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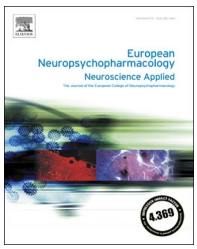

Time and psychostimulants: Opposing long-term structural effects in the adult ADHD brain. A longitudinal MR study

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Abstract
Long-term effects of psychostimulants such as methylphenidate on ADHD patients have been proved to be difficult to capture in cross-sectional studies comparing medicated and non-medicated samples and in longitudinal studies with children, with age-related maturational processes possibly confounding independent effects of medication. However, chronic psychostimulant administration at therapeutic doses has been proven to yield profound neuroadaptive changes in rodent models. Here, we present for the first time the effect of psychostimulant treatment on brain volumes in a sample of medication-naïve adult ADHD patients. We investigated grey matter volume changes in a sample of 41 medication-naïve adult ADHD patients before and after three years of psychostimulant treatment (N = 25) or no treatment (N = 16) compared to healthy adults (N = 25). We found a significant group x time interaction effect on left putamen grey matter volumes, with a decrease in left putamen volumes in the non-medicated group compared to both the medicated group and controls, and no differences

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between the medicated group and controls. Our results suggest a normalizing effect of psychostimulant treatment on the left putamen volume loss detected in non-medicated ADHD patients.

1. Introduction

Psychostimulant medication is the treatment of choice for patients diagnosed with Attention Deficit and Hyperactivity Disorder (ADHD), a typical childhood disorder characterized by inattention, impulsivity and hyperactivity (American Psychiatric Association, 2000) that prevails in around 4.4% of the adults worldwide (Kessler et al., 2006). Although functional and structural effects of psychostimulant treatment ADHD have been explored by means of cross-sectional between-group designs both in adults and children (see Rubia et al., 2014 for a review), no studies to date have directly measured the long-term effects of sustained psychostimulant treatment on adult ADHD brain structure within longitudinal study designs. Therefore, the question of whether psychostimulant medication effectively "normalizes" brain structure alterations in adult ADHD remains open.

At a cellular level, methylphenidate (MPH) has been shown to increase dopamine levels in the striatum by blocking dopamine transporters (Volkow et al., 1998), thus increasing extracellular dopamine (Volkow et al., 2001). In turn, these cellular processes have been associated with long-term ADHD symptom improvement (Rosa-Neto et al., 2005). Indeed, magnetic resonance studies seem to support striatal sensitivity to MPH and, more generally, psychostimulants. For instance, our previous neuroimaging study (Hoekzema et al., 2014) revealed decreased nucleus accumbens (Nacc) grey matter volumes in a sample of adult ADHD patients treated with psychostimulants compared to a medication-naïve ADHD sample. Moreover, a second measure after 1–2 years of MPH treatment in 10 of the patients revealed a recovery of Nacc volume abnormalities compared to controls (Hoekzema et al., 2014). Although these results seem to support the notion that psychostimulants normalize ADHD structural alterations, comparisons against non-treated ADHD patients were missing. Thus, we cannot rule out that the striatal volume recovery may have been a temporal effect.

Furthermore, other studies have identified reduced basal ganglia grey matter volumes (see Ellison-Wright et al. (2008) for a meta-analysis), and particularly putamen and caudate volumes (Soliva et al., 2010; Tremols et al., 2008; Wellington et al., 2006), in ADHD patients compared to controls, differences that have been suggested to normalize in ADHD patients treated with psychostimulants (Frodl and Skokauskas, 2012; Nakao et al., 2011). Moreover, acute doses of MPH have been proved to raise basal ganglia activity and functional connectivity to normal levels in ADHD patients (Rubia et al., 2011, 2009b). However, these conclusions have been drawn from cross-sectional between-group comparisons including stimulant-treated vs. medication-naïve ADHD patients, with no longitudinal studies targeting within-subject structural changes in the adult ADHD brain. In addition, other studies did not find significant basal ganglia volume differences associated with psychostimulant medication (Castellanos et al., 2002; Hoogman et al., 2017; Norman et al., 2016; Shaw et al., 2014).

Given these partly conflicting results and the lack of longitudinal studies on adult ADHD treatment, the aim of the present study was to test whether psychostimulant medication affects brain structure within-subjects in a sample of adult ADHD patients. For this purpose, we conducted a longitudinal magnetic resonance study, comparing structural brain images from a group of adult ADHD patients before and after 3 years of psychostimulant treatment with a group of non-pharmacologically treated ADHD patients and a group of healthy controls. If brain structural changes were to be attributed to psychostimulant treatment, we would expect significant interaction effects between session and group, thus eliminating temporal confounds that could be related to ADHD but not psychostimulant treatment. Since the basal ganglia conform a specific target for psychostimulant pharmacological action, we expected grey matter volume in the basal ganglia and, particularly, the Nacc, the putamen and the caudate, to be normalized only in the ADHD sample treated with psychostimulants.

2. Experimental procedures

2.1. Participants

This research was designed as a prospective cohort study including forty-one medication naïve adults with combined ADHD (27 men) who were asked to complete a structural MRI acquisition just after being diagnosed with ADHD (medication-naïve) and again after 3 years of either pharmacological treatment with psychostimulants (*ADHD med*, 25 participants, 16 men, 2 medicated with lysdexamphetamine, 1 with both lysdexamphetamine and MPH, and the rest with MPH) or no treatment with psychostimulants (*ADHD non-med*, 16 participants, 11 men). The two ADHD groups were compared with a sample of 25 healthy subjects (12 men) that underwent the two MRI acquisition protocols in parallel, adding up to a total of 66 participants completing a pre-post exploration. The three final groups (controls, *ADHD med*, *ADHD non-med*) were matched for age, gender and IQ (see demographics in Table 1). The ADHD patients were carefully selected by a specialized team of psychiatrists and psychologists from *the outpatient Adult ADHD Program of Hospital Universitari Vall d'Hebron* in Barcelona (Spain). All of them met the DSM-IV criteria (American Psychiatric Association, 2000) for ADHD combined subtype and were right-handed. ADHD patients in the non-medicated group were those who voluntarily decided not to

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