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Early gray-matter and white-matter concentration in infancy predict later language skills: A whole brain voxel-based morphometry study

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ABSTRACT

Magnetic Resonance Imaging (MRI) brain scans were obtained from 19 infants at 7 months. Expressive and receptive language performance was assessed at 12 months. Voxel-based morphometry (VBM) identified brain regions where gray-matter and white-matter concentrations at 7 months correlated significantly with children's language scores at 12 months. Early gray-matter concentration in the right cerebellum, early white-matter concentration in the right cerebellum, and early white-matter concentration in the left posterior limb of the internal capsule (PLIC)/cerebral peduncle were positively and strongly associated with infants' receptive language ability at 12 months. Early gray-matter concentration in the right hippocampus was positively and strongly correlated with infants' expressive language ability at 12 months. Our results suggest that the cerebellum, PLIC/cerebral peduncle, and the hippocampus may be associated with early language development. Potential links between these structural predictors and infants' linguistic functions are discussed.

1. Introduction

Information regarding structural and functional brain development in the first two years of life is very limited (Knickmeyer et al., 2008). Adult studies have revealed associations between gray-matter and white-matter volumes and a variety of behavioral measures, including general intelligence, proficiency in a second language, and phonetic learning (Golestani, Molko, Dehaene, LeBihan, & Pallier, 2007; Haier, Jung, Yeo, Head, & Alkire, 2004; Mechelli et al., 2004). Only two such studies have been conducted with infants (Ortiz-Mantilla, Choe, Flax, Grant, & Benasich, 2010; Short et al., 2013) reflecting difficulties in data collection from infants and challenges faced in analyzing infant MR images (Knickmeyer et al., 2008). Infant MR images often exhibit motion artifact, and contrast between gray-matter and white-matter is variable across regions at birth and during early development, largely due to ongoing myelination processes in white-matter tissues during infant development (Barkovich, 2005; Prastawa, Gilmore, Lin, & Gerig, 2005; Shi et al., 2010). Despite these challenges, brain development between birth and age 2, and its relationship to behavior, remains of great interest. This early period may be the most important phase of postnatal brain development in humans and is likely critical in neurodevelopmental disorders such as autism (Knickmeyer et al., 2008).

The study of brain structure early in life, and its relationship to behavior, is particularly interesting in the field of language development. There is evidence that early language performance is a powerful predictor of later language and achievement (National Institute of Child Health and Human Development & Early Child Care Research Network, 2005). Interest in neural correlates of early language skills is strong in the area of child development (Kuhl & Rivera-Gaxiola, 2008). Studies on typically developing children indicate that brain and behavioral responses early in infancy predict later performance and learning. For example, behavioral and event related potential (ERP) measures of phonetic learning in the first year of life predict language skills between 14 and 30 months (Kuhl, Conboy, Padden, Nelson, & Pruitt, 2005; Kuhl et al., 2008; Rivera-Gaxiola, Klarman, Garcia-Sierra, & Kuhl, 2005; Tsao, Liu, & Kuhl, 2004), language and pre-literacy skills at 5 years (Cardillo, 2010; Cardillo Lebedeva & Kuhl, 2009; Molfese & Molfese, 1997), and language and cognitive ability at 8 years (Molfese, 2000). In addition, variations in brain structure as early as at 6 months (i.e., size of the right amygdala) have been linked to longitudinal language outcomes up to 4 years (Ortiz-Mantilla et al., 2010), while white-matter microstructure has been associated with behavioral measures of working memory in 12 month old infants (Short et al., 2013).

While such studies inform us about the relations between brain and behavior, determination of the source of language functions in the brain is a topic of continued research. Two brain areas have long been associated with language function in adults: Broca's

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area, in the left inferior frontal lobe, and Wernicke's area, in the left posterior temporal cortex (Papathanassiou et al., 2000). Recent data suggest that multiple brain areas contribute to language processing in adults (e.g., Atallah, Frank, & O'Reilly, 2004; Doya, 1999, 2000; Hickok & Poeppel, 2007; Kuhl & Damasio, 2012; Opitz & Friederici, 2003), and research using modern brain imaging techniques has provided an expanded view of the brain areas associated with adult language processing (Murdoch, 2010). For example, in a recent study, an fMRI language localizer task was employed to identify 13 key regions implicated in high-level linguistic processing in adults (Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010). These key regions were distributed in the left frontal lobe, left temporal/parietal lobes, right temporal lobe, and cerebellum (Fedorenko et al., 2010). Within the last two decades, there has been a dramatic increase in the number of research studies that emphasize the importance of multiple brain areas (e.g., prefrontal cortex, cerebellum, hippocampus, basal ganglia) for cognitive and linguistic processing.

The foregoing studies showing that multiple brain areas are activated during language tasks have been conducted with adults. The brain areas involved developmentally, during the period in which language is acquired, are not yet clear, and this topic has been identified as an important area for research (Booth, Wood, Lu, Houk, & Bitan, 2007; Breitenstein et al., 2005; Doya, 1999, 2000; Gordon, 2007; Konczak & Timmann, 2007; Murdoch, 2010). Infant studies utilizing fMRI and MEG have shown that the left inferior frontal lobe (e.g., Broca's area) is active during speech processing (Dehaene-Lambertz et al., 2010; Imada et al., 2006), however, no whole brain longitudinal study has yet examined which specific brain areas predict language development over time in infancy.

Our aim was to explore the brain structures associated with infants' language development utilizing a longitudinal design. The 2nd year of life is characterized by an explosion of language, intensified connectivity of the two hemispheres, maturation of the prefrontal cortex and the cortical–subcortical network, and strengthened connections between the cortex and the limbic system (Herschkowitz, 2000). The present study examines brain structure early in the first year of life for evidence of structural predictors of early language acquisition. Specifically, we explore the relationship between early concentration of gray-matter and white-matter in the brain at 7 months and infants' expressive and receptive language skills at 12 months. We utilize voxel-based morphometry (VBM) of MRI data to (a) represent local concentration of gray-matter and white-matter (i.e., the probability of a specific tissue type within a region) and (b) study correlations between local concentrations of gray-matter and white-matter in the whole brain and children's later language outcomes (Ashburner & Friston, 2000; Whitwell, 2009).

2. Methods

2.1. Subjects

The 19 infants in the present study were drawn from a larger group enrolled in a comprehensive study of typically developing children which explored relationships among brain, behavior and environment across the first 2 years of life. An additional 10 subjects did not produce usable MRI data at 7 months due to failure to sleep at the imaging center ($n = 2$), waking during transition to the scanning bed or at the onset of the first scan ($n = 6$), and motion artifact ($n = 2$). One infant with usable MRI data did not return for behavioral measures at 12 months. The children were recruited from urban and suburban communities in the Seattle area (12 boys and 7 girls). Infants were born healthy and full-term (+2 weeks from due date), ranging in weight from 6 to 9 lbs. All came from English-speaking monolingual families, had uneventful pre- and perinatal circumstances, with no history of language impairment, hearing loss, or other neurological or psychiatric disorders.

Children visited the laboratory at about 7 months (Mean = 6.9, SD = .5, Range = 6.0–7.8, corrected for gestational age at birth) for brain imaging, and at about 12 months (Mean = 12.3, SD = .4, Range = 11.7–13.2, corrected for gestational age at birth) for standardized testing. A parental questionnaire was used to obtain socio-demographic data, as well as information about infant and maternal health and obstetrical history at the 7-month visit. A follow-up questionnaire provided additional infant health data at 12 months. The socioeconomic status (SES) was assessed by the Hollingshead Four Factor Index (Hollingshead, 1975) and was not related to language abilities at 12 months. Infants came from families classified as middle-to-upper-middle class (SES ranging from 39 to 66, mean = 54.41, SD = 7.05). The University of Washington Institutional Review Board approved this project and written informed consent was obtained from parents according to the principles explained in the Declaration of Helsinki. Parents were compensated for their time and infants received a toy after each visit.

2.2. Procedures

Successful structural MRI brain scans were collected by certified MR technicians during natural sleep. The MRI visits were scheduled for late mornings during naptime, so that scans were obtained without sedation during natural sleep. Children were swaddled and moldable silicon ear protectors were placed in the outer ear when they arrived at the imaging center. Inside the imaging center, normal naptime routines were replicated (e.g., soft lullaby music, rocking chair, crib, other materials to encourage sleeping) to comfort the children. After the child was asleep, s/he was moved to the scanning bed where ear protection was placed over the ears and the head was stabilized in the standard coil with foam.

Magnetic Resonance Imaging (MRI) data were obtained as follows: Sagittal images (1.0 mm slice thickness) were acquired using a GE Signa 1.5 tesla scanner (version 5.8) (General Electric, Milwaukee, WI, USA), and a 3D fast spoiled gradient echo pulse sequence. These specific imaging parameters were utilized: TR (repetition time) 11.1 ms, TE (echo time) 2.2 ms, flip angle 25°, field of view 24 cm, pixel size dimension $0.94 \times 0.94 \times 1$ mm, reconstructed matrix size $256 \times 256 \times 124$. The entire acquisition time was 4 min 36 s.

2.3. Standardized measures

The Mullen Scales of Early Learning (Mullen, 1995) is a standardized measure of early learning abilities that is widely used in research and clinical practice. The administration time typically varies with age and characteristics of the child. In the present case, a speech language pathologist with extensive experience administered the Mullen Scales. Test administration took approximately 15 min in our one-year-old children. This matches the time for test administration listed in the technical manual for children at this age (Mullen, 1995). Testing practices and guidelines for assessing and increasing children's attention level are described in full detail in the manual, and were followed by the highly trained speech pathologist who administered our tests (see Mullen, 1995). The Mullen consists of five scales: Gross Motor, Visual Reception, Fine Motor, Receptive Language, and Expressive Language that have normative scores (T-scores) with a mean of 50 and a standard deviation of 10 (Mullen, 1995). In addition, the Mullen provides a single standardized composite score (i.e., early learning index score, mean = 100, SD = 15) that represents general intelligence. Test-ret-