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H[1]-MR-spectroscopy of cerebellum in adult attention deficit/hyperactivity disorder

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ABSTRACT

Introduction: Neurobiological research has implicated the cerebellum as one possible site of neurophysiological dysfunction in ADHD. Latest theoretical conceptualizations of the cerebellum as core site of the brain to model motor as well as cognitive behavior puts further weight to the assumption that it might play a key role in ADHD pathophysiology.
Methods: 30 medication free adult ADHD patients and 30 group matched (gender, age and education) healthy controls were investigated using the method of chemical shift imaging (CSI) of the cerebellum. The vermis, left and right cerebellar hemispheres were processed separately.
Results: We found significantly increased glutamate-glutamine (Glx) to creatine (Cre) ratios in the left cerebellar hemisphere. No other differences in measured metabolite concentrations were observed.
Discussion: To our knowledge this is the first evidence for neurochemical alterations in cerebellar neurochemistry in adult ADHD. They relate well to recent hypotheses that the cerebellum might control mental activities by internal models.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a serious mental problem which begins in childhood and may persist into adult life in a substantial subgroup of patients (Biederman and Faraone, 2005). The prevalence of ADHD in adults is estimated by nearly 4% (Kessler et al., 2006). Since the level of hyperactivity tends to decline from childhood to adulthood the ADHD symptoms in adults are less obvious for the observer (Biederman et al., 2000) but still cause significant impairments in occupational performance and social life. Adult ADHD is associated with low self esteem, higher rates of motor vehicle accidents, higher risks of substance abuse and other co-occurring psychiatric disorders compared to common population (Philipsen et al., 2009; Spencer et al., 2002). The high prevalence, the global impairment and the chronicity of this disorder led the Center for Disease Control and Prevention to identify ADHD as a serious public health problem (Spencer et al., 2002).

The DSM-IV distinguishes three subtypes of attention deficit disorder: the predominantly inattentive subtype (ADD) which is characterized by predominant impairments in attention and concentration, forgetfulness and disorganized behavior, the predominantly hyperactive-impulsive subtype (ADHD) which in contrast is characterized by a combination of hyperactivity and impulsivity, and the combined subtype with symptoms of both subtypes (Biederman et al., 2000; Hesslinger et al., 2001).

The precise etiology of ADHD is not fully understood. Most current theories focus on dysfunction in the prefrontal brain as well as in striatal and thalamic structures (i.e. fronto-striato-thalamo-frontal circuits) (Ashtari et al., 2005; Castellanos et al., 2002; Hynd et al., 1990; Semrud-Clikeman et al., 2000).

However, in structural imaging research cerebellar abnormalities are among the most consistently reported findings in ADHD. Many volumetric studies reported reduced cerebellar volumes and developmental alterations of cerebellum in ADHD children (Berquin et al., 1998; Castellanos et al., 2001, 2002; Mackie et al., 2007; Mulder et al., 2008).

Because of its dense connection to the prefrontal cortex and basal ganglia, the cerebellum is thought to play an important role in cognition including verbal working memory, implicit learning, temporal information processing as well as shift in attention and emotional regulation (Ito, 2008; Ivry et al., 2002; Schmahmann and Sherman, 1998; Schmahmann, 2004; Vaidya and Stollstorff, 2008).

Neurochemically, dopamine plays the central role in most pathogenetic models of ADHD (Biederman and Faraone, 2005). This

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assumption is based on the observation of the good efficacy of the dopaminergic and adrenergic substance methylphenidate in treating ADHD symptoms but also based on clinical and neuroimaging findings (Dougherty et al., 1999; Krause et al., 2000). In a previous study we were able to show increased glutamate signals in the anterior cingulate cortex (ACC) in adult ADHD patients (Perlov et al., 2007). The model of dopaminergic/glutamatergic interaction was developed by Carlsson and coworkers for schizophrenia but seems to be applicable also to ADHD (Perlov et al., 2008a)). To our knowledge the cerebellum of ADHD patients has not been yet investigated using the Magnet-Resonance-Spectroscopy (MRS).

The current study investigates the glutamatergic metabolism in cerebellum of adult ADHD patients using the method of H1-MRS. MRS is a unique non-invasive MRI method to detect metabolites in *vivo*. Basically MRS uses the different spin-echo signal of the protons differently connected in molecules. Due to the methodological reasons only some of several known metabolites can be detected using the different methods of MRS. The most widely established detectable metabolites in the human brain are: N-acetylaspartate (NAA) – a marker of the cell integrity; choline compounds (Cho) – an important part of cell membranes and to a lesser degree of the energy metabolism; creatine (Cre) – a marker of cell metabolism especially in muscle tissue (due to the fact that it is often regarded as a rahter constant metabolite it is generally used as a denominator for building metabolite ratios if absolute quantification is not possible); myo-inositol (mI) – an important second messenger and glutamate-glutamine (Glx) – the most important excitatory amino acid in the human brain.

Based on our earlier findings in the anterior cingulate cortex (ACC) we hypothesized to observe alterations in glutamate-glutamine signals in adult ADHD patients. In order to maximize the region of interest including the vermis and both hemispheres of the cerebellum we used the method of chemical shift imaging (CSI).

2. Methods and materials

Approval from the local ethics committee was obtained before onset of the study. The data presented here are part of a larger and ongoing project at the University Hospital of Freiburg in which we are attempting to define the cross-sectional and longitudinal neuroanatomy and neurochemistry in adult ADHD patients [Freiburg ADHD Imaging Study in Adults (FAISA)]. Previous papers from this project are already published (Perlov et al., 2007, 2008b)

2.1. Patients' assessment

Thirty patients (18 male, 12 female; aged 32.1 ± 10.1 years) were identified at the ADHD-out-patient clinic of the Department of Psychiatry and Psychotherapy of the University Hospital of Freiburg which offers diagnostic and therapeutic services for adult ADHD patients. The ADHD diagnosis was assessed by experienced senior consultant psychiatrists following a detailed psychiatric interview that integrates common psychiatric and somatic differential diagnoses and the patients' medical histories. Since ADHD is not included in the Structured Clinical Interview for DSM-Disorders part I (SCID-I), additionally, the investigator rated 18 items which correspond to the current Diagnostic and Statistical Manual for Mental Disorders (DSM-IV)-criteria for ADHD adapted for the special needs for adults as proposed by the German Medical Association (http://www.bundesaerztekammer.de). Additionally, further current criteria for the diagnosis of adult ADHD were required (onset of ADHD symptoms before age 7, impairment present in two or more settings). For the diagnosis of the combined subtype, six of nine items for inattention as well as six of nine items for hyperactivity/impulsivity were required (Hesslinger et al., 2002). All patients included met the criteria for the combined subtype. ADHD symptoms in childhood were self-rated by the short-version of the Wender Utah Rating Scale (WURS), (Ward et al., 1993); German version (Retz-Junginger et al., 2002); including 25 items on a five-point Likert-scale (not at all to severe). Severity of ADHD symptoms in adulthood was also self-rated on a three-point Likert-scale (not at all to severe) corresponding to the diagnostic criteria of DSM-IV by the ADHD-Checklist (ADHD-CL, (Rosler et al., 2004))(Bach-Y-Rita et al., 1971).

Patients with co morbid current major depressive disorder, borderline personality disorder and substance abuse/dependency as well as neurological brain diseases, learning disability, or any other medical diagnoses that might affect the brain metabolism (like e.g. liver or kidney failure) were excluded. Comorbid Axis-I-disorders were assessed by the SCID-I, and comorbid Axis-II-disorders were excluded by the SCID-II (First, 1997). In order to obtain a possibly homogenous study group and to avoid an overlap to psychogeriatric problems we excluded patients with an age over 55 years. All subjects were medication free (for at least six months) at the time of the scan, 29 patients have never been treated with stimulants or atomoxetine. Patients were included after giving informed written consent to participate on a voluntary basis.

Thirty control subjects (15 male, 15 female; aged 29.9 ± 7.6 years) were recruited. Care was taken to match control subjects with respect to age, sex and years of school education. Healthy controls were assessed by two experienced psychiatrists with semi-structured interviews to exclude ADHD and other psychiatric disorders in the control group. Exclusion criteria were identical for the patient and control group. In addition, volunteers with a positive family history of any psychiatric disorder were excluded from participation.

2.2. Neuroimaging

2.2.1. Data acquisition

The Magnet Resonance Imaging (MRI) and proton magnetic resonance spectroscopy data were obtained at the Department of Medical Physics at the University Clinic of Freiburg on a 1.5 T whole-body system (Magnetom Sonata, Siemens Erlangen, Germany) using a standard quadrature head coil. For analysis of voxel localization a high resolution anatomic 3D data set was acquired using an MPRAGE (Magnetization Prepared Rapid Acquisition Gradient-Echo Imaging) sequence with the following parameters: TR (Repetition Time) = 1670 ms, TE (Echo Time) = 3.9 ms, TI (Inversion Time) = 1100 ms, flip angle = 15°, matrix 256 × 256 pixel^2, FOV (Field of View) = 256 × 256 mm^2.

A rectangular CSI slice (dimension 60 × 110 × 15 mm) was placed to cover the vermis and most parts of cerebellum hemispheres. Precisely, the slice was oriented along the length axis of the vermis; the middle of the CSI slice was located in the middle of the vermis (see Fig. 1). This placement algorithm ensured a highly reliable placement of spectroscopic slices.

We used a standard CSI-PRESS (point-resolved spectroscopy) with the following parameters: TE = 30 ms, TR = 1500 ms. Four averages were acquired with 16 × 16 voxels CSI matrix and a VOI (Volume of Interest) of 60 × 110 × 15 mm. The data acquisition required about 30 min in total.

2.3. Spectroscopic analysis

The previously published LC (Linear Combination)-algorithm (Provencher, 1993) in combination with the CSI-Lcmodel-Tool (Ko et al., 2003) and CSI-Lcmodel-read-Tool developed at our MR-imaging centre were used for analysis. These tools were also employed for mapping of the spectroscopic results onto high