Psychiatry Research: Neuroimaging 232 (2015) 65–70

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Assessment of glutamate in striatal subregions in obsessive-compulsive disorder with proton magnetic resonance spectroscopy

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ARTICLE INFO

Article history:
Received 27 June 2014
Received in revised form
14 October 2014
Accepted 10 January 2015
Available online 3 February 2015

Keywords:
Magnetic resonance spectroscopy
OCD
Striatum
Caudate

ABSTRACT

Glutamatergic signaling abnormalities in cortico-striatal circuits are hypothesized to lead to the repetitive thoughts and behaviors of obsessive-compulsive disorder (OCD). To test this hypothesis, studies have used proton magnetic resonance spectroscopy (^{1}H MRS) to measure glutamatergic compounds in the striatum of individuals with OCD. However, no studies have used methods that could measure glutamate minimally contaminated by glutamine and γ-aminobutyric acid (GABA) in striatal subregions. Therefore, in this study, a proton MRS imaging (^{1}H MRSI) technique with relatively high spatial resolution at 3.0 T was used to measure minimally contaminated glutamate levels in three striatal subregions (i.e., dorsal caudate, dorsal putamen, and ventral striatum) in 15 unmedicated adults with OCD and 16 matched healthy control subjects. No significant group differences in glutamate levels were found in any of the three striatal subregions. In contrast, a study in unmedicated pediatric OCD patients that measured glutamatergic compounds in the dorsal caudate by MRS at 1.5 T found significant elevations. Further studies are warranted to assess whether these discrepant MRS findings are due to differences in subject age or MRS methodology, or potentially are associated with glutamatergic gene variants implicated in OCD.

1. Introduction

Structural and functional imaging studies indicate that obsessive-compulsive disorder (OCD) is associated with abnormal functioning of brain circuits that include the orbito-frontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus (Milad and Rauch, 2012). Preclinical and clinical evidence suggests a role for glutamatergic abnormalities in OCD, including reports of associations between OCD and genes related to the glutamate system, of OCD-like behavior in mice following disruption of glutamatergic transmission in cortico-striatal circuits, and of the ability of glutamate-modulating drugs to ameliorate OCD symptoms (reviewed in Insel, 2012; Pittenger et al., 2011). Together, these observations have led to the hypothesis that abnormalities in glutamatergic signaling in OFC-striatal circuits may be implicated in the repetitive thoughts and behaviors that characterize OCD.

Several studies have tested this hypothesis by using proton magnetic resonance spectroscopy (^{1}H MRS) to measure levels of glutamatergic compounds in the striatum of individuals with OCD and healthy control subjects (reviewed in Brennan et al., 2012). The results have been variable, with one study reporting elevations of glutamatergic compounds in the head of the left caudate in unmedicated pediatric patients that decreased with successful treatment (Rosenberg et al., 2000), another study reporting elevated glutamatergic compounds in the left caudate in medicated adult patients (Shekhar et al., 2008), and the majority of studies in both pediatric and adult patients finding no striatal glutamatergic abnormalities (Bartha et al., 1998a; Ebert et al., 1997; Lazaro et al., 2012; O'Neill et al., 2012; Starck et al., 2008; Whiteside et al., 2006, 2012). Multiple factors differed across these studies and may explain the discrepant results, including whether OCD subjects were receiving medication at

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http://dx.doi.org/10.1016/j.pscychresns.2015.01.009
0925-4927/

the time of scanning, the magnetic field strength (ranging from 1.5 T to 4.0 T), the specific MRS methods used to derive the "glutamatergic compound" levels (and thus more or less contaminated with glutamine and γ-aminobutyric acid [GABA]), and the size and location of the striatal voxel of interest.

In the present study, we aimed to minimize or eliminate some of these potential confounds by: (a) studying only unmedicated OCD patients and (b) taking advantage of the relatively higher detection sensitivity at 3 T to implement a MRS imaging (MRSI) method that enables detection of glutamate with minimal glutamine and GABA contamination – as opposed to glutamate that is obtained with approaches that do not attempt to minimize the glutamine and/or GABA contribution, commonly referred to as "Glx" – from multiple striatal voxels. Based on the glutamatergic theory of OCD and a study at 1.5 T that found increased glutamatergic compounds in the left dorsal caudate in unmedicated pediatric OCD patients (Rosenberg et al., 2000), we hypothesized that unmedicated adults with OCD will have increased glutamate in the left dorsal caudate compared to matched healthy control subjects. We simultaneously measured glutamate levels in the left dorsal putamen and ventral striatum to establish the specificity of the caudate finding, since these striatal subregions receive glutamatergic projections from different cortical regions (Haber and McFarland, 1999).

2. Methods

2.1. Subjects

The institutional review board of the New York State Psychiatric Institute/Columbia University approved the study. Subjects were recruited by advertisements and word of mouth and provided written informed consent.

Subjects had to be between the ages of 18 and 55 and free of any significant medical problems, current or past neurological disorders (other than Tic Disorder), and history of substance or alcohol abuse or dependence (including nicotine). Pregnant, nursing, and postmenopausal women and those using hormonal contraceptives were excluded. OCD subjects had to fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for OCD for at least 1 year as their primary psychiatric disorder and not be receiving psychotropic medications (for a minimum of six weeks) or psychotherapy at the time of the study. OCD subjects

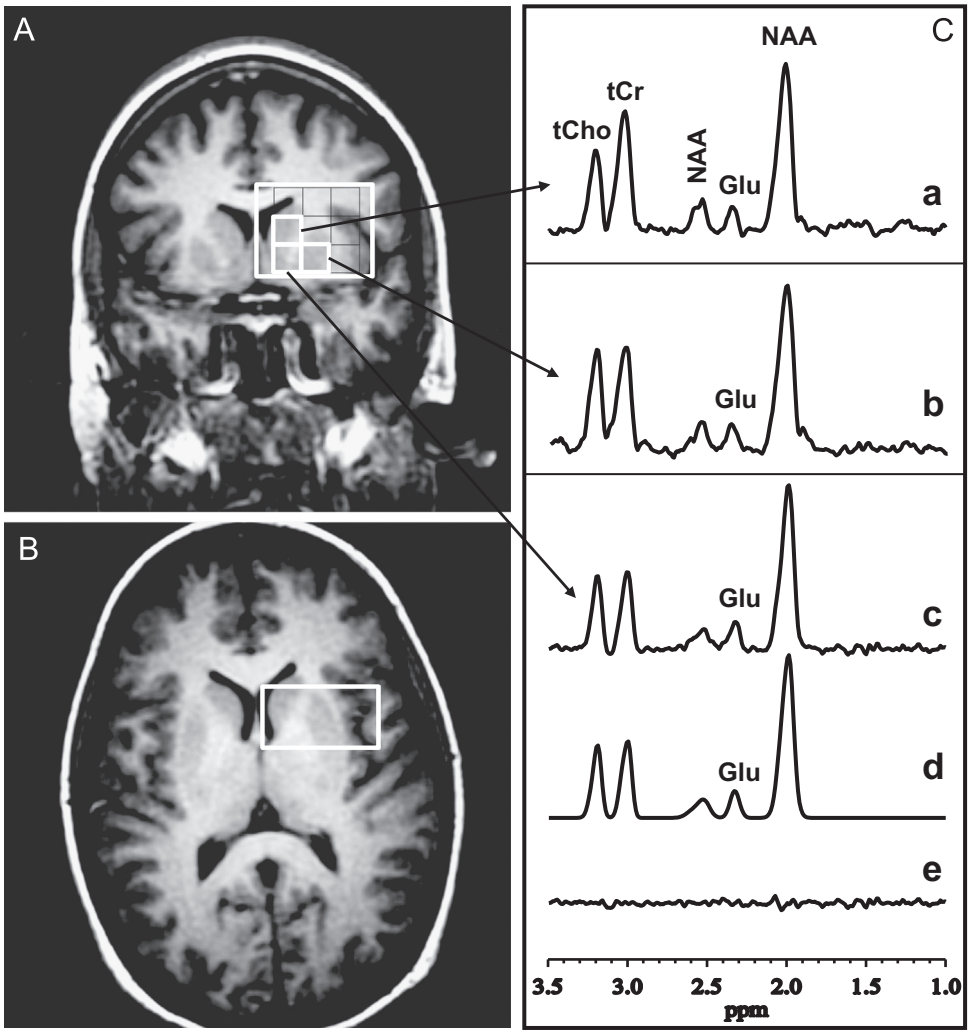

Fig. 1. Striatal subregions and associated sample ^{1}H MR Spectral Data. [A] Coronal and [B] axial localizer images showing the size and location of the volume of interest (large white box) pre-localized with the PRESS method. The spectroscopic imaging (SI) slice thickness was 20 mm, field of view 16 cm, with the slice positioned coronally anterior to the anterior commissure. The coronal view, [A], is overlaid with a grid of voxels that cover the striatum and its subregions. Within this grid, three individual voxels ($0.8 \times 0.8 \times 2.0$ cm^3) were positioned to contain the dorsal caudate, dorsal putamen, and ventral striatum. The multi-voxel PRESS data set was acquired in 20 min using TE/TR 80/1500 ms, 20×20 phase-encoding (PE) steps, 2 excitations per PE. The arrows point to sample ^{1}H spectra recorded from these three striatal voxels, labeled as follows in panel [C]: (a) dorsal caudate; (b) dorsal putamen; and (c) ventral striatum; Shown left-to-right in each spectrum are the resonances for total choline (tCho), total creatine (tCr), N-acetyl-L-aspartate (NAA, methylene), uncontaminated glutamate (Glu), and NAA (methyl); (d) a nonlinear least-squares best-fit spectrum obtained by fitting the experimental spectrum in (c) to a sum of pseudo-Voigt lineshape functions in the frequency domain; (e) the residuals of the difference between (d) and (e). The fitting procedure yields areas under the metabolite resonances, which are proportional to concentrations.