgroups	"Psychiatric" (n = 9)		"Organic" DI (n = 7)		p-Value
	Mean	sd	Mean	sd	
Age (years)	69.1	9.4	80.4	4.2	0.01[a]
Gender (M/F)	5/4		2/5		0.03[b]
Duration of DI symptom expression (years)	4.1	2.5	11.1	13.7	0.15[a]
Total intracranial volume (ml)	1382.5	115.5	1287.3	133.6	0.15[a]

n. a. indicates not applicable.
[a] t-test.
[b] χ^2 test.