European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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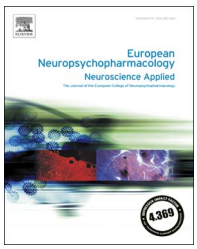

Striatal structure and its association with N-Acetylaspartate and glutamate in autism spectrum disorder and obsessive compulsive disorder

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Received 2 June 2017; received in revised form 11 October 2017; accepted 3 November 2017

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[1]See acknowledgements

https://doi.org/10.1016/j.euroneuro.2017.11.010

KEYWORDS
OCD;
ASD;
Glutamate;
N-Acetylaspartate;
Striatum;
Structure

Abstract
Autism spectrum disorders (ASD) and obsessive compulsive disorder (OCD) are often comorbid and are associated with changes in striatal volumes and N-Acetylaspartate (NAA) and glutamate levels. Here, we investigated the relation between dorsal striatal volume and NAA and glutamate levels. We additionally compared striatal volume and shape between ASD, OCD and controls. T1-weighted magnetic resonance (MR) images, proton spectra (1H-MRS) in the left striatum, and phenotypic information were collected from 54 children with ASD, 32 with OCD, and 56 controls (aged 8–13 years) in a four-site study. Dorsal striatal volume and shape were determined using the FMRIB integrated registration and segmentation tool (FIRST). Spectra were processed with Linear Combination Model. The relationship of left striatal volume with NAA and glutamate was investigated, and group comparisons were performed for NAA levels and for bilateral striatal volume and shape. NAA levels were lower in subjects with ASD compared with controls ($t=2.86$, $p=0.005$) and were associated with striatal volume ($\beta=0.37$, $t=2.78$, $p=0.008$). Glutamate levels were also associated with volume in the ASD group ($\beta=0.38$, $t=2.46$, $p=0.018$). No group differences were found for striatal volume or shape, but a post-hoc diagnosis-by-hemisphere interaction ($F_{(2,129)}=3.86$, $p=0.024$) revealed greater asymmetry (right > left) in striatal volume for the disorder-groups compared with controls. Our findings show involvement of NAA and glutamate in striatal volume in ASD and suggest greater asymmetry in paediatric ASD and OCD compared with controls, pointing to overlapping subcortical abnormalities. The lower NAA in ASD reflects reduced neuronal integrity or impaired neuronal functioning.

1. Introduction

Autism spectrum disorders (ASD) and obsessive compulsive disorder (OCD) are neurodevelopmental disorders, which are often comorbid and are both characterized by compulsive behaviors (American Psychiatric Association, 2013). Structural neuroimaging studies investigating these disorders have highlighted alterations in similar brain regions (Hrdlicka, 2008; Radua and Mataix-Cols, 2009). Among the most investigated areas is the dorsal striatum, as are the caudate nucleus and putamen separately. These regions are central to the functioning of the fronto-striatal circuits (e.g. Walhovd et al., 2015; Morris et al., 2016), which have been shown to be affected in ASD and OCD (Langen et al., 2012; Melloni et al., 2012). Several studies found increased caudate volume (Hollander et al., 2005; Voelbel et al., 2006; Qiu et al., 2016) and increased putamen volume (Sato et al., 2014) in participants with ASD compared with controls. However, elevated repetitive behavior has been shown to correlate with decreased bilateral putamen volumes as well in children with ASD (Estes et al., 2011). In a shape study, which is more sensitive to subtle morphological changes, a steeper increase in concavity with age in both caudate and putamen of participants with ASD was found (Schuetze et al., 2016). In OCD, increased putamen (Real et al., 2016) and caudate and putamen volumes (Zarei et al., 2011) have also been reported, but other studies did not show differences in both regions (Szeszko et al., 2004) or decreased left putamen volume (Hoexter et al., 2012). Additionally, positive correlations between putamen volume and obsessive-compulsive symptoms in the healthy population (Kubota et al., 2015), but also negative correlations between contamination/washing symptoms (Van Den Heuvel et al., 2009), total Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) (Scahill et al., 2006) scores, and caudate volume (Narayanaswamy et al., 2013) have been reported. One shape study found deformity of the caudate in OCD (J. S. Choi et al., 2007). There have also been studies in both disorders reporting regional asymmetries in subcortical volumes (Kang et al., 2008; Dougherty et al., 2016), which may suggest deficits in regional specialization.

Structural abnormalities may be related to neurochemical abnormalities. N-Acetylaspartate (NAA), which is hypothesized to reflect neuronal density and viability, indicating neuronal integrity and functioning (Moffett et al., 2007; Urenjak et al., 1992; Kalra et al., 1998; Rigotti et al., 2007), may be a marker for structural abnormalities. NAA concentrations can be measured with proton magnetic resonance spectroscopy (1H-MRS), and both ASD and OCD have been associated with decreased NAA concentrations in several brain regions, including the striatum (Aoki et al., 2012a, 2012b; Aoki et al., 2012a, 2012b; Ford and Crewther, 2016). NAA is metabolically connected with glutamate, the most abundant excitatory neurotransmitter in the human central nervous system (Pittenger et al., 2011; Mehta et al., 2013); mitochondrial energy production from glutamate is enhanced through NAA, making both viable markers for neuronal health (Moffett et al., 2007; Moffett et al., 2013). Glutamate has also been found altered in OCD and ASD (J Naaijen et al., 2015).

The relation between these metabolites and measures of brain structure has hardly been investigated in ASD or OCD. In ASD, a single study investigated thalamic volume and metabolites (Say et al., 2014); they found increased lateralization in ASD for thalamic volume and no differences in