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Review

# Age-related change of neurochemical abnormality in attention-deficit hyperactivity disorder: A meta-analysis

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ABSTRACT

Prevalence and symptoms of attention-deficit hyperactivity disorder (ADHD) change with advancing age. However, neurochemical background of such age-related change is yet to be elucidated. We therefore conducted a meta-analysis of 16 proton magnetic resonance spectroscopy studies comprising 270 individuals with ADHD and 235 controls. Standardized mean differences were calculated and used as an effect size. Sensitivity analyses and meta-regression to explore the effect of age on neurochemical abnormality were performed. A random effects model identified a significantly higher-than-normal N-acetylaspartate (NAA) in the medial prefrontal cortex (mPFC), but no significant differences of other metabolites in that area. No significant difference in metabolite levels was demonstrated in any other region. Sensitivity analysis of children with ADHD revealed significantly higher-than-normal NAA, whereas no significant difference was found in adults with ADHD. Meta-regression revealed significant correlation between advanced age and normal levels of NAA in the mPFC, suggesting that age-dependent abnormality of NAA level in the mPFC is a potential neural basis of age-related change of symptoms of ADHD.



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## 1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is defined in the DSM-IV-TR as a disorder of age-inappropriate impulsiveness, inattention, and hyperactivity. ADHD has an estimated prevalence of 5–8% in children, persisting into adulthood in 65% of cases in the United States (Faraone et al., 2006). Disabilities associated with ADHD occur across life span, affecting academic performance, socioeconomic status and employment (reviewed in Valera et al., 2007).

A number of neuroimaging studies have consistently reported abnormal regional volume and BOLD fMRI activation in particular brain regions, including the medial prefrontal cortex (mPFC), striatum, thalamus, and cerebellum, suggesting that these brain regions are neural bases of abnormal behavior of ADHD (Nakao et al., 2011; Cortese et al., 2012). They also demonstrated significant effects of age on these abnormalities (Nakao et al., 2011; Cortese et al., 2012). These regions are thought to be related to attention, executive function, motor control, response inhibition and working memory, and disturbances in these domains are considered part of the pathophysiology of symptoms of ADHD (reviewed in Bush, 2010).

$^1$H magnetic resonance spectroscopy ($^1$H MRS) is a non-invasive neuroimaging technique for estimating specific chemical metabolite levels in vivo (Kato et al., 1998). Previous studies have used $^1$H MRS to quantify levels of glutamine/glutamate (referred to collectively as "Glx"), a marker of glutamatergic system (reviewed in Rothman et al., 2003), and N-acetylaspartate (NAA), a marker of neuronal activity (reviewed in Baslow, 2011). To uncover the neurochemical bases of ADHD, Perlov et al. (2009) conducted a meta-analysis of MRS studies published before 2007 that integrated eight studies. However, the number of $^1$H MRS studies examining ADHD has increased dramatically since Perlov et al.'s analysis (Perlov et al., 2009), yielding inconsistent results. Some studies have reported below-normal NAA levels in individuals with ADHD compared with controls, while other studies have reported above-normal (Rüsch et al., 2010; Yang et al., 2010). One potential explanation for this inconsistency is that the statistical power of each single $^1$H MRS study is relatively small. However, it should be noted that meta-analyses of structural and functional neuroimaging studies demonstrated an effect of age on abnormalities related to ADHD symptoms (Nakao et al., 2011; Cortese et al., 2012), and epidemiological studies also showed age-related change of symptoms (Faraone et al., 2006; Carrey et al., 2007). Thus, it is rationally expected that the inconsistent results of previous $^1$H MRS studies stem from discrepancies in age. To test the hypothesis that metabolite abnormality of individuals with ADHD changes according to advancing age and inconsistency of results of previous $^1$H MRS studies involving individuals with ADHD derives from this age-related change of neurochemical abnormality, we conducted a systematic review and meta-analysis of $^1$H MRS studies comparing ADHD individuals with controls.

## 2. Method

### 2.1. Data sources

$^1$H MRS studies examining metabolite measures in the brains of individuals with ADHD and controls were obtained through the digital MEDLINE, Embase and Web of Science databases. A comprehensive literature search was performed using the terms "*hyperkinetic*", "*attention deficit hyperactivity disorder*" and "*ADHD*" combined with "*magnetic resonance spectroscopy*" or "*MRS*" (Nakao et al., 2011). The titles and abstracts of the studies were examined to determine whether or not they should be included. The reference lists of the included articles were also examined to search for additional relevant studies to include.

### 2.2. Selection of studies

Studies were included in our data set if (1) they were peer-reviewed brain $^1$H MRS studies published between 1980 and Sep 2012, (2) they examined individuals with ADHD and a control group, (3) they reported sufficient data to estimate their effect sizes, (4) they recruited more than 10 individuals in one comparison to conduct analyses with sufficient power, and (5) they located VOIs in at least one region among the frontal cortex, striatum, or cerebellum. The literature search was performed without language restriction. If the study did not provide sufficient data, we emailed the corresponding author to obtain more comprehensive results. In cases where the author did not respond, we excluded the study. Two of the authors (Y.A. and A.A.) independently performed the study screening.

### 2.3. Data extraction

To perform the meta-analyses, we defined a standardized mean difference as the Cohen's d effect size statistic (Aoki et al., 2012b), calculated as the difference between the mean of the experimental group and the mean of the comparison group, divided by the pooled standard deviation.

In the current meta-analyses, the mean metabolite level in individuals with ADHD was subtracted from that in the control group in each volume of interest (VOI), divided by the pooled standard deviation of these VOIs.

### 2.4. Analysis

We grouped the data by brain region (frontal cortex, striatum, and cerebellum). Although we attempted to explore metabolite levels in the thalamus, only one study investigated metabolite levels in the thalamus (Ferreira et al., 2009), thus a meta-analysis could not be conducted for this region. In studies reporting metabolite levels in the left and right hemispheres (Jin et al., 2001; Courvoisie et al., 2004; Colla et al., 2008; Ferreira et al., 2009), we calculated the mean of the two effect sizes from both hemispheres and