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Working memory dysfunction associated with brain functional deficits and cellular metabolic changes in patients with generalized anxiety disorder

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ABSTRACT

Generalized anxiety disorder (GAD) is associated with brain functional and morphological changes in connected with emotional dysregulation and cognitive deficit. This study dealt with the neural functional deficits and metabolic abnormalities in working memory (WM) task with emotion-inducing distractors in patients with GAD. Fourteen patients with GAD and 14 healthy controls underwent functional magnetic resonance imaging (fMRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) at 3 T. In response to the emotional distractors in WM tasks, the patients concurrently showed higher activity in the hippocampus and lower activities in the superior occipital gyrus, superior parietal gyrus, dorsolateral prefrontal cortex (DLPFC) and precentral gyrus compared to the controls. MRS revealed significantly lower choline/creatine (Cho/Cr) and choline/*N*-acetylaspartate (Cho/NAA) ratios in the DLPFC. In particular, the Cho ratios were positively correlated with the brain activities based on blood oxygenation level-dependent signal change in the DLPFC. This study provides the first evidence for the association between the metabolic alterations and functional deficit in WM processing with emotion-inducing distractors in GAD. These findings will be helpful to understand the neural dysfunction in connection with WM impairment in GAD.

1. Introduction

Patients with generalized anxiety disorder (GAD) suffer symptoms of psychological distress including excessive, pervasive and uncontrollable anxiety in daily life (Rickels et al., 2002). More seriously, the rate of suicidal attempts in patients with GAD is higher than patients with other anxiety disorders (Bernal et al., 2007). Recent studies (Moon et al., 2014, 2015a) reported that severe anxiety symptoms lead to emotional disorders including unsuppressed anger and low frustration tolerance, and/or cognitive disorders including low attention and memory deficits. The diagnosis of GAD relies on traditional evaluation methods based on clinical questionnaires (Rickels et al., 2002). Since the typical GAD symptoms negatively affect emotional regulation and cognitive function, a combined study for the evaluation of simultaneously occurring brain functional deficit and metabolic alterations is needed to reveal the neural mechanism of the GAD symptoms.

During the past two decades, neuroimaging studies (Wu et al., 1991; Blair et al., 2008; Monk et al., 2008; McClure et al., 2011; Price et al., 2011; Ball et al., 2013) have demonstrated brain functional abnormalities in patients with GAD using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Several fMRI studies (Blair et al., 2008; Monk et al., 2008; McClure et al., 2011; Price et al., 2011; Ball et al., 2013) discriminated the differential brain activation patterns for negative emotional responses between patients with GAD and healthy controls. The key brain areas associated with emotional dyfunctional deficits and morphological alterations in patientssregulation and attentional deficits on GAD symptoms involve the amygdala, medial prefrontal cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex. In particular, functional studies (Price et al., 2011; Ball et al., 2013) suggested that abnormal activation of the DLPFC during negative emotional regulation was associated with emotional dysregulation and attentional deficit in GAD.

The DLPFC plays an important role in cognitive functions

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including attention and working memory (WM), as well as in the regulation of emotional responses (Moon and Jeong, 2015b). Therefore, the DLPFC is considered as an important core region of interest on the neural mechanisms underlying the cognitive control and emotion regulation in GAD. Recently, a preliminary study (Moon and Jeong, 2015b) reported the functional neuroanatomy on the WM with emotional dysfunction in GAD. In addition to fMRI, the use of proton magnetic resonance spectroscopy (^{1}H-MRS) would be useful to gain more valuable information on the neural mechanism associated with GAD symptoms, because ^{1}H-MRS is capable of providing the brain metabolic information related to the pathogenesis, status of axonal damage and neuronal loss prior to functional changes in brain tissue (Meyerhoff et al., 1994; Maddock and Buonocore, 2012). Negative blood oxygenation level-dependent (BOLD) response in the visual cortex correlates with decreases in neuronal activity mediated by inhibitory neurotransmitters (Shmuel et al., 2006; Devor et al., 2007; Northoff et al., 2007). Therefore, it is assumed that both brain functional deficits and cellular metabolic alterations might be associated with GAD symptoms. However, the nature of the causality between functional and metabolic brain alterations is unclear, since brain functional or neurochemical studies (Blair et al., 2008; Mathew et al., 2008; Monk et al., 2008; McClure et al., 2011; Price et al., 2011; Ball et al., 2013; Strawn et al., 2013) have been separately performed. A combined fMRI and ^{1}H-MRS study would be valuable to investigate whether the brain functional abnormality is associated with the metabolic changes in connection with emotional dysregulation and cognitive deficit in patients with GAD.

In this study, we used fMRI in combination with a localized ^{1}H-MRS to assess the association between functional brain deficits and cellular metabolic changes in the DLPFC in patients with GAD.

2. Methods

2.1. Subjects

The 28 right-handed subjects included 14 patients (mean age, 36.6 ± 8.8 years), who had been diagnosed with GAD with mild levels of depression by a psychiatrist using the DSM-IV-TR (American Psychiatric Association., 2000) and 14 age-matched healthy controls (mean age, 37.8 ± 7.8 years). The duration of the patients' illness was 3.2 ± 3.5 years (Table 1). Eleven patients received prescriptions for multiple psychiatric medications including anxioytics: buspirone (n=7), alprazolam (n=3) and tofisopam (n=1); and/or antidepressants: escitalopram (n=10), bupropion (n=3), fluvoxamine (n=2), and duloxetine (n=1), and three patients received a single psychiatric medication comprising escitalopram (n=2) or bupropion (n=1).

All subjects submitted informed written consent before participating in this study. The Institutional Review Board of Chonbuk National University Hospital in Korea approved the study protocol.

2.2. Assessment of anxiety levels

The subjects underwent structured clinical interviews for their DSM-IV diagnoses (First et al., 1995). Anxiety levels were then assessed using various psychiatric rating scales (Moon et al., 2015b): Hamilton Anxiety Rating Scale (HARS; 14 items with a 5-level scale, cutoff score > 14; Hamilton, 1959), Hamilton Rating Scale for Depression 17 (HAMD-17; 8 items with a 5-level scale and 9 items with a 3-level scale, cutoff score > 7; Hamilton, 1960), Generalized Anxiety Disorder Scale 7 (GAD-7; 7 items with a 4-level scale, cutoff score > 4; Spitzer et al., 2006), State-Trait Anxiety Inventory I (STAI-I; 20 items with a 4-level scale; cutoff score > 51; Spielberger et al., 1970), State-Trait Anxiety Inventory II (STAI-II; 20 items with a 4-level scale, cutoff score > 53; Spielberger et al., 1970), and Anxiety Sensitivity Index-Revised (ASI-R; 36 items with a 5-level scale, cutoff score > 28; Taylor and Cox, 1998) (Table 1).

Table 1
Characteristics of patients with GAD and healthy controls.

	GAD (n=14)		Control (n=14)	p-value	t-value
Age (years)	36.6 ± 8.8		37.8 ± 7.8	0.854*	0.185
Gender (male/female)	8/6		8/6	1.000†	
Education (years)	14.1 ± 1.8		14.7 ± 2.3	0.461*	0.748
Duration of illness (years)	3.2 ± 3.5		–	–	
Psychiatric rating scales					
HARS[a]	18.0 ± 5.4	>	0.7 ± 1.3	< 0.001*	11.932
HAMD-17[b]	10.5 ± 2.4	>	0.5 ± 0.7	< 0.001*	15.045
GAD-7[c]	12.0 ± 4.2	>	0.6 ± 0.9	< 0.001*	10.156
STAI-I[d]	58.2 ± 11.8	>	34.7 ± 5.9	< 0.001*	5.995
STAI-II[e]	56.6 ± 11.8	>	36.7 ± 5.7	< 0.001*	5.646
ASI-R[f]	76.6 ± 22.3	>	16.9 ± 23.3	< 0.001*	6.797
Visual scale for unpleasant level[g]					
Emotion-inducing distractors	7.1 ± 2.4		8.1 ± 1.6	0.497*	0.688
Facial recognition task					
Accuracy (%)[h]	56.9 ± 0.9		69.3 ± 0.7	0.045*	2.106

* Mann-Whitney U test.
† Chi-square test.
[a] HARS: Hamilton Anxiety Rating Scale.
[b] HAMD-17: Hamilton Rating Scale for Depression 17.
[c] GAD-7: Generalized Anxiety Disorder Scale 7.
[d] STAI-I: State-Trait Anxiety Inventory I.
[e] STAI-II: State-Trait Anxiety Inventory II.
[f] ASI-R: Anxiety Sensitivity Index-Revised.
[g] Visual scale for unpleasant level: 11-point visual scale ranging from 0 (least unpleasant) to 10 (most unpleasant).
[h] the number of correct response during the 10-face trials.

2.3. Paradigm for brain activation

Participants were exposed to the negative emotion-inducing images to evoke anxiety related with GAD symptoms. Prior to the fMRI experiment, 50 emotion-inducing images were collected from the international affective picture system (IAPS) (Lang et al., 2008) and a variety of Internet sites. Emotion-inducing images consisted of photographs of life-threatening behaviors, traffic accidents, disasters, and other events that would spawn emotions of misgiving or anxiety. Ten college students nominated 30 emotion-inducing images from a pool of 50 images as appropriate experimental stimulators. A psychiatrist selected 20 emotion-inducing images from the 30 images. After the fMRI experiments, the subjects rated the unpleasant level from the emotion-inducing images using an 11-point visual scale ranging from 0 (least unpleasant) to 10 (most unpleasant) (Table 1).

The activation paradigm (Kim et al., 2015; Moon and Jeong, 2015b) consisted of a string of cue and encoding (6 s)-delay (4 s)-distractor (6 s)-button ready (2 s)-retrieval (2 s)-intertrial rest (12 s) (Fig. 1). The string was repeated 10 times. In the 'cue' period, each trial started with the presentation of the 'face' word. In the 'encoding' period, three different expressionless human faces masked with an oval-shaped hood were randomly presented once (1.66 s each). During the 'delay' period, the subjects were instructed to maintain WM of the encoded faces. In the 'distractor' period, two emotion-inducing images were presented as the distractors to disturb the WM maintenance of the subjects. During the 'retrieval' period, either a new face or the face presented in the 'encoding' period was presented. At this time, subjects were