NeuroImage: Clinical 8 (2015) 594–605

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Parietal dysfunction during number processing in children with fetal alcohol spectrum disorders

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ARTICLE INFO

Article history:
Received 1 September 2014
Received in revised form 25 March 2015
Accepted 26 March 2015
Available online 1 April 2015

Keywords:
fMRI
Fetal alcohol spectrum disorders
Fetal alcohol syndrome
Prenatal alcohol exposure
Number processing
Magnitude comparison
Parietal

ABSTRACT

Number processing deficits are frequently seen in children prenatally exposed to alcohol. Although the parietal lobe, which is known to mediate several key aspects of number processing, has been shown to be structurally impaired in fetal alcohol spectrum disorders (FASD), effects on functional activity in this region during number processing have not previously been investigated. This fMRI study of 49 children examined differences in activation associated with prenatal alcohol exposure in five key parietal regions involved in number processing, using tasks involving simple addition and magnitude comparison. Despite generally similar behavioral performance, in both tasks greater prenatal alcohol exposure was related to less activation in an anterior section of the right horizontal intraparietal sulcus known to mediate mental representation and manipulation of quantity. Children with fetal alcohol syndrome and partial fetal alcohol syndrome appeared to compensate for this deficit by increased activation of the angular gyrus during the magnitude comparison task.

1. Introduction

Prenatal alcohol exposure causes impairment in brain structure and function, leading to cognitive and behavioral deficits that range in severity (Archibald et al., 2001; Sowell et al., 2001; Riley and McGee, 2005; Astley et al., 2009). Fetal alcohol syndrome (FAS), the most severe of the fetal alcohol spectrum disorders (FASD), is characterized by distinctive craniofacial dysmorphology (short palpebral fissures, thin vermilion, flat philtrum), small head circumference and pre- and/or postnatal growth retardation (Hoyme et al., 2005). The craniofacial dysmorphology is also seen in partial FAS (PFAS), together with either small head circumference, retarded growth, or neurobehavioral deficits. Heavily exposed (HE) individuals lacking the distinctive dysmorphology are diagnosed with alcohol-related neurodevelopmental disorder (ARND) if they exhibit cognitive and/or behavioral impairment (Stratton et al., 1996).

Prenatal alcohol exposure is associated with a broad range of cognitive deficits, including low IQ (Streissguth et al., 1990; Jacobson et al., 2004), poor attention and executive function (Kodituwakku et al., 1995; Coles et al., 1997; Mattson et al., 1999; Burden et al., 2005a), and slower cognitive processing speed (Streissguth et al., 1990; Jacobson et al., 1993; Jacobson et al., 1994; Coles et al., 2002). Among the cognitive deficits seen in relation to prenatal alcohol exposure, arithmetic is especially sensitive, and mathematical deficits are seen even after controling for IQ (Coles et al., 1991; Streissguth et al., 1990; Streissguth et al., 1994; Chiodo et al., 2004; Jacobson et al., 2004; Burden et al., 2005b), and impaired numerosity is already seen in infants with FAS (S. Jacobson et al., 2011a). When academic achievement tests are administered to exposed individuals, arithmetic is consistently more impaired than reading or spelling (Streissguth et al., 1991; Goldschmidt et al., 1996; Kerns et al., 1997; Howell et al., 2006).

Although the parietal lobe has been known to be involved in number processing since the beginning of the 20th century (Henschen, 1919), fMRI has provided a more extensive understanding of the neuroanatomy of this domain of processing. Based on brain lesion and neuroimaging findings, Dehaene and associates (Dehaene, 1992; Dehaene and Cohen, 1996) have proposed a triple-code model of number processing that incorporates the three different systems of representation that may be used in number processing tasks: the quantity system, the verbal

Abbreviations: AA, absolute alcohol; ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; ARND, alcohol-related neurodevelopmental disorder; DD, developmental dyscalculia; EA, exact addition; EA_CTL, control block in the exact addition task; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorders; HE, heavily exposed; IPS, intraparietal sulcus; LSD, least-squares difference; PFAS, partial fetal alcohol syndrome; PJ, proximity judgment; PJ_CTL, control block in the proximity judgment task; PSPL, posterior superior parietal lobule; ROI, region of interest; TS, Turner syndrome; UCT, University of Cape Town; VBM, voxel-based morphometry; WISC-III, Wechsler Intelligence Scale for Children, Third Edition

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http://dx.doi.org/10.1016/j.nicl.2015.03.023

system and the visual system. In addition, they have posited a core quantity system—a nonverbal abstract representation of numerical quantity, which has been localized bilaterally in the anterior portion of the horizontal segments of the intraparietal sulcus (IPS). This area is hypothesized to support number processing irrespective of the notation used; that is, whether represented symbolically as Arabic numbers or sequences of words or analogically by numbers of dots. The verbal processing of numbers is posited to be based on the left angular gyrus (close to the language areas), while the bilateral posterior superior parietal lobules (PSPLs) are hypothesized to be involved in spatial and non-spatial attentional processes contributing to the visual processing of numbers. Rivera et al. (2005) found age-related increases in activation of the anterior IPS during number processing between school age and early adulthood, which they attributed to the development of increasing functional specialization of this region as symbolic number processing becomes increasingly automatic. Results from a meta-analysis of studies comparing number processing in children vs. adults generally support Dehaene's model but suggest that the localization of parietal activations is more notation-specific in children and that right IPS activations in non-symbolic magnitude comparison are slightly more anterior than those observed in adults (Kaufmann et al., 2011).

Data from behavioral studies that we have conducted in two different cohorts suggest that a specific deficit in the ability to represent and manipulate quantity may play a critical role in the poor arithmetic performance seen in FASD (J. Jacobson et al., 2011). A 224-item, 7-subtest, computer-based number processing test that we developed in collaboration with S. Dehaene, was administered to 262 adolescents from the Detroit Longitudinal Prenatal Alcohol Exposure Cohort. A factor analysis of the seven subtests yielded two factors, one reflecting exact and approximate calculation ("Calculation"). The other factor, on which number comparison and proximity judgment loaded most strongly, reflected the ability to represent and manipulate quantity ("magnitude comparison"), corresponding to Dehaene's core quantity system. In a path analytic model, the relation of prenatal alcohol exposure to calculation was fully mediated by its effects on magnitude comparison, suggesting that magnitude comparison is a core deficit involved in the poor arithmetic performance seen in these children. These findings were subsequently confirmed in a sample of school-age children in Cape Town, South Africa (S. Jacobson et al., 2011a). In the Detroit cohort, attention-deficit/hyperactivity disorder (ADHD) was related to poorer performance on all seven number processing subtests, but, by contrast to the pattern seen in the alcohol-exposed children, the associations were markedly stronger with calculation than magnitude comparison. Moreover, IQ significantly mediated the effect of ADHD on calculation, suggesting that the effects of ADHD on aspects of calculation not specific to the representation of number, such as attention and executive function, mediate the poorer number processing seen in that disorder.

This behavioral evidence linking prenatal alcohol exposure to impairment in the core quantity system is consistent with evidence from MRI studies reporting alcohol-related structural impairment in the parietal region, including disproportionate size reductions in the parietal lobe (Archibald et al., 2001; Chen et al., 2012). A high resolution structural MRI, surface-based image analysis indicated that the brains of alcohol-exposed individuals were narrower in the inferior parietal and perisylvian regions (Sowell et al., 2002), and voxel-based morphometry (VBM) analysis revealed gray matter abnormalities that were most prominent in the left perisylvian cortices of the parietal and temporal lobes (Sowell et al., 2001). In addition, significant cortical thickness excesses were observed in children with FASD in large areas of bilateral temporal, bilateral inferior parietal and right frontal regions (Sowell et al., 2008).

In the first fMRI study of number processing in FASD, adults with and without prenatal alcohol exposure were administered a task involving subtraction from 11 of a series of numbers that appeared on the screen (Santhanam et al., 2009). Exposed individuals with alcohol-related dysmorphology exhibited poorer task performance and lower activation in regions known to be associated with arithmetic processing, including the right inferior and left superior parietal regions and medial frontal gyrus, compared with controls. However, it was not clear whether the reduced activation in the dysmorphic participants reflected a specific deficit in fronto-parietal function or completion of fewer problems due to the difficulty of the task. Using simpler proximity judgment and single-digit addition problems, we found that children activate the same fronto-parietal regions activated in number processing by adults (Meintjes et al., 2010a). Although children with FAS and PFAS performed as well as controls on the simple tasks administered in the scanner, they activated a markedly more diffuse parietal region extending into the angular gyrus, precuneus and posterior cingulate and for, exact addition, also the postcentral gyrus (Meintjes et al., 2010b). However, the FAS/PFAS and control groups did not differ significantly in the degree of activation in the anterior portion of the IPS and other regions linked by Dehaene and associates to number processing, possibly due to the lack of statistical power in the small sample on which that whole brain voxel-wise analysis was conducted.

In this study, we examine the effects of both FASD diagnosis and continuous measures of prenatal alcohol exposure on brain activation in the five parietal structures found by Dehaene and associates to mediate number processing in a larger sample that includes not only children with FAS/PFAS and nonexposed controls, but also nonsyndromal heavily-exposed (HE) children (Suttie et al., 2013). We have found that continuous measures of prenatal alcohol exposure based on a maternal report obtained during pregnancy are often more sensitive in detecting effects of prenatal alcohol exposure than diagnoses based on dysmorphic features in studies using diverse neuroimaging techniques, including tensor-based morphometry (Meintjes et al., 2014) and magnetic resonance spectroscopy (du Plessis et al., 2014). Based on the behavioral findings from our Detroit and Cape Town studies, our central hypothesis was that prenatal alcohol exposure would be associated with reduced activation of the anterior IPS, the region believed to mediate abstract representation of numerical quantity.

2. Methods

2.1. Participants

Participants were 65 right-handed, 8- to 12-year-old children from the Cape Coloured (mixed ancestry) community in Cape Town, South Africa, of whom 40 had been heavily exposed to alcohol prenatally and 25 were controls in the same age range (S. Jacobson et al., 2011b). The Cape Coloured community is composed primarily of descendants of white European settlers, Malaysian slaves, Khoi-San aboriginals, and black African ancestors. The incidence of FASD in this population is exceptionally high due to poor socioeconomic circumstances and historical practices of compensating farm laborers with wine, which have contributed to a tradition of heavy recreational weekend binge drinking (May et al., 2007). Thirty-seven children were the older siblings of participants in our Cape Town Longitudinal Cohort (Jacobson et al., 2008). The others were identified by screening all of the 8- to 12-year-old children from an elementary school in a rural section of Cape Town, where there is a very high incidence of alcohol abuse among local farm workers (Meintjes et al., 2010b).

2.2. Procedure

Our research nurse and staff driver transported the mother and child from their home to our child development laboratory at the Faculty of Health Sciences campus of the University of Cape Town (UCT) for a 3-hour neuropsychological assessment and to Groote Schuur Hospital for a neuroimaging assessment, which was administered on the following day. All examiners were blind with regard to maternal alcohol history and the child's FASD diagnostic status, except in the most severe