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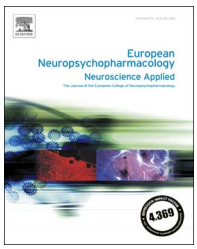

Anterior cingulate cortex glutamate and its association with striatal functioning during cognitive control

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Abstract
Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by structural, functional and neurochemical alterations of the fronto-striatal circuits and by deficits in cognitive control. In particular, ADHD has been associated with impairments in top-down fronto-striatal glutamate-signalling. However, it is unknown whether fronto-striatal glutamate is related to cognitive control dysfunction. Here we explored whether and how anterior cingulate cortex (ACC) glutamate relates to striatal BOLD-responses during cognitive control. We used proton magnetic resonance spectroscopy to evaluate glutamate-to-creatine ratios in 62 participants (probands with ADHD $n=19$, unaffected siblings $n=24$ and typical controls $n=19$, mean age=20.4). Spectra were collected from the ACC and the dorsal striatum and glutamate-to-creatine ratios were extracted. Thirty-two participants additionally took part in a functional magnetic resonance imaging (fMRI) Stroop task to investigate neural responses during cognitive control. Given small sample sizes we report all effects with $p<0.10$ along with effect sizes. ADHD subjects showed decreased glutamate-to-creatine ratios in the ACC ($F=3.81$, $p=0.059$, $\eta_p^2=0.104$; medium to large effect-size) compared with controls. Importantly, decreased ACC glutamate-to-creatine ratios were associated with increased striatal

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BOLD-responses during cognitive control ($rho = -0.41$, $p=0.019$; medium effect-size), independent of diagnosis. Increased striatal responses tended to be associated with more errors during the task and more hyperactivity/impulsivity symptoms ($rho=0.34$, $p=0.058$ and $rho=0.33$, $p=0.068$, respectively); the latter two being correlated too ($rho=0.37$, $p=0.037$), all with medium effect sizes. Our results suggest that ACC glutamate in ADHD might be associated with striatal (dys)functioning during the Stroop task, supporting the role of fronto-striatal glutamate in cognitive control.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders and is characterized by pervasive symptoms of inattention and/or hyperactivity and impulsivity (American Psychiatric Association, 2013) with prevalence rates of approximately 5% in children and adolescents (Polanczyk et al., 2007). Many patients show symptom persistence and impairment of functioning well into adulthood (Biederman and Faraone, 2005; Faraone et al., 2015).

Patients with ADHD show deficits in cognitive control, which can be defined as the ability to suppress inappropriate behaviours in favour of appropriate ones, and therefore flexibly adapting behaviour in changing situations. Cognitive control is associated with structure and functioning of the fronto-striatal circuitry (Casey et al., 2007; Durston et al., 2011; Arnsten and Rubia, 2012) and modulated by monoamine neurotransmitter systems (dopamine, noradrenaline and serotonin) shown to be involved in ADHD (e.g. Faraone et al., 2015).

Glutamate is the major excitatory neurotransmitter in the human brain. Similarly to the monoamine transmitters, glutamate affects fronto-striatal circuitry signalling (Calabresi et al., 1996; Pittenger et al., 2011) e.g. by direct glutamatergic projections from the frontal cortex to the striatum (Schwartz et al., 2012). Furthermore, the frontal cortex modulates neuronal activity in the striatum indirectly via GABAergic innervations which are activated by frontal glutamate (Carlsson et al., 1999). The fronto-striatal deficits in ADHD and the central role of glutamate signalling in these brain regions have led to increased focus on the role of glutamate in ADHD. Indeed, glutamate abnormalities in fronto-striatal regions have been confirmed for ADHD, as shown by magnetic resonance spectroscopy (MRS) studies (Naaijen et al., 2015). In adults with ADHD, low glutamate concentrations in the prefrontal cortex (PFC) have been reported when compared with typical controls (Dramsdahl et al., 2011; Maltezos et al., 2014). Results have been less consistent in the striatum, which itself is not glutamatergic but receives cortical excitatory input, with both increased and decreased levels in patients with ADHD compared with controls (Ferreira et al., 2009; Maltezos et al., 2014). In addition to neurochemical studies, candidate glutamatergic gene and gene-set studies have shown associations with ADHD (Dorval et al., 2007; Elia et al., 2012), particularly with hyperactivity/impulsivity symptoms (Naaijen et al., 2017). Only one study in healthy volunteers has investigated frontal glutamate in relation to activity in the striatum, but focused on reward anticipation (Gleich et al., 2014). Using functional magnetic resonance imaging (fMRI) in combination with magnetic resonance spectroscopy (MRS), glutamate in the anterior cingulate cortex (ACC) was found to be associated with reward anticipation BOLD responses in the ventral striatum in healthy adolescents, but not in adults (Gleich et al., 2014).

Here we aimed to explore whether and how ACC glutamate is related to striatal BOLD responses during cognitive control in a sample of participants with ADHD, unaffected siblings (brothers/sisters of participants with ADHD) and healthy controls. Unaffected siblings can be informative in the search for traits underlying the vulnerability for a disorder, providing insight into the familial risk of ADHD (Durston et al., 2004). We used MRS and an adapted version of the Stroop task (Stroop, 1935) as a cognitive control task during fMRI. In the Stroop paradigm, participants have to suppress automatic task responses in favour of less automatic responses. This task has been used in ADHD before, showing deficits in suppressing this automatic response (see for example Bush et al., 1999; Durston et al., 2011).

We predict participants with ADHD to show altered glutamate-to-creatine ratios in the ACC compared with controls. Since no MRS studies before have been performed including siblings we additionally explore the comparison with siblings. Based on previous findings in a genetic study including 900 patients with ADHD (Naaijen et al., 2017), we especially hypothesise that hyperactivity/impulsivity symptoms would be associated with glutamate-to-creatine ratios. As cognitive control deficits are common in ADHD, we expect patients to perform worse than controls on the Stroop task, and unaffected siblings to perform better on the task than patients but worse than controls. Finally, because of the top-down frontal glutamate projections to the striatum, we expect glutamate in the ACC to be associated with BOLD activity in the striatum during cognitive control, which could underlie cognitive control dysfunction in ADHD.

2. Experimental procedures

2.1. Participants

Participants ($n=62$) were part of the NeuroIMAGE II study, a follow-up study of NeuroIMAGE (von Rhein et al., 2015) and consisted of probands with ADHD ($n=19$), unaffected siblings ($n=24$) and typical controls ($n=19$) within the age range of 12-27 years. Within and across the three groups some participants were members of the same family. This family relatedness was taken into account in all

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