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Chemosensory processing in children with attention-deficit/hyperactivity disorder

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ABSTRACT

Background: In attention-deficit/hyperactivity disorder (ADHD) not only deficits in dopamine-related cognitive functioning have been found but also a lower dopamine-sensitive olfactory threshold. The aim of the present study was to proof that only olfactory but not trigeminal sensitivity is increased in ADHD. Structural magnetic resonance imaging (MRI) was used to show increased olfactory bulb (OB) volume- a structure which is strongly shaped by olfactory performance through the mechanism of neuroplasticity (e.g. synaptogenesis). To elucidate whether cortical mechanisms are involved in altered olfaction in ADHD, functional MRI (fMRI) was introduced.
Methods: A total of 18 boys with ADHD and 17 healthy controls (aged 7–12) were included in the study. Olfactory as well as trigeminal detection thresholds were examined. OB sizes were measured by means of structural MRI and an analysis of effective functional (fMRI) coupling of primary olfactory cortex was conducted. The frontal piriform cortex (fPIR) was chosen as seed region because of its importance in processing both trigeminal and olfactory stimuli as well as having profound influence on inner OB-signaling.
Results: Increased olfactory sensitivity as well as an increase in OB volume was found in ADHD. There were no group differences in sensitivity towards a trigeminal stimulus. Compared to healthy controls, the fPIR in ADHD was more positively coupled with structures belonging to the salience network during olfactory and, to a lesser extent, during trigeminal stimulation.
Conclusions: Olfactory functioning is superior in subjects with ADHD. The observed increase in OB volume may relate to higher olfactory sensitivity in terms of neuroplasticity. During the processing of chemosensory stimuli, the primary olfactory cortex in ADHD is differently coupled to higher cortical structures which might indicate an altered top-down influence on OB structure and function.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a world-wide prevalence of 5–7% (Willcutt, 2012). Alterations in dopaminergic pathways are thought to be involved in the underlying pathology, which not only leads to symptoms of inattention and/or hyperactivity (American Psychiatric Association, 2000) but possibly also to alterations in

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olfactory processing. It was shown that children with ADHD show higher sensitivity towards olfactory stimuli when compared to both healthy controls (HC) and children with ADHD being treated with methylphenidate (MPH) (Romanos et al., 2008). MPH is regarded as the first-line treatment in ADHD and blocks dopamine reuptake in the mesolimbic system and the prefrontal cortex (PFC) (Heal et al., 2009; Wilens, 2008).

The orbitofrontal cortex (OFC), amygdala, hippocampus, and pirifom cortex (PIR) are core structures of the human olfactory system (Benarroch, 2010; Zald and Pardo, 2000). Contrary to all other sensory systems (e.g. trigeminal or visual) olfactory processing does not rely on thalamic gating: The olfactory bulb (OB) is the critical relay in stimulus processing (Kay and Sherman, 2007) and the olfactory threshold is linked to OB size (Buschhüter et al., 2008). The trigeminal system is also involved in the perception of chemosensory stimuli with its free nerve endings extending into the nasal mucosa. It mediates sensations like burning, stinging or cooling via the brainstem and thalamus before reaching the somatosensory/insular cortex and converging with the olfactory system (Hummel and Livermore, 2002). There is strong evidence for lower OB volume being accompanied by reduced olfactory sensitivity in patients suffering from a loss of nigrostriatal dopaminergic neurons (e.g. Parkinson) (Brodoehl et al., 2012; Wang et al., 2011). It remains unclear, however, why ADHD is accompanied with higher olfactory sensitivity.

It was proposed that striatal dopaminergic dysregulation may cause a decrease in inner-bulb-mediated inhibition of neuronal signals (Romanos et al., 2008; Schecklmann et al., 2011a,b). They assume an indirect mechanism of decreased neurogenesis of inhibitory dopaminergic interneurons. In addition, there is also direct cortical influence on inner-bulb circuits. Animal studies have shown that so-called centrifugal structures (PIR and anterior olfactory nucleus), which are dopamine sensitive in part (Fallon and Moore, 1978; Ikemoto, 2007), exert tonic inhibitory influence on the OB by dampening neuronal signals (Boyd et al., 2012). Alterations in the cortical dopamine system might lead to a cascade of decreased centrifugal downscaling on the OB transmission, resulting in higher excitation and increased olfactory sensitivity. By means of neuroplastic processes this may cause increased OB volume.

To test the hypothesis that children suffering from ADHD show a higher olfactory sensitivity, detection thresholds and OB volumes were measured. By introducing a trigeminal stimulus it was intended to show that higher sensitivity in ADHD is restricted to the olfactory system and not due to unspecific hypersensitivity (Ghanizadeh, 2011). To test the hypothesis of alterations in cortical olfactory circuits exerting direct centrifugal influence on OB, explorative functional magnetic resonance imaging (fMRI) was conducted to evaluate the effective connectivity of PIR during intensity-controlled chemosensory stimulus processing.

2. Methods and materials

2.1. Participants

18 patients with ADHD and 17 healthy controls (HC) aging from 7.9 to 12.8 years were examined. All participants were diagnosed by the Kiddie-SADS-PL, a semi-structured diagnostic interview (Kaufman et al., 1997) according to the DSM-IV classification system. Eleven patients fulfilled ADHD-criteria for the predominantly hyperactive subtype and seven patients fulfilled criteria for the inattentive subtype. Eight patients had a co-morbid oppositional defiant disorder (three of the inattentive and five of the hyperactive subtype). Participants were also screened for psychopathological symptoms by parental ratings based on the Child Behavior Checklist (CBCL) (Achenbach, 1991). Exclusion criterion for HC was a T-value of 60 in any of the syndrome- and summed scales. Intellectual ability was assessed with the German version of the Culture Fair Intelligence Test (CFT-20) (Weiß, 2006) and the CFT-1 (Weiß and Osterland, 2013). Exclusion criterion was an IQ under 85. Most participants were in prepubescent phase, two patients and two HC were in early puberty as measured with the German version of the Pubertal Development Scale (Watzlawik, 2009). There was no statistical significant group difference in age but a marginally significant difference in IQ. For details see Table 1. Exclusion criteria for all participants were acute or chronic disease of the respiratory tract or usual MRI exclusion criteria. Fifteen patients were MPH-naïve. Three patients had received MPH at least one year ago and for a period not longer than six months. All families gave informed consent. The study was approved by the Ethics Committee of the Medical Faculty of the University of Kiel.

2.2. Chemosensory threshold

Individual olfactory as well as trigeminal detection thresholds were assessed using the "two-alternative-staircase-detection"-method (Doty et al., 1995). Two serial dilutions were prepared: one with the olfactory stimulus phenylethyl alcohol (PEA, rose-like) and one with the trigeminal stimulus L-menthol (peppermint-like). The chemical preparation and testing procedure were conducted according to Pause et al. (2001). The Substances were diluted 1:2 in propylene glycol (v/v). This stock solution was further diluted in 16 half-decimal logarithmic steps [lowest concentration 1:63000000 (v/v)]. Finally, each of the sixteen brown glass bottles contained 6.5 ml chemical solution. Both tests on olfactory as well as trigeminal thresholds were conducted in the same session separated by a half an hour. The order of the presentation was counterbalanced across the groups. Participants were instructed to decide which of the two bottles smelled more intensive (one containing the chemosensory stimulus and one containing only the solvent). A higher threshold score (in terms of dilution step) corresponded to higher sensitivity. To avoid habituation, there was an intertrial interval (ITI) of 20 s. The procedure took place in an air-conditioned room at a constant 19 °C. Participants were not allowed to eat a half an hour before chemosensory testing and were instructed to avoid spicy foods like garlic prior to testing that day.

2.3. Volumetry of OB

The MRI measurements were performed with a 3 T Philips Intera Achieva (Best, The Netherlands) using a 32-channel head coil. A T2-weighted turbo-spin-echo-sequence (TR = 3000 m, TE = 80 m, 220 mm (FH) × 175 mm (RL), slice thickness 2 mm, 30 coronal slices, in plane resolution 0.43 × 0.43 mm^2, 5:42 scan time) was applied. A feature of the DRIVE (driven equilibrium radio-frequency reset pulse)-sequence is the relatively short acquisition time with high resolution. Data was analyzed independently by two experimenters who were blind to the groups (final results as mean value of both). Inter-rater reliability for the right OB was r = .926 and for the left r = .939. Manual contouring of the left and right OB in each coronal slice was performed using the ITK-Snap software (www.itksnap.org). A sudden change in diameter marked the beginning of the olfactory tract and therefore the proximal end of the OB (Abolmaali et al., 2002). Individual OB volumes were also calculated as a percentage of the whole brain volume which was defined as the sum of the grey and white matter (SPM Toolbox Easy Volume, http://www.sbirc.ed.ac.uk/LCL/LCL_M1.html).