Journal of Affective Disorders 191 (2016) 36–40

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Brief report

# Decreased medial frontal gyrus in patients with adjustment disorder

Woojae Myung [a], Kyoung-Sae Na [b,*], Byung-Joo Ham [c], Sei-Joong Oh [d], Hyun-Woong Ahn [e], Han-Yong Jung [f]

[a] Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Department of Psychiatry, Gachon University Gil Medical Center, Incheon, Republic of Korea
[c] Department of Psychiatry, Korea University Anam Hospital, Seoul, Republic of Korea
[d] Department of Psychiatry, Jecheon Hospital, Jecheon, Republic of Korea
[e] Department of Psychiatry, Chungmu Sarang Hospital, Cheonan, Republic of Korea
[f] Department of Psychiatry, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea

ARTICLE INFO

*Article history:*
Received 19 May 2015
Received in revised form
2 November 2015
Accepted 15 November 2015
Available online 19 November 2015

*Keywords:*
Adjustment disorders
Prefrontal cortex
Magnetic resonance imaging
Gray matter
Adaptation

ABSTRACT

*Backgrounds:* Adjustment disorder is a frequent mental illness that occurs under various stressful situations. Whereas adjustment disorder has distinct clinical manifestations and diagnostic entity, few studies have investigated its underlying neural substrate. This study aimed to identify brain structural abnormalities among patients with adjustment disorder.
*Methods:* Twenty-five patients with adjustment disorder and 25 healthy controls participated in the study. Structural magnetic resonance imaging was performed, and a voxel-based morphometry was applied. Family-wise error-corrected p values for statistical analysis of comparative gray matters between patients with adjustment disorder and healthy controls were used.
*Results:* Patients with adjustment disorder had decreased gray matter volume in the right medial frontal gyrus as compared to healthy controls. There were no brain regions that were decreased in the healthy controls as compared to patients with adjustment disorder.
*Limitations:* This study was a cross-sectional design.
*Conclusions:* Our results suggest that adjustment disorder arises from characteristic neural abnormalities, contrary to previous notions suggesting that adjustment disorder is a non-specific and/or residual diagnostic term. Moreover, future studies should examine the underlying neural substrates responsible for successful adaptation to unfamiliar and stressful situations.



## 1. Introduction

Adjustment disorder is manifested by clinically significant symptoms and psychosocial impairment disproportionate with the severity or intensity of the stressor (American Psychiatric Association, 2013). The prevalence of adjustment disorder is common and ranges from 11% to 36% among the psychiatric population (Shear et al., 2000). By definition, stressors causing adjustment disorder are not as severe as those in the posttraumatic stress disorder. The disease improves when the stressors disappear. Thus, adjustment disorder is considered as a transitional or subsyndromal mental disorder (Israelashvili, 2012; Semprini et al., 2010). However, recent studies, including ours, suggest that adjustment disorder is associated with personality problems and suicidal risk (Casey et al., 2015; Na et al., 2013). Several lines of evidence suggest that adjustment disorder has characteristic clinical features distinguished from other mental disorders such as major depressive disorder (MDD). Doherty et al. (2014) suggested that patients with adjustment disorder is less associated with personality problems than those with major depressive disorder (Doherty et al., 2014). Casey et al. (2015) reported that underlying factors for the suicidal behaviors between patients with adjustment disorder and major depressive disorder would be different.

These clinical evidences strongly suggest that adjustment disorder is not a transitional or residual disorder, but a separate psychiatric disorder with its own neurobiological mechanisms. However, there is a paucity of literature on neural substrate for adjustment disorder distinguished form normal adjustment. A preliminary $^{18}$F-fluorodeoxyglucose positron emission tomography study was conducted among cancer patients with MDD or adjustment disorder (Kumano et al., 2007). Patients with decreased metabolism in the medial frontal gyrus and increased

* Correspondence to: Department of Psychiatry, Gachon University Gil Medical Center, 21 Namdong-daero 774-beon-gil, Namdong-gu, Incheon 405-760, Korea.
*E-mail address:* ksna13@gmail.com (K.-S. Na).

http://dx.doi.org/10.1016/j.jad.2015.11.028
0165-0327/

metabolism in the subcallosal gyrus, anterior cingulate, caudate head, and posterior cingulate later developed MDD or adjustment disorder. However, that study did not examine the risk factors of MDD or adjustment disorder. One of the barriers to identifying neural substrate for adjustment disorder is sample heterogeneity. Since the essential feature of the adjustment disorder is maladaptation to the various stressful situations, the heterogeneity of the population makes it difficult to obtain validated results. Conscripts might be one of the optimal populations for subject homogeneity in the study of adjustment disorder. Most conscripts are in their early 20s, and are strictly screened for the major psychiatric disorders before going into the army. Additionally, conscripts experience similar stressors. As cited in a psychiatric textbook, study results for adjustment disorder among the conscripts have been regarded as important clinical evidence for adjustment disorder (Katzman and Tomori, 2005).

In this study, we aimed to compare gray matter volumes between patients with adjustment disorder and healthy controls among conscripts. Brain structural abnormality, particularly reduction in the gray matter volumes, might be one of the most widely investigated neural substrates for major psychiatric disorders, including major depressive disorder (Bora et al., 2012), bipolar disorder (Selvaraj et al., 2012), and schizophrenia (Glahn et al., 2008). We hypothesized that patients with adjustment disorder have characteristic reduction in the gray matter volumes as compared to healthy controls.

## 2. Materials and methods

### 2.1. Participants

The study sample consisted of male conscripts with adjustment disorder and age- and gender matched healthy controls. All participants were recruited from an Armed Forces Hospital in the Republic of Korea. Patients who were diagnosed with adjustment disorder using the Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) were consecutively recruited. Board-certified psychiatrists evaluated the participants using the Korean version of the Mini-International Neuropsychiatric Interview (MINI) (Yoo et al., 2006).

Patients with adjustment disorder were excluded if they had (1) any past or current comorbid psychiatric diagnosis other than adjustment disorder; (2) clinically significant general medical conditions, (3) neurological diseases that may influence the imaging such as space-occupying lesions; (4) a history of antidepressant use; (5) any contraindicated factors for magnetic resonance imaging (MRI), such as an implanted pacemaker. All the participants were right-handed according to the Edinburgh Handedness Test (Oldfield, 1971).

After complete explanation and understanding the study protocol, all participants gave written informed consent. The study was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital. The study was conformed to the Declaration of Helsinki.

### 2.2. MRI acquisition

Structural brain images were obtained from 3-dimensional MRI scans using a 1.5 T Avanto SQ 1.5 (Siemens Medical Solutions, Inc., Iselin, NJ, USA) in the Armed Forces Hospital. The images were taken using a high-resolution T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence (1900-ms repetition time, 2.6-ms echo time, 220-mm field of view, $256 \times 256$ matrix size, 176 coronal slices without a gap, $1 \times 1 \times 1$ mm$^3$ voxels, 16° flip angle, number of excitations = 1).

### 2.3. Voxel-based morphometry

Voxel-based morphometry (VBM) data were managed by the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8) with the default parameters of the statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm) implemented in the Matlab R2008a (MathWorks, Natick, MA, USA). We used diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) (Ashburner, 2007) according to the VBM tutorial (Ashburner, 2010). The DARTEL is one of the most reliable nonlinear registering methods (Klein et al., 2009). The optimization in DARTEL is based on the Levenberg–Marquardt strategy (Bergouignan et al., 2009). Briefly, the VBM process is as follows: first, the images were automatically segmented into 3 main components, gray matter, white matter, and cerebrospinal fluid using the default setting in the SPM8. Second, a DARTEL was applied for subsequent processes including registration, normalization, and modulation. Lastly, an 8-mm full-width half-maximum isotropic Gaussian kernel was used for the gray matter probability map.

### 2.4. Self-rating assessment

The severity of depression and anxiety were measured by the Korean version of the Patient Health Questionnaire-9 (PHQ-9) (Han et al., 2008) and the Korean version of the State-Trait Anxiety Inventory (STAI) (Hahn et al., 1996). The PHQ-9, which is based on depressive disorders as described in the DSM-IV, is a self-rating scale for depression. The PHQ-9 consists of nine items with a relatively short completion time. The Cronbach's $\alpha$ of the Korean version of the PHQ-9 is 0.86. The STAI consists of 40 items rated on a 4-point Likert scale. The state anxiety questions (20 items) measure the transitory condition of anxiety, and the trait anxiety questions (20 items) measure the relative stability of individual differences in anxiety proneness (Spielberger et al., 1970). In this study, the Korean version of the STAI was used (Hahn et al., 1996). Cronbach's α for the state anxiety questions is 0.92 and that for the trait anxiety questions is 0.90.

### 2.5. Statistical analysis

Sociodemographic and clinical variables were compared by independent *t*-tests for continuous variables and chi square tests for dichotomous variables between groups, respectively. Statistical analyses for the sociodemographic and clinical variables were conducted using SPSS 12.0 (Chicago, IL, USA).

In the VBM analysis, the smoothed gray matter images were analyzed with an analysis of covariance model using SPM8. The total intracranial volume (TIV) was calculated as the sum of the segmented images of modulated gray matter, white matter, and cerebrospinal fluid. Age and TIV were included as covariates. The gray matter volumes of patients with adjustment disorder were compared with those of age- matched healthy controls. There are no studies on brain abnormalities among individuals with adjustment disorder. Thus, we compared whole brain gray matter volumes between adjustment disorder and healthy controls, rather than setting *a priori* regions of interest. A family-wise error (*FWE*)-corrected statistical threshold of $p < 0.05$ was applied. The Montreal Neurological Institute (MNI) coordinates were converted to the Talairach coordinates using web application (http://noodle.med.yale.edu/~papad/mni2tal/) implemented in the Yale Bioimage Suite Package (Lacadie et al., 2008). The anatomical labels were defined using Talairach Client Version 2.4.3 (http://www.talairach.org/client.html).