Potential of Resting State Connectivity and Passive fMRI to Detect Precursors of Learning Disabilities in Infants: Preliminary Results with Infants at Familial Risk for Developmental Dyslexia

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Target Audience: Clinical and academia researchers interested in infant imaging, brain connectivity, developmental disorders and translational medicine.

Purpose: The ability to detect early precursors of learning disabilities would enable early intervention and tailored education plans beginning in preschool. One of the most common learning disability is developmental dyslexia (DD), affecting 5-17% of all children. DD is a specific language-based learning disorder, characterized by difficulties with accurate and/or fluent word recognition, poor spelling and poor decoding performance. Currently DD can only be diagnosed after the onset of formal reading instructions, around 3rd grade [1], restricting the implementation of early intervention. Familial and twin studies suggest a strong genetic basis with difficulties in processing specific temporal auditory cues that can be detected as early as infancy in some children [2]. Structural and functional alterations in posterior dorsal and ventral reading networks have been reported in children at familial risk for DD prior to reading onset [5,6]. However, it remains unclear how early these differences manifest and whether they can already be detected in infancy. Functional resting-state connectivity magnetic resonance imaging (fcMRI) is a safe and non-invasive technique that can reveal functional brain network organization by measuring intrinsic cerebral deoxyhemoglobin fluctuations at rest. Resting state networks (RSNs) have been investigated in healthy infants (0-2 years old) [3] as well as in older children (9-12 years old) diagnosed with DD [4] but to date few studies in infants have been reported. Both fcMRI and passive functional MRI (fMRI) can also be performed in infants during natural sleep to assess cortical auditory function and functional organization. Here we used an independent component analysis (ICA) without *a priori* spatial information to estimate RSNs in both infants with (FHD+) and age-matched control infants without (FHD-) familial risk for DD at 7-12 months. We further assessed fMRI during a temporal auditory processing task.

Methods: Three FHD+ infants (7-12 months) and six age-matched controls (FHD-) were recruited. Infants were imaged in a 3T Siemens MRI scanner at Boston Children's Hospital, MA, USA. All infants underwent MRI without sedation [7]. fMRI images were acquired with a 32-slice echo-planar imaging (EPI) sequence with a TR of 2.85s, TE of 30ms and resolution 3x3x4 mm^3. fcMRI was acquired using an EPI sequence with a 3s TR, TE of 30ms, 85 degrees flip angle, resolution $3mm^3$, 47 axial slices and 160 time-series volumes. Anatomical images (T1) were acquired with a motion-mitigated multiecho MPRAGE sequence at a resolution of 1 mm^3. Artifact detection for fcMRI was performed using ART [8]. Contaminated volumes were removed and remaining time-series were concatenated [9]. Temporal slice correction was applied followed by a regression of motion signal. Functional data were then registered in the brain extracted anatomical space using FSL *flirt* [10]. Signal from CSF and white matter was regressed out before statistical analysis. The statistical analysis strategy consisted of estimating intrinsic RSNs using an ICA approach via *melodic* from FSL [11]. Each RSN *z*-score was thresholded at $p > 0.5$ (alternative hypothesis threshold for activation *vs* null) and superimposed on each individual brain. The fMRI auditory task was based on a previous study in school-age children [12]. Stimuli incorporated tones with rapid and slow initial frequency transitions presented in 16 active and 8 rest blocks. Differences between activation *vs* rest and rapid *vs* slow initial frequency transitions were calculated. The Mullen scales of early learning [13] were administrated prior to MRI in all children (Table 1).

Table 1 Mullen scales of early learning of FHD+ (F) and control (C) infants at the age of the MRI (7, 10 and 12 months). + good; – poor; NA not available.

Mullen Category/Subject	7-F	7-C	10-F	10-C	12-F	12-C
Gross motor	+	+	–	+	–	NA
Visual reception	NA	+	–	+	+	NA
Fine motor	+	+	+	+	+	NA
Receptive language	–	–	–	–	NA	NA
Expressive language	NA	+	+	+	–	NA

Results: Fig. 1 shows MRI results obtained from experiment during natural sleep. Top panel shows RSNs in FHD+ and FHD- infants (7-12 months). Several RSNs were detected: auditory (AU), somatosensory (SS), motor, default network, motor, medial visual, lateral visual, cerebellum, dorsal visual and executive control. The majority of the signal variance was residing in frequency range 0.01-0.1Hz. Bottom panel of Fig. 1 summarizes BOLD activation profiles during the temporal auditory processing task in three age-matched controls. All infants showed brain activation while listening to sounds compared to silence. The two infants ≥ 10 months demonstrated increased whereas the one 7-month old infant showed no difference in temporal-parietal activation for fast compared to slow initial frequency transitions.

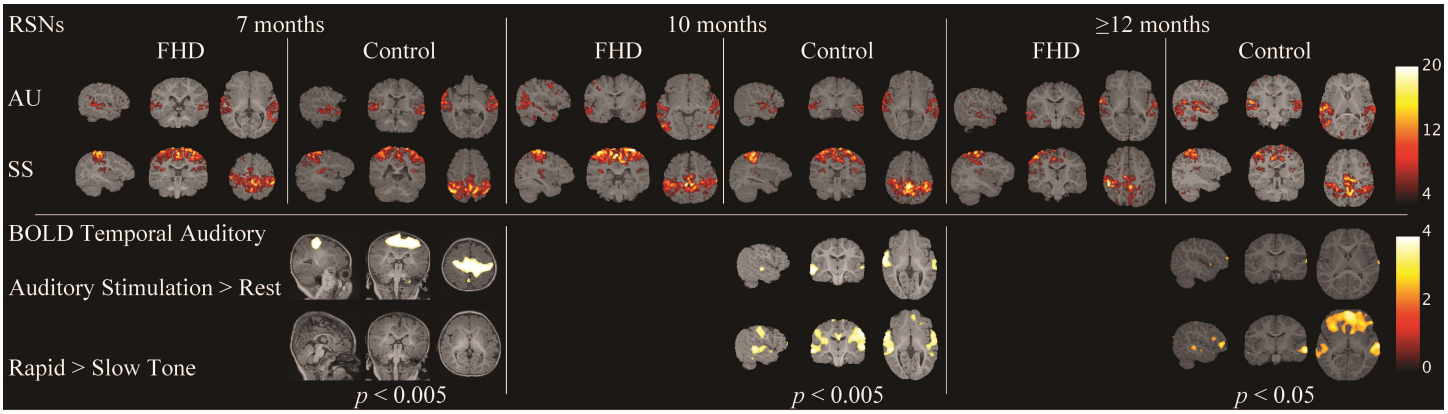

Fig. 1 Top panel corresponds to RSNs (auditory (AU) and somatosensory (SS)). Each view shows a *z*-score in radiological convention. Bottom panel depicts BOLD statistical parametric maps of brain activation during a temporal auditory processing task in three age-matched controls. Two contrasts are shown: activation profiles while listening to sounds compared to silence (Auditory Stimulation > Rest) and rapid *vs* slow initial frequency transitions (Rapid > Slow Tone).

Discussion & Conclusion: These preliminary results indicate successful detection of RSNs and passive functional brain activation is possible in 7-12 months infants during natural sleep. Overall, spatial distributions of identified RSNs are similar to networks obtained in 12-month healthy infants [3]. Detection of auditory activation profiles has the potential to examine differences in neural functions in response to language and sounds in infants with and without a familial risk for DD. Additionally, passive activation maps may be used as seed regions to identify corresponding RSNs. Future work will compare Mullen scores and RSN in a larger group of infants as well as RSNs and results of passive fMRI in a larger group of FHD- and FHD+ infants with follow-up to school age to determine if there are infant predictors of DD. Detection of infant risk factors for DD may reduce the clinical, social and psychological impact of DD.

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