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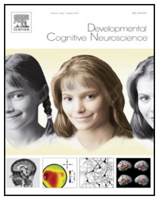

Accurate age classification of 6 and 12 month-old infants based on resting-state functional connectivity magnetic resonance imaging data

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ABSTRACT

Human large-scale functional brain networks are hypothesized to undergo significant changes over development. Little is known about these functional architectural changes, particularly during the second half of the first year of life. We used multivariate pattern classification of resting-state functional connectivity magnetic resonance imaging (fcMRI) data obtained in an on-going, multi-site, longitudinal study of brain and behavioral development to explore whether fcMRI data contained information sufficient to classify infant age. Analyses carefully account for the effects of fcMRI motion artifact. Support vector machines (SVMs) classified 6 versus 12 month-old infants (128 datasets) above chance based on fcMRI

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data alone. Results demonstrate significant changes in measures of brain functional organization that coincide with a special period of dramatic change in infant motor, cognitive, and social development. Explorations of the most different correlations used for SVM lead to two different interpretations about functional connections that support 6 versus 12-month age categorization.

1. Introduction

The 6–12 month period in infant development has not been well characterized by fcMRI. Here, we asked whether fcMRI data from 6 and 12 month-old infants contain sufficient information to support age classification after rigorous motion artifact rejection. Many sophisticated cognitive and social capacities begin to consolidate during the latter half of the first year of human life, which is characterized by the emergence of joint attention (Scaife and Bruner, 1975), specialization of face identity discrimination (Pascalis et al., 2002) and phoneme specification (Kuhl et al., 2003), the emergence of perceptual binding (Csibra et al., 2000), and perhaps the emergence of perceptual consciousness (Kouider et al., 2013). Additionally, increasing motor control and mobility (e.g., active crawling and walking, assisted and unassisted) alter the perspective by which an infant explores and accesses the world during this period. The magnitude and multifaceted nature of typical developmental changes across 6–12 months, therefore, lead us to predict significant and widespread differences in brain functional connectivity across these ages.

Typical and atypical developmental processes are hypothesized to relate to the developmental reorganization of large-scale functional brain networks that support various sensory, motor, and cognitive functions (Johnson, 2001). Functional connectivity magnetic resonance imaging (fcMRI) has shown great promise for characterizing these networks (Power et al., 2011; Yeo et al., 2011). Prior infant fcMRI studies (reviewed in Hoff et al. (2013)) have primarily covered the 0–24 month time period. These studies have demonstrated the presence of resting state functional connectivity networks at birth during natural sleep (Fransson et al., 2009); effects of prematurity (Doria et al., 2010; Smyser et al., 2010); and functional architectural changes from two weeks to one year to two years (Lin et al., 2008), with a focus on the default mode network (Gao et al., 2009). Investigators have studied changing functional network properties from three weeks to one year to two years, including small world and efficiency metrics and the characterizations of network hubs (Gao et al., 2011; see Fransson et al. (2011) for analyses of "hubs" at birth) and the development of interactions between different networks (Gao et al., 2013). Some investigators have reported increasing long- /decreasing short-range functional connectivity, with increased default mode network connectivity between four and nine months (Damaraju et al., 2013).

The 6–12-month period is important for typical development and, we believe, for the development of autism spectrum disorder (ASD), and investigators have only recently begun to characterize it in detail using fcMRI (Gao et al., 2014). During this time, gaze following and social referencing consolidate; imitative learning emerges; infants initiate the use of communicative gestures; and social interactions shift from dyadic to triadic (person–person–object). The 6–12-month period, referred to as a "social-cognitive revolution" (Tomasello, 2000, p. 38), sets the stage for a host of increasingly sophisticated social behaviors. It is, therefore, important to learn more about which brain functional connections allow for classification of age across this developmental period. Prior results in older subjects supporting hypotheses of developmental change in large-scale functional brain networks have recently been called into question because of increasing appreciation of the age-mimicking, artifactual effects that sub-millimeter movements create in fcMRI data from older subjects (Power et al., 2012, 2014; Satterthwaite et al., 2013; Van Dijk et al., 2012). In this report we use "state of the art" frame-censoring motion artifact rejection procedures (Power et al., 2014).

We examined fcMRI network changes between 6 and 12 months of age in 92 infants of whom 36 infants had both 6 and 12 month scans (128 total datasets). The current fMRI data preprocessing strategy incorporates several recent advances that minimize the impact of head motion artifact more effectively than in prior studies. We employ support vector machine (SVM) (Ben-Hur et al., 2008) multivariate pattern classification to (1) exploit the information content of fcMRI data, which intrinsically is of high dimension, (2) explore which connections contribute to significant classifications, and (3) lay the foundation for developing predictive classifiers to aid early risk assessment in ASD. fcMRI data acquired from naturally sleeping infants were processed according to recent analytic and motion cleaning recommendations (Power et al., 2014), with infant-specific adaptations to initial registration and nuisance regression steps. fcMRI matrices were constructed using 230 functionally defined seed regions (culled from 264 in Power et al. (2011) plus 16 additionally derived from Philip et al. (2012)) that were appropriately positioned in gray matter at both ages. Support vector machine (SVM) methods involved recent adaptations of those used by some of the authors (Dosenbach et al., 2010).

2. Methods

The high- and low-risk infant groups, defined below (Section 2.1), provided independent samples within which to test SVM classification of infant age. Secondary analyses explored classification of risk (not diagnosis) at each age. These results were not significant; therefore, we combined risk groups for further tests of age classification.