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A tensor-based morphometry analysis of regional differences in brain volume in relation to prenatal alcohol exposure

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ABSTRACT

Reductions in brain volumes represent a neurobiological signature of fetal alcohol spectrum disorders (FASD). Less clear is how regional brain tissue reductions differ after normalizing for brain size differences linked with FASD and whether these profiles can predict the degree of prenatal exposure to alcohol. To examine associations of regional brain tissue excesses/deficits with degree of prenatal alcohol exposure and diagnosis with and without correction for overall brain volume, tensor-based morphometry (TBM) methods were applied to structural imaging data from a well-characterized, demographically homogeneous sample of children diagnosed with FASD ($n = 39$, 9.6–11.0 years) and controls ($n = 16$, 9.5–11.0 years). Degree of prenatal alcohol exposure was significantly associated with regionally pervasive brain tissue reductions in: (1) the thalamus, midbrain, and ventromedial frontal lobe, (2) the superior cerebellum and inferior occipital lobe, (3) the dorsolateral frontal cortex, and (4) the precuneus and superior parietal lobule. When overall brain size was factored out of the analysis on a subject-by-subject basis, no regions showed significant associations with alcohol exposure. FASD diagnosis was associated with a similar deformation pattern, but few of the regions survived FDR correction. In data-driven independent component analyses (ICA) regional brain tissue deformations successfully distinguished individuals based on extent of prenatal alcohol exposure and to a lesser degree, diagnosis. The greater sensitivity of the continuous measure of alcohol exposure compared with the categorical diagnosis across diverse brain regions underscores the dose dependence of these effects. The ICA results illustrate that profiles of brain tissue alterations may be a useful indicator of prenatal alcohol exposure when reliable historical data are not available and facial features are not apparent.

1. Introduction

Prenatal alcohol exposure causes physical and behavioral impairments (Kodituwakku, 2009; Mattson et al., 2011) that range in severity and occur through the disruption of normal neurodevelopmental processes (Ismail et al., 2010; Jacobson et al., 2011; Thompson et al., 2009), impacting both the size and the structural organization of the brain (Guerri et al., 2009; Norman et al., 2009; Roebuck et al., 1998).

While the severity of physical and behavioral symptoms is related to exposure dose and frequency (e.g., Streissguth et al., 1989, 1994; Jacobson et al., 1998; Jacobson et al., 2008), these associations are difficult to characterize as the amount of alcohol use during pregnancy is often poorly recalled in retrospective case–control studies (Jacobson et al., 2002). Instead, growth deficiencies, facial dysmorphology, and central nervous system dysfunctions are typically used to diagnose and categorize severity of exposure. Diagnosis is challenging as facial anomalies may be subtle or absent (Suttie et al., 2013). Understanding the links between extent of fetal alcohol exposure and disruptions in

Abbreviations: AA, absolute alcohol; CSF, cerebrospinal fluid; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorders; ICA, independent component analyses; MDT, minimal deformation target; MEMPRAGE, multiecho magnetization prepared rapid gradient echo; TBM, tensor-based morphometry; WISC-IV, Wechsler Intelligence Scale for Children.

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the structural development of the brain may thus be helpful for distinguishing individuals with fetal alcohol spectrum disorders (FASD) and elucidating vulnerable functional systems.

Few studies examining the impact of fetal alcohol exposure on brain development (for review see Lebel et al., 2011; Norman et al., 2009) have employed advanced computational image analysis methods to simultaneously determine global and local changes in brain tissue architecture. Tensor-based morphometry (TBM) uses Jacobian determinant values obtained from the linear and non-linear deformation fields required to match structures with similar intensity patterns of individual subjects to a population specific atlas. Since TBM matches structures with similar intensity patterns, it can detect local volumetric excesses and deficits in brain tissue at the voxel level (e.g., Chiang et al., 2007; Gogtay et al., 2008; Ho et al., 2010; Hua et al., 2008; Leow et al., 2006; Lepore et al., 2010; Yanovsky et al., 2009).

Only one prior investigation has applied TBM to compare children with heavy prenatal exposure to alcohol or methamphetamine and controls (Sowell et al., 2010). Although this study, which examined local changes after removing global scaling differences from the imaging data, found volumetric deficits in several regions, prenatal alcohol exposure was also associated with *expansions* in several regions. The latter effects, which are not consistent with findings from other neuroimaging and autopsy studies, may be due to over-compensatory expansions in local volumes occurring as a function of normalization for brain size.

Here we characterize the nature and extent of cerebral abnormalities in FASD in a prospectively recruited, demographically homogeneous sample of FASD subjects and controls using TBM methods to quantitatively map volumetric differences throughout the brain. We compared voxel-level variations in brain tissue volume in relation to both a continuous measure of oz of absolute alcohol consumed per day during pregnancy and diagnosis based on discrete classifications of FASD severity, both with and without taking global brain size differences into account. In addition, using objective, data-driven independent component analyses (ICA), we addressed whether patterns of volumetric deviation can separately predict the presence and extent of prenatal alcohol exposure.

2. Materials and methods

2.1. Participants

Participants were 55 9- to 11-year-old children (28 males, mean age 10.4 ± 0.4 years) from Cape Town, South Africa, who are enrolled in a prospective, longitudinal study of FASD (Jacobson et al., 2008, 2011). Of these, 39 were heavily exposed to alcohol and 16 were demographically similar controls. All children were from the Cape Coloured (mixed ancestry) community, which is composed mainly of descendants of white European settlers, Malaysian slaves, Khoi-San aboriginals, and black African ancestors. The incidence of fetal alcohol syndrome (FAS) in this community, situated in a geographical region supporting a wine-producing industry, is estimated to be 18–141 times greater than that in the United States (May et al., 2000, 2007). Poor socioeconomic circumstances and historical practices of compensating farm labor with wine have contributed to a tradition of heavy recreational weekend binge drinking in a portion of this population, leading to the increased incidence of FAS.

During 1998–2002, mothers initiating antenatal care at a clinic serving a predominantly Cape Coloured community were interviewed regarding their alcohol consumption using a timeline follow-back approach (Jacobson et al., 2002). At recruitment the mother was interviewed regarding incidence and amount of her drinking on a day-by-day basis during a typical 2-week period at time of conception. Volume was recorded for each type of beverage consumed each day and converted to oz absolute alcohol (AA) (Jacobson et al., 2008). The mother was then asked whether her drinking had changed since conception; if so, when the change occurred and how much she drank on a day-by-day basis during the last 2 weeks. Two groups of women were recruited: (1) heavy drinkers, who consumed 14 or more standard drinks/week (≈1.0 oz AA/day) and/or engaged in binge drinking (5 or more drinks/occasion) and (2) controls, 14 of whom abstained from drinking and 2 who drank only minimally during pregnancy (one averaged 3 drinks/occasion twice monthly, and the other drank 2 drinks on 4 occasions). The timeline follow-back interview was repeated in mid-pregnancy and again at 1 month postpartum to provide information about drinking during the latter part of pregnancy. Data from the three alcohol consumption interviews were tabulated to provide three continuous measures of drinking during pregnancy: average oz AA consumed/day (AA/day), AA/drinking day (dose/occasion), and frequency (days/week). Smoking during pregnancy was reported in terms of cigarettes smoked per day; one outlier with cigarettes/day > 3SD above the mean for this sample was recoded to 1 unit above the next highest observed value as recommended by Winer (1971). Exclusionary criteria included age < 18 years, diabetes, epilepsy, cardiac problems requiring treatment, and observant Muslims whose religious practice prohibits alcohol consumption.

In 2005 we organized a clinic, in which each child was examined for growth and FAS anomalies by two expert dysmorphologists using a standard protocol (see Jacobson et al., 2008). Based on the revised Institute of Medicine guidelines, FAS is characterized by microcephaly, growth retardation, and a distinctive craniofacial dysmorphology, including short palpebral fissures, a flat philtrum, and a thin vermilion (upper lip) (Hoyme et al., 2005). A partial FAS (PFAS) diagnosis requires the presence of at least two of these facial features, as well as microcephaly, retarded growth, or neurobehavioral deficits. Children with alcohol-related neurodevelopmental disorder exhibit neurobehavioral deficits without the characteristic facial features. Of the 39 children born to heavy drinking mothers, 7 met the criteria for full FAS, 18 for PFAS, and 14 for neither syndrome. Approval for human research was obtained from the Wayne State University Institutional Review Board and University of Cape Town Faculty of Health Sciences Human Research Ethics Committee. All mothers provided informed written consent; the children provided oral assent.

2.2. Neuropsychological assessment

Intellectual ability (IQ) for each child was assessed at our University of Cape Town Child Development Research Laboratory using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) in English or Afrikaans, depending on the language used in the child's elementary school classroom (see Diwadkar et al., 2013).

2.3. Image acquisition

High-resolution T1-weighted structural MR images were acquired on a 3 T Allegra MRI scanner (Siemens, Erlangen, Germany) using a 3D EPI-navigated (Tisdall et al., 2009) multiecho magnetization prepared rapid gradient echo (MEMPRAGE) (van der Kouwe et al., 2008) sequence optimized for morphometric analyses using FreeSurfer software. Imaging parameters were as follows: FOV: 256 × 256 mm; 128 sagittal slices; TR: 2530 ms; TE: 1.53/3.21/4.89/6.57 ms; TI: 1100 ms; flip angle: 7°; voxel size: 1.3 × 1.0 × 1.3 mm^3; and acquisition time: 8:07 min. The 3D EPI navigator provided real-time motion tracking and correction, substantially reducing motion artifacts in the images, even in the presence of frequent subject motion.

2.4. Image processing

TBM is an advanced, relatively unbiased and mostly automated image analysis approach that allows variations in brain tissue structure (gray and white matter and cerebrospinal fluid (CSF)) to be determined and compared between subjects throughout the entire brain. In brief, TBM identifies brain structural differences from the gradients of linear