International Journal of Psychophysiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Psychophysiology

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

Regional white matter volume abnormalities in first-episode somatization disorder

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ARTICLE INFO

Keywords:
Somatization disorder
White matter volume
Inferior frontal gyrus
Inferior longitudinal fasciculus

ABSTRACT

Background: Alterations of white matter integrity have been implicated in patients with somatization disorder (SD). However, changes of white matter volume (WMV) remain unclear. This study is designed to examine regional WMV in patients with SD and to investigate the potential relationships between WMV abnormalities and personality traits, cognitive function, and symptom severity.

Methods: We recruited 25 first-episode, drug-naive patients with SD and 28 sex-, age-, and education-matched healthy controls for the study. Personality traits, cognitive function, and symptom severity were assessed for all participants. Data were analyzed with the computational anatomy toolbox (CAT12) methods.

Results: Patients with SD exhibited a significantly increased WMV in the right inferior frontal gyrus (IFG) ($t = 4.4009$) and a significantly decreased WMV in the left inferior longitudinal fasciculus (ILF) ($t = -3.4292$) relative to healthy controls. No correlation was found between abnormal WMV and clinical/cognitive variables in the patients.

Conclusions: Our findings suggest the presence of significant regional WMV abnormalities in first-episode, drug-naive patients with SD, which might improve understanding the pathophysiology of SD.

1. Introduction

Characterized by unexplained physical complaints, somatization disorder (SD) is a subset of somatoform disorders. Physical complaints typically involve problems in the gastrointestinal, urogenital, cardiorespiratory, and other internal systems, or in the musculoskeletal system (Katon et al. 1991).As a result, patients are often treated in departments of cardiology, gastroenterology, and pulmonology, which lead to great medical costs (Barsky et al. 2005). Thus, exploring efficient and accurate approaches for diagnosing SD is critical.

With advances in neuroimaging techniques, an increasing number of studies have revealed neuroimaging abnormalities in mental diseases, such as schizophrenia (Agarwal et al. 2010; Guo et al. 2015; Ren et al. 2013), depression (Ballmaier et al. 2004; Koolschijn et al. 2009; Lacerda et al. 2004; Liu et al. 2013), and social anxiety disorder (Liu et al. 2015; Phan et al. 2006; Stein et al. 2002; Straube et al. 2004), thereby suggesting that neuroimaging techniques can be an objective standard for studying mental diseases.

Recent studies have reported structural and functional abnormalities in patients with SD. Hakala et al. reported that in comparison with healthy controls, patients with SD showed bilateral enlargement of caudate nuclei volumes (Hakala et al. 2004); whereas other studies reported abnormalities in the amygdala (Atmaca et al. 2011), and pituitary gland (Yildirim et al. 2012). Moreover, some researchers suggested that the default mode network (DMN) played an important role in the pathophysiology of SD (Su et al. 2014; Wang et al. 2016; Wei et al. 2016). Su et al. (Su et al. 2014) found a dissociation pattern of the anterior and posterior DMN in first-episode, drug-naive patients with SD. Moreover, patients with SD had increased functional connectivity strength in the right inferior temporal gyrus (ITG) (Su et al. 2015). However, these studies have some limitations, such as big slice thickness; using manual tracing method as the analysis technique, which is time-consuming in nature; the requirement for rater reliability; and the failure to include a large number of subjects (Atmaca et al. 2011). Thus, a more convenient and effective technique is important. Computational anatomy toolbox (CAT12) is one of the most important neuroimaging analysis techniques that can assess structural differences in regional gray/white matter volume (Besteher et al. 2017). Moreover,

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https://doi.org/10.1016/j.ijpsycho.2018.09.003
Received 18 March 2018; Received in revised form 31 August 2018; Accepted 14 September 2018

CAT12 can avoid operational bias of selecting of brain regions and automated measurement of the whole brain.

Moreover, most studies focused on regional gray matter (GM) abnormalities and few studies explored white matter (WM) alterations. The WM, which connects GM brain regions and carries neuronal impulses, may be impaired by demyelination and axonal elimination (Boos et al. 2007). The alterations of WM may reflect damaged neural circuits associated with abnormalities of behavior, cognition, and emotion (Wagner et al. 2011). Recent studies have reported impaired WM in emotional disorders, such as major depressive disorder (Jia et al. 2014) and panic disorder (Kim et al. 2015). WM integrity abnormalities have been reported in some studies. For example, Zhang et al. (Zhang et al. 2015) found decreased fractional anisotropy (FA) values in the cingulum and inferior fronto-occipital fasciculus and increased mean diffusivity (MD) values in the anterior thalamic radiation and corticospinal tract in patients with SD. However, no studies are designed to examine changes of WM volume (WMV) in patients with SD.

Personality traits may be associated with the occurrence of SD. Stern et al. found that compared with healthy controls, patients with SD had higher prevalence of personality disorders, such as passive-dependent, histrionic, and sensitive-aggressive personality disorder (Stern et al. 1993). Personality traits are important during the course of SD (Battaglia et al. 1998; Russo et al. 1994). Song et al. (2015) found that in patients with SD, the neuroticism scores of Eysenck Personality Questionnaire (EPQ) were positively correlated with increased regional homogeneity (ReHo) in the left angular gyrus (AG). However, the relationship between personality traits and regional WMV in patients with SD remains unclear.

In the present study, we conducted CAT12 to analyze whole brain WMV in patients with SD, and explored the potential relationships between regional WMV and symptom severity/personality traits/cognitive function in patients with SD. We expected that patients with SD would show decreased WMV which would correlate with symptom severity/personality traits/cognitive function, and these abnormalities might improve understanding the pathophysiology of SD.

2. Materials and methods

2.1. Participants

We recruited 26 patients with SD from the Mental Health Center of the First Affiliated Hospital, Guangxi Medical University in China, and 30 age-, sex-, and education-matched healthy controls from the community. The patients were of Han Chinese ethnicity, aged from 18 to 60 years, right-handed, and diagnosed according to the Structured Clinical Interview of the DSM-IV. The exclusion criteria for all participants included a history of major diseases, especially the neurological and mental illnesses (not including patients with comorbid depression because the comorbidity rate is high), a history of antidepressant use, and contraindications for MRI. Subjects with neuropsychiatric diseases or a family history of neuropsychiatric diseases were excluded as healthy controls.

All participants were assessed using the following tests, including the Hamilton Anxiety Scale (HAMA) (Hamilton 1959), Hamilton Depression Scale (HAMD, 17 items) (Hamilton 1960), somatization subscale of Scl-90 (Derogatis et al. 1976), EPQ (Eysenck and Eysenck 1972), Wisconsin Card Sorting Test (WCST)(Greve et al. 2005), and digit symbol coding of Wechsler Adult Intelligence Scale (WAIS) (Christensen et al. 2007), which were applied to evaluate the severity of anxiety, depression and somatization symptoms, personality dimensions, and cognitive function, respectively.

The EPQ is designed to examine the personality traits, which includes four subscales: extraversion/introversion, neuroticism/stability, psychoticism/socialization, and lie/social desirability. The extraversion subscale represents positive affect, outgoing and talkative; and the neuroticism subscale is characterized by negative affect, and emotional unstableness. The psychoticism subscale is associated with the psychotic episode and aggression, and the lie subscale is a validity scale which also indicates unsophisticated feature of an individual.

All participants signed an informed consent. This study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University.

2.2. Imaging acquisition

The scan was performed on a 3.0 T Siemens scanner. All participants were required to lie motionless during the image capturing. The MRI sequence type was a 3D magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence. The parameters for imaging sequence were as follows: repetition time = 8.5 ms, echo time = 2.98 ms, inversion time = 900 ms, flip angle = 9°, acquisition matrix = 256 × 256, field of view = 240 mm × 240 mm, slice thickness = 1 mm, no gap, and 176 slices.

2.3. Data preprocessing

Each image was inspected manually for gross structural alterations and artifacts. A CAT12 (http://dbm.neuro.unijena.de/cat) method of the Statistical Parametric Mapping software package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to preprocess the structural MRI data. The procedure of data analysis was as follows:

1) Registration of all the images to the same template image.
2) Normalization of the whole anatomic images to the same standard stereotactic space.
3) Segmentation of the anatomic image with signal intensity and probably information to normalize customized template.
4) Modulation for the intensity of the white matter images with the surrounding voxels compressed or expanded (modulation for nonlinear effects only in terms of relative changes corrected for total intracranial volume).
5) Smoothing with an 8 mm Gaussian Kernel for the group analysis.
6) Using the automated anatomical labeling atlas software and anatomical atlases to determine the most significant clusters.

2.4. Statistical analysis

Analyses of demographic characteristics were conducted using *t*-tests and a chi-square test. Voxel-wise two-sample *t*-tests were used to compare the differences of WMV between patients and controls, with HAMA scores, HAMD scores, sex and age as covariates of no interest. The statistical maps were corrected for multiple comparisons by Gaussian Random Field (GRF) theory at $p < 0.05$ (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$).

The correlation analyses between abnormal WMV and clinical/cognitive parameters (including illness duration, somatization subscale of scl-90, EPQ, WCST and digit symbol coding of WAIS) were performed by a whole-brain voxel-wise correlation analysis with HAMA scores, HAMD scores, sex and age as covariates of no interest. The significance level set at $p < 0.05$(GRF corrected).

3. Results

3.1. Demographics and clinical characteristics

Data between 25 patients with SD and 28 healthy controls were compared (1 patient and 2 healthy controls were excluded for excessive head movement). No significant difference was found in terms of age, sex ratio, education years, EPQ extraversion/lie scores, digit symbol coding of WAIS, and WCST (Table 1). However, patients with SD obtained higher scores in HAMD, HAMA, somatization subscale of Scl-90, and EPQ psychoticism/neuroticism scores.