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Critical examination of a correlation between brain gamma-aminobutyric acid (GABA) concentrations and a personality trait of extroversion in healthy volunteers as measured by a 3 Tesla proton magnetic resonance spectroscopy study

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ABSTRACT

We hypothesized that brain gamma-aminobutyric acid (GABA) levels are associated with neuroticism, a trait associated with depression and anxiety disorders. We examined the correlation between brain GABA concentrations and the five factors included in the NEO Five-Factor Inventory (NEO-FFI) in healthy volunteers using magnetic resonance spectroscopy (MRS) at 3 T. Forty-one healthy subjects (21 males, 20 females; age: 35±7 years) were enrolled in this study. Each subject underwent a 3 T 1H-MRS study with a MEGA-PRESS sequence. Spectroscopy voxels (3 cm×3 cm×3 cm) were placed in the frontal lobe and the parieto-occipital lobe. A negative correlation was found between the GABA/creatine ratios in the frontal lobe and scores of extroversion on the NEO-FFI. These results suggest that GABAergic neurons are related to personality traits of healthy subjects.

1. Introduction

Personality typically refers to an integrated pattern of thinking, feeling, and behaving that varies among individuals, but is stable within a single individual over time (Sugiura et al., 2000). The Five-Factor Model of personality has recently emerged as the dominant model of normal personality (Liveley, 2001). According to this model, all phenotypical variation present in overt behavior can be explained by five higher-order factors (extroversion, neuroticism, openness, agreeableness, and conscientiousness) (Goldberg, 1992). Extroversion and neuroticism are two core traits of personality and are considered to be associated with individual differences in positive and negative affectivity (McCrae and Costa, 1999). Extroverted individuals are typically described as using positive emotional terms such as "excited," "engaged," and "enthusiastic," whereas neurotic individuals are typically described as using negative emotional terms such as "fearful," "anxious," "angry," and "distressed" (Eysenck and Eysenck, 1991). Levels of extroversion and neuroticism are known to be highly heritable (Polmin and Caspi, 1999) and have been linked to a vulnerability to depression, as well as to anxiety disorders (Duggan et al., 1995; Watson and Clark, 1997). Wright et al. (2007) reported that the thickness of specific lateral prefrontal cortex regions correlated with introversion and neuroticism in elderly healthy subjects. In addition, recent functional and structural brain studies have indicated that affective processing is associated with individual differences in neuroticism and extroversion, and such processing may provide a basis for important associations between personality traits and an individual's emotional responses (Knutson et al., 2001; Canli, 2004; Wright et al., 2006; Kim et al., 2008).

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. Found in both inhibitory–inhibitory and inhibitory–excitatory synapses, GABA is a critical neurotransmitter in circuits connecting the prefrontal and limbic cortex. These structures are of relevance to impulsivity and related behavior because of their central importance in behavioral inhibition (Horn et al., 2003) and affective processing (Phan et al., 2002). Consistent with their overlapping neurobiology, disruptions in affective processing can result in increased impulsivity and aggression (Schmidt et al., 2004). The effects of net increases or decreases in GABA on prefrontal and limbic cortex function would be expected to vary from circuit to circuit, and might show considerable inter-individual differences (Semyanov, 2003). The GABA system has been repeatedly implicated in anxiety- and depression-related traits (Petty, 1995). In addition, postmortem studies have suggested that mood disorders are associated with a reduced number of GABAergic neurons in the frontal cortex (Bielau et al., 2007). Taken together, such findings imply that GABA neurotransmissions might play an important role in constructing individual personalities. To the best of our knowledge, only one study has demonstrated an association between brain GABA levels and emotional

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or cognitive processing (Wright et al., 2007). Based on the findings of that single study, we hypothesized that a correlation could be identified between brain GABA levels and neuroticism. To examine this hypothesis, we investigated associations between the five factors on the NEO Five-Factor Inventory (NEO-FFI) (Costa and McCrae, 2000) and brain GABA concentrations, as determined using 3 T proton magnetic resonance spectroscopy (1H-MRS) in healthy subjects. 1H-MRS is a noninvasive method of investigating neurochemical changes in the context of various pathologic and physiologic conditions, and 1H-MRS at 3 T has enabled separate measurements of GABA, glutamic acid (glu), and glumamine (gln) (Shibuya-Tayoshi et al., 2008).

2. Methods

2.1. Subjects

The study participants were 41 healthy volunteers (21 males, 20 females; age: 35±7 years) without any history of significant head injury, seizure, or neurological condition. The subjects were eligible to participate in the protocol if they had never been diagnosed with a current or past axis I or II psychiatric disorder, as confirmed by the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 1995), and if they had no history of psychotropic medication use within the prior 6 months. All participants were examined with MRS in the early evening (from 4:00 p.m. to 5:00 p.m.). This study was approved by the Ethics Committee of the University of Occupational Environmental Health. All participants gave their written informed consent to participate in the study.

2.2. MRS procedures

The subjects were all examined by 1H-MRS using a 3 T MR system (Signa EXCITE 3 T; GE Medical Systems) equipped with a standard quadrature head coil (GE Medical Systems). Standard PRESS spectra were acquired at TE = 26 ms (used to quantify brain metabolites, with exception of GABA) and 68 ms for quantification. The GABA concentration was measured using a MEGA-PRESS sequence (Mescher et al., 1998) for voxel localization (TR = 3 s, TE = 68 ms, 128 averages, 6-min acquisition time). Unwanted resonance in the PRESS spectrum was removed from the edited spectra by using J-coupling between the GABA resonances at 3.0 ppm and 1.9 ppm. By applying a frequency-selective 180° pulse to the 1.9-ppm GABA resonance in alternate acquisitions, a modulation was introduced to the phase of the 3.0-ppm resonance. Uncoupled resonances such as the creatine (Cr) resonance at 3.0 ppm, which overlaps the GABA peak at the same time point in the chemical shift, were left unaffected by the frequency-selective 180° pulse, as were coupled resonances, such as that of glutathione, which does not have a coupling partner within the frequency range of the MEGA-PRESS pulse. All spectra were analyzed using an LC model (Provencher, 1993) and phantom-generated basis functions for the PRESS and MEGA-edited spectra. The line width, signal-to-noise ratio, and baseline of each spectrum were checked to ensure the robustness of the data. Spectra with a Cramer-Rao showing binding of greater than 20% were rejected. The eddy-current correction technique was applied in the acquisition of all data by using an unsuppressed water spectrum at the appropriate echo time. For the analysis of the edited spectra, LCM-basis functions (GABA, glu, and gln) that had been generated from phantom measurements using the MEGA-PRESS sequence with the appropriate acquisition parameters were employed. The metabolite concentrations were evaluated as ratios to Cr, as ratios of various metabolites to Cr are commonly used in spectroscopy studies for the purposes of normalization.

The regions of interest (ROIs) for the 1H-MRS were set for the frontal lobe, left basal ganglia, and parieto-occipital lobe (ROI size = 3.0 cm × 3.0 cm × 3.0 cm) using two oriented images (axial and sagittal) for each region. We placed a voxel in the frontal lobe (Fig. 1a) and the parieto-occipital lobe (Fig. 1b). All of the ROIs were placed in a manner that enabled avoidance of the lateral ventricle and skull. Typical 1H-MRS spectra are shown in Fig. 2.

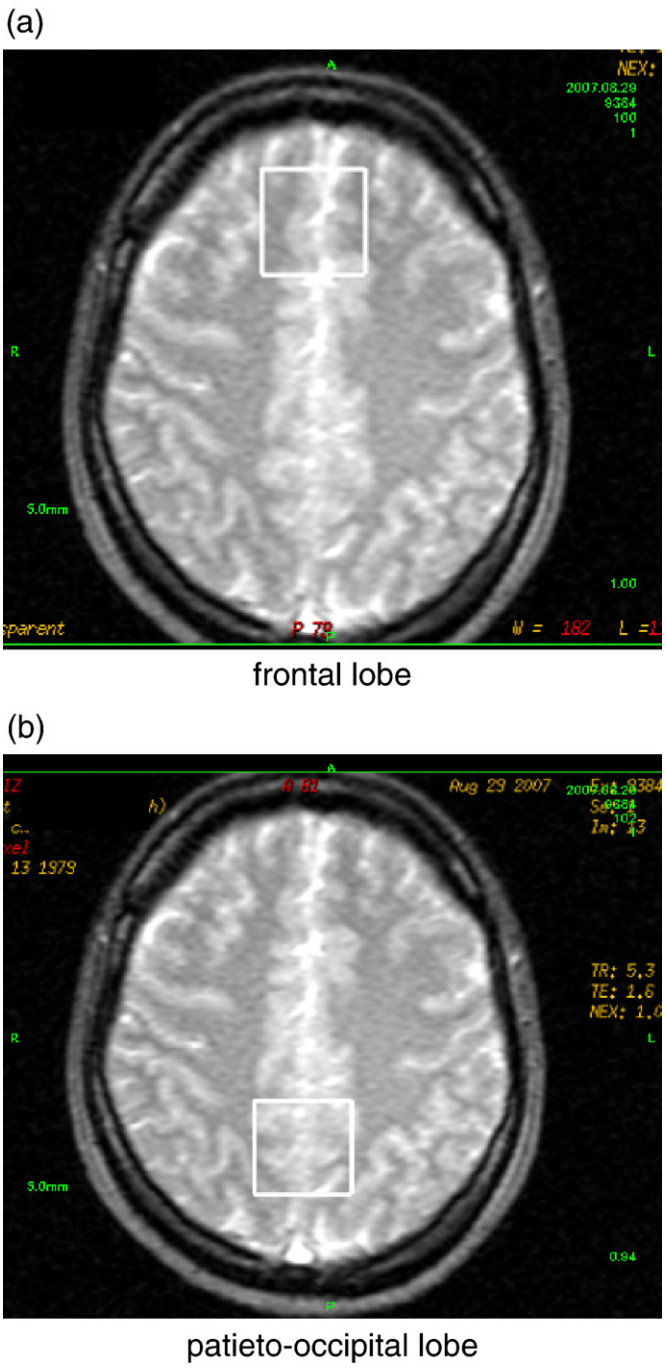

Fig. 1. Voxel positions for spectroscopic measurement using a MEGA-PRESS sequence to examine the frontal lobe (a) and parieto-occipital lobe (b). The white box represents the location of the voxel (3.0 cm × 3.0 cm × 3.0 cm) in an axial image.

2.3. Statistical analysis

The values are presented as means ± standard deviation (S.D.). Statistical analysis was performed using Pearson's correlation coefficients to investigate the brain ratios of GABA/Cr and the NEO-FFI scores. The level of significance was set at $P<0.05$.