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Neural correlates of executive attention in adults born very preterm

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ABSTRACT

Very preterm birth is associated with an increased prevalence of attention problems and may especially impair executive attention, i.e., top-down control of attentional selection in situations where distracting information interferes with the processing of task-relevant stimuli. While there are initial findings linking structural brain alterations in preterm-born individuals with attention problems, the functional basis of these problems are not well understood. The present study used an fMRI adaptation of the Attentional Network Test to examine the neural correlates of executive attention in a large sample of N = 86 adults born very preterm and/or with very low birth weight (VP/VLBW), and N = 100 term-born controls. Executive attention was measured by comparing task behavior and brain activations associated with the processing of incongruent vs. congruent arrow flanker stimuli. Consistent with subtle impairments of executive attention, the VP/VLBW group showed lower accuracy and a tendency for increased response times during the processing of incongruent stimuli. Both groups showed similar activation patters, especially within expected fronto-cingulo-parietal areas, but no significant between-group differences. Our results argue for a maintained attention-relevant network organization in high-functioning preterm born adults in spite of subtle deficits in executive attention. Gestational age and neonatal treatment variables showed associations with task behavior, and brain activation in the dorsal ACC and lateral occipital areas, suggesting that the degree of prematurity (and related neonatal complications) has subtle modulatory influences on executive attention processing.

Abbreviations: ACC, anterior cingulate cortex; ANT, Attentional Network Test; BLS, Bavarian Longitudinal Study; BW, birth weight; CSF, cerebrospinal fluid; DLPFC, dorsolateral prefrontal cortex; DNTI, duration of neonatal intensive treatment; EHI, Edinburgh Handedness Inventory; ELBW, extremely low birth weight; EP, extremely preterm; fMRI, functional magnetic resonance imaging; FWE, familywise error; GA, gestational age; GM, gray matter; ICV, intracranial volume; IVH, intraventricular hemorrhage; INTI, intensity of neonatal intensive treatment; PFC, prefrontal cortex; VLBW, very low birth weight; VP, very preterm; WM, white matter.

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1. Introduction

Attentional problems are among the most consistently reported cognitive impairments related to prematurity (Aarnoudse-Moens et al., 2009; Anderson, 2014; Bhutta et al., 2002; Hack et al., 2009; Jaekel et al., 2013b; Mulder et al., 2009; Wilson-Ching et al., 2013), representing a hallmark feature of a "preterm behavioral phenotype" (Johnson and Marlow, 2011). This is supported by many behavioral studies that assess specific attentional functions in children (Anderson et al., 2011; Geldof et al., 2013), adolescents (Luu et al., 2011; Wilson-Ching et al., 2013) or adults (Eryigit-Madzwamuse et al., 2015; Nosarti et al., 2007; Solsnes et al., 2014) who were born very (VP, <32 weeks gestation) or extremely preterm (EP, <28 weeks gestation), or had a very (VLBW, <1500 g) or extremely low (ELBW, <1000 g) birth weight. They show significant impairments in task domains such as selective attention, sustained attention or shifting attention (Aarnoudse-Moens et al., 2009; Mulder et al., 2009), which afford increased "top-down" (=executive) control of attentional resources. Recent studies using the *Attentional Network Test* (ANT: Fan et al., 2002; Geldof et al., 2013; Pizzo et al., 2010) indicated that preterm children were selectively impaired in the executive attention component of the task (which assesses the ability to focus attention on a task-relevant central arrow stimulus despite interference by task-irrelevant incongruent vs. congruent flanker stimuli), while they showed intact alerting and orienting (Geldof et al., 2013; Pizzo et al., 2010), suggesting that the brain networks subserving executive attention are especially vulnerable to the detrimental effects of preterm birth.

Yet, although various studies show prematurity-related deficits in tasks measuring executive attention via similar interference processing tasks (e.g., Stroop and Flanker tasks: de Kieviet et al., 2014; Luu et al., 2011; Solsnes et al., 2014), other studies do not find significant differences (Aarnoudse-Moens et al., 2012; Elgen et al., 2004) or detect impairments only in younger children, suggesting the possibility of a developmental "catch-up" (e.g., Ritter et al., 2013). The latter observation points to the possibility that preterm-born individuals develop compensatory brain mechanisms to cope with existing functional deficits secondary to neonatal brain injury or aberrant brain development, e.g., by stronger recruitment of prototypical task related areas, or by recruiting alternative processing pathways (e.g., Nosarti et al., 2006; Peterson et al., 2002). While functional neuroimaging studies can help to test these assumptions, relevant evidence from preterm-born populations is limited, and shows either no differences (de Kieviet et al., 2014) or reduced activation of task-related brain networks (Griffiths et al., 2013) in preterm-born children. Complementary studies in preterm-born adults are not yet available.

1.1. Study aims

The present study investigated the neural correlates of executive attention (as measured by contrasting brain responses during the processing of incongruent versus congruent flanker stimuli of an ANT fMRI paradigm) in VP/VLBW and term-born controls at age 26, with the following aims. *First*, group comparisons examined whether the location and level of task-induced brain activations in VP/VLBW adults differed significantly from controls. In line with previous theoretical accounts (e.g., Just and Varma, 2007), it was expected that adults born preterm would compensate prematurity-related brain dysfunctions by an over-recruitment of task-relevant areas, which include the dorsal anterior cingulate cortex (ACC)/presupplementary motor area and lateral prefrontal cortex (PFC), as well as lateral parietal areas (de Kieviet et al., 2014; Fan et al., 2005; Neufang et al., 2011). *Second*, to explore whether VP/VLBW behavioral performance and activation patterns were influenced by the degree of immaturity at birth or neonatal risk factors (e.g., Kalpakidou et al., 2012; Narberhaus et al., 2009), we examined whether they were predicted by neonatal variables which are known risk factors for poor neurological outcome (e.g., Aanes et al., 2015): Gestational age (GA), birth weight (BW), duration of ventilation, and duration of neonatal intensive care.

2. Methods

This fMRI study was conducted as a part of the prospective Bavarian Longitudinal Study (BLS), a geographically defined whole-population sample of VP/VLBW and term-born individuals, who were followed from birth into early adulthood (Riegel et al., 1995; Wolke and Meyer, 1999). To examine their developmental status, they were repeatedly assessed with neurological and psychological test batteries, and parental interviews, during childhood, adolescence, and, most recently, at 26 years of age, by specially trained psychologists. Following the behavioral assessments in adulthood, eligible participants were invited for an additional MRI examination (including the ANT paradigm) on a separate occasion. For each participant, a careful screening for MR-related contraindications (e.g., severe claustrophobia, pregnancy, electrical or ferromagnetic implants) was conducted.

MRI examinations were conducted at two sites: The Department of Neuroradiology of the Klinikum Rechts der Isar, Technische Universität München, and the Department of Radiology of the University Hospital Bonn. All travel expenses and attendance were reimbursed. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and approved by the local Institutional Review Boards of both hospitals. All participants gave written informed consent.

2.1. Participants

2.1.1. VP/VLBW group

VP/VLBW infants were recruited from the whole population of at-risk infants born alive in Southern Bavaria between January 1985 and March 1986 who required admission to one of the 17 children's hospitals within the first 10 days after birth ($N = 7505$; 10.6% of all live births). Of this initial cohort, 682 children were born VP/VLBW (GA < 32 weeks, and/or BW < 1500 g). 172 died during initial hospitalization and 12 died between discharge and 26 year assessments. Seven parents did not give consent to participate, while 43 parents and their children were non-German speakers and excluded as cognitive assessments could not be administered. No contact information was available for 37 VP/VLBW adults. Of the eligible 411 VP/VLBW survivors, 260 (63.3%) participated in psychological assessments at 26 years, with 104 (25.3%) undergoing the additional MRI examination. For four of these participants, ANT imaging data were not available, one was excluded due to severe image artifacts, two due to either deviant Executive Network Scores (see Section 2.4) or high error/omission rates (both: >3SD from mean), and six because of excessive scan-to-scan movements (>2 mm in any direction). A further five cases where excluded due to unavailable IQ data at 26 years. In total, the present analysis included 86 VP/VLBW.

2.1.2. Term-born controls

A comparison sample of term-born born infants (GA > 36 weeks) was recruited from normal postnatal wards in the same obstetric hospitals. Of the initial 916 control children, 350 were randomly selected as term controls within the stratification variables sex and family socioeconomic status (SES) to be comparable with the VP/VLBW cohort at age 6 years 3 months. Of these, 308 were eligible for 26 year follow-up assessments, with 229 (74.4%) participating in the psychological assessments, and 110 (35.6%) undergoing the additional MRI examination. For two of these participants, ANT imaging data were not available, one was excluded because of severe image artifacts, two due to high error/omission rates (>3 SD above mean), and two because of excessive scan-to-scan movements (>2 mm in any direction). A further three