Full length article

Functional MRI in prenatally opioid-exposed children during a working memory-selective attention task

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ARTICLE INFO

Keywords: Brain Executive function fMRI Opioid Prenatal drug exposure

ABSTRACT

Background: Opioid induced cerebral changes may contribute to neuropsychological difficulties, like attention problems, frequently reported in prenatally opioid-exposed children. Reduced regional brain volumes have been shown after prenatal opioid exposure, but no study to date has explored the possible impact of prenatal opioids on brain activation patterns.

Materials and methods: A hospital-based sample of prenatally opioid-exposed school-aged children (n = 11) and unexposed controls (n = 12) underwent functional magnetic resonance imaging (fMRI) during a combined working memory-selective attention task. Within-group- and between-group analyses of blood-oxygen-level-dependent (BOLD) activation were performed using the SPM12 software package and group differences in task performance were analyzed using Cox proportional hazards modeling.

Results: Overall, similar patterns of task related parietal and prefrontal BOLD activations were found in both groups. The opioid-exposed group showed impaired task performance, and during the most cognitive demanding versions of the working memory-selective attention task, increased activation in prefrontal cortical areas was found in the opioid-exposed group compared to controls.

Conclusion: Our findings suggest that prenatal opioids affect later brain function, visible through changes in BOLD activation patterns. However, results should be considered preliminary until replicated in larger samples better suited to control for potential confounding factors.

1. Introduction

Recent studies on the prevalence of neonatal abstinence syndrome (NAS), a common consequence of prenatal opioid exposure, indicate a widespread increase in the number of children exposed to opioids in utero (Davies et al., 2016; Patrick et al., 2012). Consequences of prenatal opioid exposure beyond NAS are still debated (Mactier et al., 2014; Jones et al., 2014) and the research base is scarce, especially when it comes to possible long-term effects (Behnke and Smith, 2013). A web of interconnected risk factors complicates the interpretation of repeatedly reported suboptimal neurocognitive outcomes in prenatally opioid-exposed children (Hunt et al., 2008; Nygaard et al., 2015; Ornoy et al., 2001).

Both cognitive and behavioral effects of prenatal opioid exposure have been demonstrated in animal models (Chen et al., 2015; Wang and Han, 2009). Possible mechanisms underlying altered brain function, as suggested by cell culture and animal studies, include increased apoptosis of neurons and glia cells (Hu et al., 2002), altered neuronal differentiation (Dholakiya et al., 2016), decreased neurogenesis (Wu et al., 2014), and altered myelination (Vestal-Laborde et al., 2014). Both opioid receptors and opioid ligands are expressed in the fetal brain, and there is growing evidence of the endogenous opioid system as a regulator of neurogenesis, with inhibitory effects of opioids (Sargeant et al., 2008). Opioids can affect several neurotransmitters in the
Functions have been demonstrated in children with prenatal opioid exposure. Executive dysfunction is regarded as a key factor in the complex neuropsychological impairments observed in prenatally exposed children. Results from a recent longitudinal brain imaging study suggested that several early life factors have an impact on the brain and cognition for the entire life course (Walhovd et al., 2016). Neuroimaging studies have made important contributions to our understanding of how prenatal drug exposures can affect normal brain development, and evidence of brain structures and patterns of functional activation being altered in exposed children is accumulating (Rousotte et al., 2010; Derauf et al., 2009). However, very few studies have investigated possible brain alterations after prenatal opioid exposure. Structural brain changes in opioid-exposed children have been reported in a few small-scale samples, including one report on ten children born to mothers with histories of heroin abuse during pregnancy that showed subtle alterations in structures involved in frontal-striatal circuitry (Walhovd et al., 2007). Confounding factors difficult to account for in such small samples preclude firm conclusions, but some of the changes could still be linked to attentional difficulties in the exposed group (Walhovd et al., 2007). To date, no studies have examined possible effects of prenatal opioid exposure on brain activation patterns.

The aim of the present study was to investigate brain activation patterns in school-aged children with prenatal opioid exposure using functional magnetic resonance imaging (fMRI). In children with prenatal drug exposure, very high rates of attention-deficit/hyperactivity disorder (ADHD) have been reported, regardless of the type of drug exposure (Elgen et al., 2007), and increased risk of attention problems and ADHD has been widely reported in prenatally opioid-exposed groups (Ornoy et al., 2001; Ornoy et al., 2016; Sundelin Wahlsten and Sarman, 2013; Nygaard et al., 2016). Associations between attention problems and prenatal opioid exposure have also been found in studies trying to account for the impact of genetic vulnerabilities and postnatal environmental influences (Ornoy et al., 2001; Ornoy et al., 2016). Executive dysfunction is regarded as a key factor in the complex neuropsychology of ADHD (Willcutt et al., 2005), and impaired executive functions have been demonstrated in children with prenatal opioid exposure (Konijnem and Melinder, 2015). In the present study, a task combining working memory and selective attention was chosen. These are executive functions crucial for normal cognitive function, and most likely implicated in the neurodevelopmental impairments reported in prenatally opioid-exposed children. We hypothesized that prenatally opioid-exposed children would show impaired task performance with corresponding differences in blood-oxygen-level-dependent (BOLD) activation as compared with unexposed controls.

2. Materials and methods

2.1. Participants

The opioid-exposed group was derived from a larger group of children with prenatal drug exposure referred to the pediatric department at Haukeland University Hospital in Bergen, Norway, between 1997 and 2012. A total of 70 children, aged 10–14 years, identified as prenatally drug-exposed, were invited to undergo an MRI examination, as previously described (Sirnes et al., 2017). Children were identified as prenatally drug-exposed if they had been admitted to the neonatal department due to maternal drug use, in most cases treated for withdrawal symptoms, or if they were referred to a pediatric neurologist at a later age with a medical history of prenatal drug exposure and symptoms of attention and/or behavioral problems. Among the initial 43 children who agreed to participate, 20 children were exposed to opioids, either from heroin abuse or from opioids given as part of opioid maintenance treatment (OMT), and were therefore included in the present study. Information regarding exposure was based on history, but given the presence of heavy substance abuse, detailed information about the frequency or amounts of opioids and the type of other drugs used during pregnancy was not readily available. However, children were only included in the study if prenatal opioid exposure could be confirmed, either in medical records (obstetric or pediatric) or by information from their mother.

For each drug-exposed child included in the study, the first child of the same gender born at Haukeland University Hospital on the same date, with a birth weight above the 10th percentile (≥3000 g), was invited to serve as a matched control. If they declined, the next child born on the same date (or the nearest date) was contacted. For the 20 opioid-exposed children included, only 17 controls were successfully recruited, hence 20 exposed children and 17 control children underwent MRI-scanning. Eight children (five opioid-exposed and three controls) were excluded from analyses due to abortion of the fMRI protocol by the child. In addition, scans from two opioid-exposed children and two controls had to be excluded due to head movement artifacts (>5 mm translation in any of the four experimental conditions) and scans from two opioid-exposed children were excluded due to dental braces distorting the images. Thus, the final sample for this study consisted of 11 prenatally opioid-exposed children and 12 unexposed controls. Response logging failed for one participant (unexposed control) during fMRI. As scanner observational data revealed appropriate task performance, data from this participant was still included in the analyses of the BOLD fMRI data, while analyses of task performance were run with n = 11 + 12.

All structural images were inspected by an experienced pediatric neuroradiologist. No major structural abnormalities were found. Somatic growth parameters (height, weight, and head circumference) were obtained prior to MRI scanning. Background and clinical characteristics were obtained from medical records and/or questionnaires filled in by parents or foster parents. The prevalence of ADHD was determined by medical record review. Reports from earlier follow-up of the 11 children in the opioid-exposed group showed a mean intelligence quotient (IQ) score of 110.6 (SD: 13.9, median: 111, range: 82–130), as assessed by the Wechsler Intelligence Scale for Children, fourth edition and Wechsler Preschool and Primary Scale of Intelligence-R.

The project was approved by the Regional Ethics Committee for Medical Research in Western Norway (REK-Vest 2010/3301). Written consent was obtained from parents or foster parents and Child Welfare Services, as appropriate, for all participants. Written consent was also obtained from all children above the age of 12 years, and verbal consent from participants younger than 12 years.

2.2. fMRI task

A working memory-selective attention task combining the n-back task and the Stroop color word task was used (Braver et al., 1997; Stroop, 1935). The protocol of the present study has been used earlier by our group in a study on extremely preterm children. See ref. (Griffiths et al., 2013) for the complete description of the procedure. In short, the words RED, BLUE, GREEN, and YELLOW, each written in the three incongruent colors (e.g. red written in blue, green, or yellow), were presented sequentially through LCD goggles mounted on the head coil. The participants were asked to press a response key when either the word or the ink color of the word matched the one presented either 1- or 2-stimuli backwards in the presentation sequence, yielding four different experimental conditions (word 1-back, word 2-back, color 1-back, color 2-back). These four experimental conditions were presented in a pseudorandom order to avoid any order effects. A block design with alternating ON and OFF blocks was used, with four ON blocks and four OFF blocks in each of the four conditions. In each ON block, three to five target stimuli were randomly presented within a sequence of 16 stimuli in total, each presented for 2250 ms. All participants were introduced to the procedure through a short computer program test.
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