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Associations between white matter microstructure and infants' working memory

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ABSTRACT

Working memory emerges in infancy and plays a privileged role in subsequent adaptive cognitive development. The neural networks important for the development of working memory during infancy remain unknown. We used diffusion tensor imaging (DTI) and deterministic fiber tracking to characterize the microstructure of white matter fiber bundles hypothesized to support working memory in 12-month-old infants ($n = 73$). Here we show robust associations between infants' visuospatial working memory performance and microstructural characteristics of widespread white matter. Significant associations were found for white matter tracts that connect brain regions known to support working memory in older children and adults (genu, anterior and superior thalamic radiations, anterior cingulum, arcuate fasciculus, and the temporal–parietal segment). Better working memory scores were associated with higher FA and lower RD values in these selected white matter tracts. These tract-specific brain–behavior relationships accounted for a significant amount of individual variation above and beyond infants' gestational age and developmental level, as measured with the Mullen Scales of Early Learning. Working memory was not associated with global measures of brain volume, as expected, and few associations were found between working memory and control white matter tracts. To our knowledge, this study is among the first demonstrations of brain–behavior associations in infants using quantitative tractography. The ability to characterize subtle individual differences in infant brain development associated with complex cognitive functions holds promise for improving our understanding of normative development, biomarkers of risk, experience-dependent learning and neuro-cognitive periods of developmental plasticity.

Introduction

Working memory is an early, emerging cognitive building block that plays a formative role in the development of other executive functions early in life (Diamond, 1985, 1991; Zelazo et al., 2008). Broadly speaking, working memory is the capacity to temporarily maintain and subsequently manipulate information in the service of goal-oriented actions (Baddeley, 1992). Visuospatial working memory emerges around six months of age, which is followed by a dramatic increase in memory capacity that continues to improve into early adulthood (Diamond et al., 2005; Pelphrey et al., 2004; Reznick et al., 2004; Zald and Iacono, 1998; Zelazo et al., 1996). Individual differences in working memory performance are associated with language development, problem solving, and complex reasoning (Reznick, 2009), but the sources of these differences remain unknown. In school-aged children and adults, performance on working memory tasks is supported by a clearly delineated set of neural circuits that appears to refine from late childhood to adulthood as the function of brain networks becomes more specialized (Durston et al., 2006; Fair et al., 2007; Klingberg, 2006; Nagy et al., 2004; Scherf et al., 2006; Uddin et al., 2011). Evidence from positron emission tomography, functional magnetic resonance imaging, and diffusion tensor imaging (DTI) has identified a set of overlapping brain regions–prefrontal, frontal, temporal, and parietal regions–that support working memory processes during childhood and adulthood (Courtney et al., 1997; Jonides et al.,

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1993; Klingberg, 2006; Klingberg et al., 2002; Kwon et al., 2002; Nagy et al., 2004). The neural networks and brain regions that support working memory during infancy, however, have yet to be determined. Thus, we sought to investigate the association between short-term visuospatial working memory performance and the putative neural circuits underlying this cognitive capacity in 12-month-old infants.

Efficient signal transmission allows for efficient information processing. This relationship depends in part on the organizational integrity of white matter connections within the brain. Animal and postmortem studies have shown that the most prolific period of white matter myelination occurs between mid-gestation and two years of age (Brody et al., 1987; Yakovlev and LeCours, 1967). Until recently, technological and methodological limitations have prevented researchers from non-invasively characterizing this critical period of dynamic maturation. Diffusion tensor imaging (DTI) has emerged, however, as a way to non-invasively measure white matter microstructure in vivo throughout the life span and has been used to investigate changes in white matter at different stages of brain development, including during infancy (Dubois et al., 2009; Gao et al., 2009a; Geng et al., 2012a; Lebel et al., 2008; Mukherjee et al., 2001; Paus et al., 2001; Schmithorst et al., 2002).

Diffusion measures commonly used to characterize microstructural features of white matter include fractional anisotropy (FA), apparent diffusion coefficient axial diffusivity (AD) and radial diffusivity (RD). While FA has been more widely used to describe diffusion anisotropy in brain tissue, Song et al. (2003, 2005) suggested that greater insight about the underlying microstructural properties can be derived from separating the three eigenvalues that comprise FA to reflect diffusion parallel to ($AD = \lambda_1$) and perpendicular to ($RD = (\lambda_2 + \lambda_3)/2$), the sampled white matter fibers. Using these additional indices of diffusion to better characterize white matter microstructure, recent tract-based longitudinal DTI studies of infant brain development (Gao et al., 2009a; Geng et al., 2012a, 2012b) showed dramatic changes in FA, RD, and AD during the first two years of life. The developmental trajectories of these diffusion properties show tract-specific heterogeneity with more rapid changes over the first year of life, compared to the second. Analysis of neural network formation in infancy also reveals rapid changes in the development of functional neural networks that resemble adult-like default networks by two years of age (Gao et al., 2009b, 2011). Research efforts to non-invasively characterize infant brain development and its functional correlates represent a burgeoning field in developmental cognitive neuroscience, with great promise and many questions to address.

Microstructural characteristics of white matter fiber bundles have also been described in relation to diseases (multiple sclerosis, schizophrenia), developmental disorders (cerebral palsy, autism), and cognitive capacities (language, working memory) (Karlsgodt et al., 2008; Schmithorst et al., 2005; Thomas et al., 2005; Werring et al., 1999; Wolff et al., 2012). However, the majority of studies examining associations between white matter and cognitive ability have been conducted in older children, adolescents, and aging populations. These investigations have reported differences in white matter characteristics associated with information processing speed, cognitive control, language, reading/literacy, and arithmetic competence, among other skills (Bengtsson et al., 2005; Catani et al., 2007; Hu et al., 2011; Liston et al., 2006; Nagy et al., 2004; Penke et al., 2010). Thus, there is a need to study how and when the structural characteristics of white matter influence the formation of cognitive functions. Identifying the structural characteristics associated with individual differences in working memory early in life could provide an early indicator of impending deficits, as well as clues for how to foster optimal learning (Keller and Just, 2009; Markham and Greenough, 2004; Quartz and Sejnowski, 1997). Furthermore, deficits in working memory are a core feature of many developmental and neuropsychiatric disorders (Gottesman and Gould, 2003). Accurately identifying early brain–behavior relationships could help us better understand such disorders and prevent downstream effects that poor working memory can have for competency in other cognitive domains, including language, reading, planning, and mathematics. Toward this end, we used measures of white matter microstructure (FA, RD, and AD) obtained from quantitative fiber tractography of DTI data to investigate the relation between early brain development and working memory capacity in a large group of healthy infants.

Based on studies of the brain regions and neural circuitry known to support working memory processes during late childhood and adulthood (Courtney et al., 1997; Jonides et al., 1993; Klingberg, 2006; Klingberg et al., 2002; Kwon et al., 2002; Nagy et al., 2004), we hypothesized that the following white matter tracts would be associated with infants' working memory capacity: genu of the corpus callosum, bilateral anterior cingulum, arcuate fasciculi, anterior and superior thalamic radiations, and temporal–parietal segments. To assess the specificity of the structure–function relationships of our hypothesized tracts, we also analyzed the microstructure of control tracts less likely to support the emergence of working memory: the body and splenium of the corpus callosum, inferior longitudinal fasciculi, spinothalamic radiations, and the optic nerves. To determine whether brain–behavior associations were in fact specific to working memory and not a reflection of general intelligence or developmental level, other standard measures of early cognitive development were included in the analyses. To confirm our expectation that working memory is specific to particular white matter tracts and not to total white matter or global brain volumes, we examined whether working memory was associated with brain development in general. To our knowledge, this study is among the first demonstrations of brain–behavior associations in infants using DTI and tractography.

Materials and methods

Participants

Diffusion weighted imaging (DWI) scans and tests of short-term visuospatial working memory and general cognitive development were acquired in 73 typically developing 12-month-old infants (41 boys and 32 girls). Mean age at assessment was 12 months ± 21 days. Infant participants included 29 singletons and 44 twins (12 of which were twin pairs). Typically developing infants were selected from two ongoing longitudinal studies: normal controls from a study of early brain development in children at risk for neurodevelopmental disorders (Gilmore et al., 2010a) and a twin study of brain development (Gilmore et al., 2010b). Exclusion criteria were major maternal illness or infection during pregnancy, severe congenital abnormality on fetal ultrasound, and maternal diagnosis of a major psychiatric disorder. Written informed consent was obtained from the parents of all infant participants. The Institutional Review Boards of the University of North Carolina School of Medicine and Duke University Medical Center approved this study. Pregnant women were recruited from the outpatient OB-GYN clinics at these two institutions.

Working Memory Assessment

For the Working Memory Assessment task, infants sitting on their mothers' laps were engaged in 1–2 administrations of a 12-trial hiding game previously described (Reznick, 2009). Administrations were 30 min apart. Toys that were determined to be highly attractive to the infant were used. Two hiding wells were used on trials 1–6 and 3 hiding wells were used for trials 7–12. Location of the wells was counterbalanced. Intervals between hiding and encouragement to find the toy were 3, 9, and 15 s, and this sequence of delays was repeated 4 times through the 12 possible trials per administration. The same order of location and delay was used for all administrations and all infants. For each trial, the infant watched the toy being placed in a well. All wells were then covered simultaneously, the tray was pulled back from the infant, eye contact was established, and the researcher counted and clapped to continue to draw the infant's gaze away from