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Research report

Decreased thalamic glutamate level in unmedicated adult obsessive–compulsive disorder patients detected by proton magnetic resonance spectroscopy

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ABSTRACT

Background: Previous neuroimaging studies implied that the dysfunction of cortico–striato–thalamo–cortical (CSTC) circuit served as the neural basis for the pathophysiology of obsessive–compulsive disorder (OCD). The imbalances in neuronal metabolite and neurotransmitter within CSTC circuit have been shown as the leading reasons of the OCD onset. The aim of this study is to investigate the metabolic alterations, especially the glutamatergic signal dysfunction within CSTC circuit, and the relationships between neural metabolites and the symptom severity of OCD patients.
Methods: Single voxel magnetic resonance spectroscopy (MRS) was conducted in medial prefrontal cortex (mPFC) and bilateral thalamus areas for thirteen unmedicated adult OCD patients with age-, gender-, and education-matched healthy controls. Quantification and multivariate analysis were performed to identify vital metabolic biomarkers for patients and healthy controls group differentiation. Moreover, we performed Spearman's rank correlation analysis for OCD patients to examine the relationship between the metabolite concentration level and OCD symptomatology.
Results: Patients with OCD showed significantly decreased glutamate level in mPFC ($p=0.021$) and right thalamus ($p=0.039$), and significantly increased choline compounds in left thalamus ($p=0.044$).The glutamate in right thalamus was shown as the most important metabolite for group separation from multivariate analysis ($Q^2=0.134$) and was significantly correlated with the patients' compulsion scores (Spearman $r=-0.674$, $p=0.016$).
Limitations: Limited sample size, the use of creatine and phosphocreatine (Cr) ratios rather than absolute concentrations and unresolved glutamine (Gln) are limitations of the present study.
Conclusion: Our study results consolidated the hypothesis about glutamatergic signaling dysfunction in OCD. To our knowledge, it is the first finding about a reduced thalamic glutamate level in adult unmedicated OCD patients. The dysregulation of glutamate serves as a potential target for the OCD pharmacotherapy and the detailed mechanisms underlying the glutamate alterations within CSTC circuits merit further investigations.

1. Introduction

Obsessive–Compulsive Disorder (OCD) is characterized by obsessive thoughts and compulsive behaviors with high lifetime prevalence rate (Gnanavel et al., 2013; Ruscio et al., 2008; Sarris et al., 2012). Structural and functional neuroimaging data indicated that the cortico–striato–thalamo–cortical (CSTC) circuit played an important role in the pathophysiology of OCD (Alexander et al., 1986; Brennan

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et al., 2013; Gilbert et al., 2008; Milad and Rauch, 2012; Rosenberg and Keshavan, 1998; Saxena and Rauch, 2000; Wu et al., 2012). The CSTC pathway originates from specific frontal cortex regions, including the medial prefrontal cortex (mPFC)/ anterior cingulate cortex (ACC), the orbito-frontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC). It then connects with the corresponding targets within striatum and then thalamus, finally returning to its original cortex regions (Aoki et al., 2012; Maia et al., 2008; Milad and Rauch, 2012; Weber et al., 2014). The mPFC/ACC is involved in cognitive and affective functions primarily associated with motivation-related behaviors, while the OFC is responsible for the integration of limbic and emotional information into behavioral responses (Aouizerate et al., 2004; Bonelli and Cummings, 2007). The thalamus plays a critical role in perception and thoughts integration (Baxter, 1992; Insel, 1992; Modell et al., 1989). All of these behaviors are closely related to OCD psychopathology. Numerous OCD neuroimaging studies employing computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) technologies have reported structural, functional and metabolic abnormalities along the CSTC circuit, such as in the mPFC/ACC, OFC, caudate nucleus and thalamus (Alptekin et al., 2001; Saxena et al., 2001b; Szeszko et al., 2004). Enhanced functional activities in mPFC/ACC, OFC, and thalamus in adult OCD patients has been observed using PET/SPECT technology (Alptekin et al., 2001; Lacerda et al., 2003a; Mazziotta et al., 1988; Perani et al., 1995; Saxena et al., 2001b; Swedo et al., 1989). Structurally, reduced OFC volume was shown in adult OCD patients while increased gray matter volume was found in the ACC and OFC using MRI (Kang et al., 2004; Kim et al., 2001; Szeszko et al., 1999, 2004). Also, increased gray matter density in the thalamus was detected in adult OCD patients (Kim et al., 2001). To bring additional insights into the neurobiology of OCD, complementary approaches have been performed to investigate the neurochemistry within these abnormal regions.

Proton magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive technology that enables quantification of metabolite concentrations in tissues in vivo. It has been applied to study the neurobiology of OCD (Rosenberg et al., 2001). Several metabolites were found to be highly relevant to the mechanisms of CSTC circuit dysfunction in OCD, such as N-acetylaspartate (NAA), phosphorylcholine and glycerophosphorylcholine (Cho), myoinositol (ml), glutamate (Glu), glutamine (Gln), and Glx (Glu and Gln). In addition, the imbalances in neuronal metabolites and neurotransmitters within CSTC circuit were proposed to be the cause for the onset of OCD (Bartha et al., 1998; Russell et al., 2003). Studies discovered biochemical variations in mPFC/ACC, OFC and thalamus in patients with OCD, which could lead to OCD pathogenesis (Simpson et al., 2012; Smith et al., 2003). Although the MRS data vary due to subject and acquisition heterogeneity, some findings converge such as reduced NAA levels in mPFC/ACC (Besiroglu et al., 2011; Ebert et al., 1997; Gnanavel et al., 2013; Jang et al., 2006; Sumitani et al., 2007; Yücel et al., 2007) and increased Cho levels in thalamus (Mohamed et al., 2007; Rosenberg et al., 2001; Smith et al., 2003).

In addition, Pittenger and others (Carlsson, 2001; Grant et al., 2007; Kariuki-Nyuthe et al., 2014; Pittenger et al., 2011; Rosenberg et al., 2000; Ting and Feng, 2008; Wu et al., 2012) proposed that the glutamatergic abnormalities in CSTC circuit may contribute to OCD, supported by increasing evidence from both animal and human studies (Arnold et al., 2006; Campbell et al., 1999; Welch et al., 2007; Yücel et al., 2008). The dysregulation of glutamate in OCD and the glutamatergic system serves as a potential target for the pharmacotherapy of this disorder (Boardman et al., 2011; Delorme et al., 2004; Grant et al., 2007; Kariuki-Nyuthe et al., 2014; Rosenberg et al., 2000). As the key excitatory neurotransmitter, glutamate played an important role within CSTC circuit (Carlsson, 2001; Maia et al., 2008; Pauls et al., 2014; Saxena and Rauch, 2000; Ting and Feng, 2008; Wu et al., 2012). One of the classic models of OCD is based on the imbalance between direct and indirect pathways within CSTC circuit, in which the direct pathway leads to thalamic stimulation of cortex and the indirect pathway leads to thalamic inhibition of cortex. A dynamic balance is reached between the two pathways for healthy individuals. Based on convergent findings from animal and clinical studies, the prevailing model of OCD postulates that the excessive activity of the direct pathway over the indirect pathway leads to disinhibition of CSTC circuit and consequent compulsion and obsession behaviors (Saxena and Rauch, 2000; Wu et al., 2012). The overactivity in orbitofrontal-subcortical circuits and associated hyperactivity of glutamate attribute to the imbalance between direct and indirect striatopallidal pathways (Maia et al., 2008; Pauls et al., 2014; Saxena et al., 2001a; Saxena and Rauch, 2000; Ting and Feng, 2008). Direct evidence for glutamatergic dysfunction in OCD patients was obtained from a variety of MRS studies including reduced Glx in ACC, elevated Glx in caudate and CSF in OCD patients (Chakrabarty et al., 2005; Rosenberg et al., 2000, 2004; Yücel et al., 2008). However, there have been discrepant results about elevated or unaltered Glx level in mPFC/ACC regions of OCD adults (Gnanavel et al., 2013; Simpson et al., 2012). In thalamus, no Glx abnormalities were found in both adult OCD patients on medication (Bédard and Chantal, 2011; Gnanavel et al., 2013) and pediatric OCD unmedicated patients compared to controls (O'Neill et al., 2012). Moreover, most reports focused on the Glx level rather than Glu or Gln levels, due to technical difficulties in acquisition of their signals. Therefore, to reconcile the contradictory reports, it is necessary to perform more detailed investigations to understand the glutamatergic dysfunction in OCD.

In this study, we utilized MRS to analyze a variety of biochemical markers in mPFC and bilateral thalamus regions of unmedicated adult OCD patients. First, we aimed to detect and quantify Glu and Glx to test the CSTC glutamatergic dysfunction hypothesis in OCD. In addition, we applied multivariate analysis to identify composite metabolic biomarkers in mPFC and thalamus that lead to group separation between OCD patients and healthy controls. Moreover, we explored the correlations between neural metabolites and the symptom severity of OCD patients.

2. Materials and methods

2.1. Subjects

Thirteen patients with OCD and thirteen healthy subjects 18–54 years old and matched for age, gender, handedness and educational status, participated in this study (Table 1). The written informed consent approved by Shanghai Mental Health Center Ethics Committee was obtained from each participant prior to the study. All subjects were required to have junior high school and higher education level, were right-handed, and not taking psychotropic drugs for at least two months. The exclusion criteria included diagnosis of comorbid Axis I psychiatric disorders, severe physical illness, traumatic brain injury or a history of central nervous system disorders, psychoactive substance abuse, suicide attempts, pregnancy or lactation, dentures, pacemakers, stents, metal implants, and other MRI-incompatible devices. OCD patients were recruited from the Shanghai Mental Health Center and the control subjects were recruited through advertising. All patients were interviewed by a trained psychiatrist using the Mini-International Neuropsychiatric Interview (MINI) to provide DSM-IV diagnoses of Axis I psychiatric disorders. The MINI was utilized to determine whether they met DSM-IV criteria for OCD and other mental disorders.

At the time of MRI scanning, the OCD patients reported the OCD symptom severity using Yale-Brown Obsessive Compulsive Scale (YBOCS), which scores obsession and compulsion features. For all subjects, the Hamilton Depression Scale (HAMD) and Hamilton