Progress in Neuro-Psychopharmacology & Biological Psychiatry 76 (2017) 72–79

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Cortical features of distinct developmental trajectories in patients with delusional infestation

Dusan Hirjak [a,*,1], Markus Huber [b,1], Erwin Kirchler [b], Katharina M. Kubera [f], Martin Karner [c], Fabio Sambataro [d], Roland W. Freudenmann [e], Robert C. Wolf [f]

[a] Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University Mannheim, Germany
[b] Department of Psychiatry, General Hospital Bruneck, South Tyrol, Italy
[c] Department of Radiology, General Hospital Bruneck, South Tyrol, Italy
[d] Department of Experimental and Clinical Medical Sciences, Udine University, Italy
[e] Department of Psychiatry and Psychotherapy III, University of Ulm, Ulm, Germany
[f] Center for Psychosocial Medicine, Department of General Psychiatry, Heidelberg University, Germany

ARTICLE INFO

Article history:
Received 21 December 2016
Received in revised form 23 February 2017
Accepted 27 February 2017
Available online 28 February 2017

Keywords:
Delusional infestation
MRI
Freesurfer
Gyrification
Cortical thickness
Surface area

ABSTRACT

Background: Although there is strong neuroimaging evidence that cortical alterations are a core feature of schizophrenia spectrum disorders, it still remains unclear to what extent such abnormalities occur in monothematic delusional disorders. In individuals with delusional infestation (DI), the delusional belief to be infested with pathogens, previous structural MRI studies have shown prefrontal, temporal, parietal, insular, thalamic and striatal gray matter volume changes. Differential contributions of cortical features of evolutionary and genetic origin (such as cortical thickness, area and folding) which may distinctly contribute to DI pathophysiology are unclear at present.

Methods: In this study, 18 patients with DI and 20 healthy controls (HC) underwent MRI scanning at 1.0 T. Using surface-based analyses we calculated cortical thickness, surface area and local gyrification index (LGI). Whole-brain differences between patients and controls were investigated.

Results: Surface analyses revealed frontoparietal patterns exhibiting altered cortical thickness, surface area and LGI in DI patients compared to controls. Higher cortical thickness was found in the right medial orbitofrontal cortex ($p < 0.05$, cluster-wise probability [CWP] corrected). Smaller surface area in patients was found in the left inferior temporal gyrus, the precuneus, the pars orbitalis of the right frontal gyrus, and the lingual gyrus ($p < 0.05$, CWP corr.). Lower LGI was found in the left postcentral, bilateral precentral, right middle temporal, inferior parietal, and superior parietal gyri ($p < 0.01$, CWP corr.).

Conclusion: This study lends further support to the hypothesis that cortical features of distinct evolutionary and genetic origin differently contribute to the pathogenesis of delusional disorders. Regions in which atrophy was observed are part of neural circuits associated with perception, visuospatial control and self-awareness. The data are in line with the notion of a content-specific neural signature of DI.

1. Introduction

Delusional infestation (DI) is a severe psychiatric disorder characterized by patients presenting with the monothematic tenacious/fixed belief that their skin, other body parts or their immediate environment are infested by small creatures such as parasites, insects, worms, bacteria, or fungi or, less common, inanimate pathogens (Bewley et al., 2010; Freudenmann and Lepping, 2009; Heller et al., 2013). The symptoms of DI are further associated with abnormal cutaneous sensations such as crawling, itching, burning and soreness explained by these imaginary pathogens (Altaf et al., 2016). In the course of this experience, patients with DI exhibit serious self-destructive behavior trying to remove the pathogens from 'infested' bodily areas often causing severe dermatological complications (Heller et al., 2013). In the current ICD-10 and DSM-5 version, DI is categorized either as a delusional disorder (somatic type) (primary DI), or within the context of a psychiatric or medical disorder affecting brain function (secondary DI) (Freudenmann and Lepping, 2009; Kolle et al., 2010; Tsai et al., 2016). Although the exact number of DI patients is not known, the average prevalence in hospitals is estimated with approximately six cases per one million patients (Trabert, 1991, 1995). The estimated incidence rate was approximately 2.6

* Corresponding author at: Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, D-68159 Mannheim, Germany.
E-mail address: dusan.hirjak@zi-mannheim.de (D. Hirjak).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.pnpbp.2017.02.018
0278-5846/

(95% CI 1.4–3.8) per 100,000 persons between 2006 and 2010 (Bailey et al., 2014). From a socioeconomic perspective, especially the primary form of DI is a chronic disease that constantly causes enormous individual suffering, significant morbidity, and financial burden on patients and society (Altaf et al., 2016; Lepping et al., 2010). Despite of the clear clinical delineation of DI, there is a paucity of systematic studies on neurobiology and treatment of DI. A possible explanation might be the fact that many DI patients reject the referral to the psychiatric department (Heller et al., 2013) or do not consent to any study protocol investigating their brain, because of their false concept of their illness.

In the last two decades, various neuroimaging techniques have been used to detect brain alterations and response to antipsychotic treatment in DI. Functional abnormalities have been detected by single-photon emission computed tomography (SPECT) that provided evidence for aberrant fronto-striato-thalamo-parietal network underlying core symptoms of DI (Freudenmann et al., 2010; Narumoto et al., 2006). Hence, most existing knowledge about DI comes from structural brain imaging studies that have investigated gray matter (GM) and volume abnormalities (Huber et al., 2008; Huber et al., 2016; Wolf et al., 2014, 2013). GM volume reduction has been detected predominantly in the 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 areas (Wolf et al., 2014, 2013). However, volumetric studies so far provided a gross index of GM alterations underlying DI and hence, cortical volume is a product of two morphometric features – cortical thickness and surface area – that are highly heritable, but separately affected by neurodevelopment (Hogstrom et al., 2013; Rakic, 2009). Furthermore, cortical folding serves as a stable cytoarchitectural parameter to assess early defects in fetal neurodevelopment. To date, however, none of the previous MRI studies employed a methodology specifically designed to investigate the contribution of these three markers of neurodevelopment to the pathogenesis of DI or other (monothematic) delusional disorders.

In this study, we investigated cortical features of distinct evolutionary and genetic origin (such as cortical thickness, area and folding) using surface-based morphometry (SBM) in patients with DI. SBM account for cortex abnormalities more specifically (Palaniyappan and Liddle, 2012a; Thayer et al., 2016) and could help gain better understanding of the pathogenesis of DI. The aims of the present study were to (1) provide a fine-grained analysis of GM abnormalities detected in two previous MRI studies (Wolf et al., 2014, 2013) in an expanded patient sample and (2) determine whether cortical thickness, area, and folding alterations differentially contribute to DI. Eventually, this study might contribute to a better biological understanding of distinct clinical hallmarks (somatic delusions, abnormal tactile sensations and self-destructive behavior) of DI.

2. Methods

2.1. Participants

The patient sample consisted of 18 cases of DI (Table 1). MRI data from 16 patients were previously reported in the context of voxel-based morphometry (VBM) based analyses (Wolf et al., 2014, 2013). All patients fulfilled the diagnostic criteria for delusional disorder 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 mood disorders. These cases were pooled as "psychiatric", i.e. non-medical or non-organic cases, whereas the remaining cases were pooled as "organic" cases because they had a clear underlying medical pathology. Medical conditions in the patient sample included subcortical vascular encephalopathy (n = 5), hearing loss and blindness (n = 1), hyperthyroidism (n = 1), Parkinson's disease (n = 1) and iron deficiency (n = 1) . In patients, there were no clinical signs of major neurocognitive impairment, as indicated by patient's reports and clinical examination. All patients had a Mini Mental State Examination sum score above 26/30. Patients were treated with antipsychotic monotherapy according to their psychiatrist's choice. Antipsychotic agents included risperidone (n = 8), amisulpride (n = 3), haloperidol (n = 2), quetiapine (n = 1), sulpiride (n = 1), olanzapine (n = 1), aripiprazole (n = 1), and ziprasidone (n = 1). The control sample consisted of healthy volunteers matched for gender, age and handedness. Eligible participants – healthy controls (HC) - 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.

Table 1
Clinical and demographic data.

	Controls (n = 20)		Patients (n = 18)		
	Mean	SD	Mean	SD	*p*-value
Age (years)[a]	70.4	11.9	74.3	8.9	<0.23[a]
Gender (m/f)[b]	8/12	–	8/10	–	0.56[b]
Disease duration (years)	–	–	6.6	8.9	–

[a] *t*-test.
[b] Chi-square test.

2.2. Structural MRI 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. Image processing

Entire cortex analyses were computed with Freesurfer 5.3 (for detailed description of the method see (http://surfer.nmr.mgh.harvard.edu/) (Khan et al., 2008) in order to explore local cortical thickness, surface area and gyrification index (LGI) in DI and HC (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999). Briefly, the stream consists of multiple stages such as removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004); affine registration with Talairach space specifically designed to be insensitive to abnormalities and to maximize the accuracy of the final segmentation; tissue classification and correction of the variation in intensity resulting from the B1 bias field (Sled et al., 1998); tessellation of the gray matter white matter boundary; automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999). After the automatic processing, the entire cortex of each patient and healthy participant was visually inspected and if necessary manually edited. After creation of cortical masks the cerebral cortex has been parcellated into units based on gyral and sulcal structure, resulting in values for cortical thickness and surface area (Desikan et al., 2006; Fischl et al., 2004).

2.3.1. Cortical folding - local gyrification index (LGI)

Based on the pial surface reconstruction, an algorithm for measuring 3D LGI at each vertex across each hemisphere, including the default smoothing of individual LGI maps at a full width at half maximum (FWHM) kernel of 25 mm, was performed using FreeSurfer and Matlab. Details of the LGI computation process can be found in the validation paper (Schaer et al., 2012), previous studies in psychiatric patients (Klein et al., 2014; Nesvag et al., 2014; Palaniyappan and Liddle, 2014), and at https://surfer.nmr.mgh.harvard.edu/fswiki/LG. Briefly,