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RESTING STATE FCMRI IN THE SOCIAL COGNITION NETWORK AS A PREDICTIVE MEASURE FOR SCORES OF SOCIALIZATION OF PRETERM NEONATES

by

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Department of Psychology

Submitted in Partial Fulfillment

of the requirements for the degree of

Bachelor of Arts

In

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Abstract

Many resting state networks have been detected in newborn infants using functional connectivity Magnetic Resonance Imaging (fcMRI). Few studies have looked at a social cognition network in adults and none have looked at this network in infants. Social cognition plays an important role in social competence at school age and beyond, and infants born prematurely tend to have difficulties with peer relationships and lower academic performance by school-age. This study had two purposes: to find a social cognition network in our preterm and neurologically diagnosed sample, and to find a relationship to social interaction scores from the Vineland Adaptive Behavior Scales-II (VABS-II). Results showed a positive correlation between an adult fcMRI and neonate fcMRI social cognition network, $r(64) = .59$, $p < .05$, however, no correlation was found between fcMRI similarity (to adults) scores in the first six months, $r(30) = .17$, $p > .05$, or the second six months, $r(30) = .09$, $p > .05$ of life using the VABS-II social interaction category. Results also show no correlation between fcMRI scores of neonates and gestational age, $r(30) = .20$, $p > .05$, nor birth weight, $r(30) = .22$, $p > .05$). There are important implications for government spending, educational support, and child outcomes if we can predict which children need intervention, and implement them sooner than school-age. More research is needed to further assess and confirm the social cognition network in infants and find connections to later social adeptness in children so we can benefit this population sooner.

Keywords: fMRI, preterm, Vineland, social cognition

Contributions

Conor Wild was responsible for conceptualization of the design for this experiment, MRI analysis, use of technical terminology in the methods section, matrix figures, and guidance all throughout the experiment. The author was responsible for background research, behavioural analysis and all other figures. The author was responsible for writing of the manuscript with valuable input from Conor Wild.

Acknowledgments

I wish to express my heartfelt gratitude to Conor Wild for first accepting me as a volunteer in the lab and then agreeing to be my advisor. He helped and encouraged me throughout the entire process of this thesis and offered valuable guidance so that I could learn to think critically myself specifically in data analysis and what results mean and do not mean. I wish to thank Dr. Cole for being my second reader and my measuring post as I worked through each and every figure. Frequently the phrase “would Dr. Cole think this is good” passed through my thoughts, and this made me strive to be precise and comprehensive. I wish to thank Dr. Tsang for her guidance throughout the years; her reality checks along the way and her encouragement helped me to continue plugging away despite many challenges. I wish to thank Huron University College, specifically Andrea Legato, Jane Parker, and Lou the parking guy. This institution is made up of people who care about its students and has created an atmosphere of extended family and I am grateful my experience was at Huron.

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I wish to thank Douglas Westgate, my father, who was always wise, with practical academic advice, who encouraged me to stay at Huron because I loved it, and who always thought I should be in school. Wherever you are, I hope I continue to make you proud dad! I wish to express my gratitude to Kathryn Westgate, my mother, for always being a strong loving voice in my head, and for making things easier as I tried to go to school with many babies. I could not have done it without you! I wish to express my deep appreciation and gratitude to Michael Hasstedt for helping me organize my thoughts, for knowing my thoughts often before I do, and for every edit and suggestion throughout this process. Thank you for our children and for making everything about our life better!

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List of Abbreviations

Frontal-Med	Medial Superior Frontal Gyrus
Inf-Frontal-Med	Superior Frontal Gyrus Medial Orbital
L-IFG	Left Inferior Frontal Gyrus
R-IFG	Right Inferior Frontal Gyrus
L-Ant-Temp	Left Anterior Temporal Pole
R-Ant-Temp	Right Anterior Temporal Pole
SMA	Supplementary Motor Area
L-Angular/TPJ	Left Angular Gyrus/Temporoparietal Junction
R-Angular/TPJ	Right Angular Gyrus/Temporoparietal Junction
L-Cereb	Left Cerebellum
R-Cereb	Right Cerebellum

Introduction

It is estimated that there are more than sixty thousand preterm infants born each year in North America and Europe alone (Doria, Arichi, & Edwards, 2014; Fischi-Gómez et al., 2015) and this number is currently trending upward. Premature or preterm infants are characterized by birth occurring before the 37th week of a typical 40 week gestation or postmenstrual age (PMA). Infants are considered Very Preterm (VPT) when birth occurs prior to the 32nd week PMA (Beaino et al., 2010). Rates of prematurity tend to be higher in populations of lower socioeconomic status (Beaino et al., 2010), that is, infants born to mothers who are likely to suffer from higher levels of stress and where maternal health care is deficient or even non-existent (Doria et al., 2014; Jones, Champion, & Woodward, 2013) and mothers who have limited access to education on prenatal and infant care and breastfeeding (Beaino et al., 2010).

Advanced technologies and medical innovations mean more and more infants are surviving prematurity younger and younger. A negative side effect of this benefit is that studies show 30-60% of infants and children are suffering physical, psychological, behavioural and social deficits (Rogers et al., 2012), depending on the severity of prematurity and other medical factors. Premature infants have to contend with many medical interventions, sometimes painful, as well as maternal separation due to their immediate medical needs (Welch et al., 2015). Infants in a neonatal intensive care unit (NICU) are deprived of maternal soothing of voice, touch, eye gaze, skin to skin contact and heat exchange (Welch et al., 2015). This is a highly stressful environment for infant and parents both, and likely affects the vital early relationships that are so important for social development.

Infants born prematurely can suffer a wide range of medical problems shortly after birth including hypoxia, interventricular hemorrhage, cerebral palsy, respiratory problems, sleep apnea, poor sucking reflex leading to reduced nutrition, infection, stroke and even death (Arichi et al., 2010; Beaino et al., 2010; Cusack et al., 2015; Doria et al., 2014). There is ample evidence that shows the long term consequences of preterm birth in a number of areas as well. Preterm children at age two showed higher rates of behavioural problems (Spittle et al., 2009) when compared with their term counterparts. There are difficulties in vision, audition, language both receptive and expressive, attention, social attribution, social relatedness and executive function (Alduncin, Huffman, Feldman, & Loe, 2014; De Schuymer, De Groote, Desoete, & Roeyers, 2012; Foster-Cohen, Edgin, Champion, & Woodward, 2007; Grunau, Kearney, & Whitfield, 1990; Hille et al., 2007; Vohr, 2014; Welch et al., 2015; Williamson & Jakobson, 2014). Rates of Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are both higher in children born prematurely (De Schuymer et al., 2012; Doria et al., 2014; Rogers et al., 2012; Welch et al., 2015) and the World Health Organization statistics show 1 in 68 children are diagnosed with ASD (Baio, 2014) Children in this group have difficulty inferring the mental states of others (Williamson & Jakobson, 2014), have low academic achievement (Doria et al., 2014), are less socially competent than their peers in preschool (Alduncin et al., 2014) and by the time they become adults they self-report a higher rate of negative self-esteem and less social interactions, less social relationships and often live alone (Gallagher & Frith, 2003; Hallin & Stjernqvist, 2011; Jones et al., 2013).

Although it is possible to detect, at birth, some developmental impairments that can be caused by preterm delivery, such as hearing and vision impairment, we are not presently able to predict which children will have other more complex cognitive deficits by school-age (Cusack et al., 2015). Assessments for older children and adults can be straightforward (e.g., using tests or tasks), but assessing infants is much more complicated (Cusack et al., 2015). In particular, it is only possible to detect developmental delays in social cognition when a child is of an age when they would be able to demonstrate normal behaviour.

Social cognition encompasses a few specific behavioral adaptations including the concept of Theory of Mind. Theory of Mind is a psychological concept that defines the human skill that allows us to understand that our thoughts and beliefs are not the same as the thoughts and beliefs of others (Gallagher & Frith, 2003). This is sometimes referred to as mentalizing and it includes empathy towards others, cooperation behaviours, pretending, imagining the past, present, or future, and predicting what others would do in many varied and complex situations (Gallagher & Frith, 2003; Gallese & Goldman, 1998; Tversky & Kahneman, 1974). There is some evidence that newborn infants are equipped with the faculties to develop these important social skills. For example, an infant, only an hour old, can stick out his tongue in response to the visual stimulus of an adult sticking out his tongue even though he isn’t even aware he has a face (Meltzoff & Decety, 2003). This cognitive ability appears to be an innate system, that is, a neurological system present at birth that is ready to respond to experiential learning, and forms the basis for Theory of Mind and Social Cognition (Meltzoff & Decety, 2003). The infants’ ability to imitate forms the basis of learning, crucial to all social interactions (Social Cognition) throughout the lifespan (Meltzoff & Decety, 2003; Rizzolatti & Craighero, 2004).

All social competence begins with evaluating and understanding the thoughts and beliefs of others, predicting the behaviour of others and responding accordingly (Hamlin, Wynn, & Bloom, 2007). It is a complex process that involves the rapid identification of social cues and it is a biological adaptation that forms the basis of our own set of moral thoughts and beliefs and aids in our emotion regulation and social organization (Hamlin et al., 2007; Jones et al., 2013; Rizzolatti & Craighero, 2004). Social incompetence is characterized by poor academic performance, behaviour problems, difficulty with attention span, difficulty processing emotions, difficulty adjusting and transitioning between social environments, ADHD patterns, inhibitory control issues and difficulty maintaining relationships and conflict with siblings and peers (Fan, Portuguez, & Nunes, 2013; Fischi-Gómez et al., 2015; Jones et al., 2013; Rice, Sell, & Hadley, 1991).

Infants born VPT are often unable to catch up with their peers, as was once the assumption; this can result in, or may be a consequence of social competence deficits (Jones et al., 2013; Rogers et al., 2012). In one study, poor social behaviour of preterm infants at Age 2 was predictive of poor social behaviour at Age 5 (Rogers et al., 2012), VPT preschool-aged children had several social difficulties that made them withdrawn and passive resulting in poor academic performance (Jones et al., 2013) and another study showed that children with language impairments due to prematurity had less social engagement with peers and teachers, affecting their learning and performance which limited their social experiences during play and made them less likely to ask for help from teachers (Rice et al., 1991). The increased survival rate of preterm infants means that these social deficits are affecting not only families but schools, teachers and government funding for programs to help meet the needs of these children.

When children enter school at Ages 4 and 5, differences are often apparent and can be noticed by teachers and staff who then alert parents and administrators who then help the children by assessments, interventions and programs designed to improve cognitive ability and performance. But what if we were able to intervene sooner? Studies have shown that mothers who talk soothingly to their infants in the NICU and exchange clothing so mother and baby have each other's scents when they are not together and who share sustained eye contact show improved development as assessed by the Bailey III (Welch et al., 2015). Intervention programs that educate first-time mothers with their 3-month old infants on attentiveness and responsiveness help mother and baby interact bi-directionally. This improved their mutual social cuing and showed improved mother and infant social scores at 12 months using the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care (2005) (Ravn et al., 2011). If we are able to predict which infants have an increased chance of developing social cognitive deficits, we can implement programs like these early when we can help close the developmental gap of not only the dyadic relationships of mother and baby, vital to social development, but also the gap between socially maladroit children and their socially adept peers (Ravn et al., 2011; Smyser, Snyder, & Neil, 2011).

Determining which children will need help by school-age is currently impossible to accurately predict. Early detection and intervention is imperative in the prevention of later deficits, as can be seen in the case of Cochlear Implants (Nikolopoulos, O'Donoghue, & Archbold, 1999) and language intervention (Kennedy et al., 2006) Several assessment tools have been used to try to tackle the detection of cognitive deficits, such as the social network, with some limited success.

Child behavioural assessments for social development include the Wechsler Intelligence Scale for Children (WISCIII) (2005), child behaviour checklists, Denver II (1992), Bailey III (2006) and the Vineland Adaptive Behavior Scales-II (VABS-II; 2005) (Alduncin et al., 2014; Fan et al., 2013). Most of these tests are not appropriate for detecting social cognitive deficiency for infants as they require advanced behavioural functions of older children making data acquisition difficult or impossible. Bailey assessments are excellent tools however they are complex and require several hours of testing by a skilled professional to collect and assess. The VABS-II, by contrast, is a fairly simple assessment that can be completed by a parent and addresses four main areas of skill - motor, social, language and self-care (Sparrow, Cicchetti, & Balla, 2005).

Assessments are not the only tools available to us in diagnosing developmental delays in children. Common neuroimaging tools such as Ultrasound, electroencephalography (EEG), positron emission tomography (PET), and magnetic resonance imaging (MRI) are also widely used in research as a means to detect differences in brain anatomy or function. Ultrasound is used to assess brain lesions in infants and can be a good tool due to its non-invasive nature, ease of use and availability, however, detail is poor and smaller anatomical abnormalities can often get missed (Beaino et al., 2010; Doria et al., 2014). EEG which measures bulk electrical activity in the brain, shows promise for detecting abnormal patterns of brain activity following injury due to premature birth (Watanabe, Hayakawa, & Okumura, 1999) but it does not have the spatial resolution necessary to localize the affected brain regions. PET which gives an image of brain function by measuring metabolic activity, has been used to study prematurely born infants (Y. Shi et al., 2009) but is not often used for infant research (or clinical scans of infants) due to radiation exposure.

MRI, on the other hand, is non-invasive and does not expose subjects to radiation, and it can provide highly detailed images of brain structure and function. Specifically, diffusion tensor imaging (DTI), a kind of MRI that measures white matter pathways in the brain, (structural connectivity), has been used to show differences between preterm and term infants (Doria et al., 2010, 2014; Fischi-Gómez et al., 2015; Rogers et al., 2012; Smyser & Neil, 2015). Structural MRI has also been used to demonstrate the impact of preterm birth on gray matter density in various brain regions (Ball et al., 2012; Boardman et al., 2006; Hao Huang, Jiangyang Zhang, Setsu Wakana, Weihong Zhang, Tianbo Ren, Linda J. Richards, Paul Yarowsky, Pamela

Donohue, Ernest Graham, Peter C.M. van Zijl, 2006). Functional MRI (fMRI), which estimates brain activity by measuring the blood oxygenation level dependent (BOLD) signal, has excellent spatial resolution and reasonable temporal resolution, and is proving to be an invaluable tool for understanding the impacts of preterm birth on brain development. Functional MRI can be used to measure the infant brain's response to external stimuli (Arichi et al., 2010) or to characterize brain networks using functional connectivity (fcMRI). Importantly, fcMRI has been used to demonstrate that many of the functional brain networks that are seen in adults are also present in premature and term born infants (Doria et al., 2010), and furthermore, that there are detectable differences in these networks as a consequence of preterm birth (Smyser & Neil, 2015). Given that many functional brain networks can be measured in very young infants with fcMRI, this method holds promise as an assessment tool for early social functioning by detecting abnormal functional development of the brain regions that support social cognition. This could be an important predictive tool so that we can recommend interventions that would have a higher success rate if introduced earlier than preschool age (Cusack et al., 2015; Smyser et al., 2011; Welch et al., 2015).

Neuroscientific research has shown that there are systems in the brain that support social cognitive function. For example, research with non-human primate models has shown that there are specific neurons located in the ventral premotor cortex (mirror neurons) that activate when an action is performed as well as when the action is witnessed (Gallese & Goldman, 1998). It has been proposed that this neural "action/observation matching system" could provide a mechanism for learning, and is involved in other important aspects of Theory of Mind (Gallese & Goldman, 1998) though this theory is not without its criticisms (Hickok, 2009; Rizzolatti & Craighero, 2004). Nonetheless, there is a wealth of functional neuroimaging studies that implicate specific brain regions in social functioning.

In a meta-analytic review there was evidence that somatomotor areas which include the temporoparietal junction (TPJ), posterior cingulate and medial prefrontal cortex activate together during social tasks that require participants to judge body language, mind reading, understanding the intentions of others, mirroring behaviours and deducing personality traits (Van Overwalle, D'aes, & Mariën, 2015). Patients who had lesions in the TPJ had incorrect responses to false belief tasks (Rebecca Saxe, Schulz, & Jiang, 2006); the right posterior temporal sulcus which runs through the TPJ activates when participants observe intentional actions (R. Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004) and the medial prefrontal cortex showed activation when participants were asked to imitate the goals of others (Meltzoff & Decety, 2003). Imagining others thoughts activated regions including the ventral, medial and dorsal medial prefrontal cortex (Rebecca Saxe & Powell, 2006). Reasoning about the mental state of others showed a stronger BOLD response in the TPJ in both the left and right hemispheres but when verbal stimulus was used, the left side was stronger and when non-verbal photos were used, the right side showed a stronger signal (R Saxe & Kanwisher, 2003).

All of this research has been done in adult models so what does that mean for infants? Babies likely develop this social neural network early, possibly as early as the third trimester of gestation (Doria et al., 2010) when axonal migration is prolific. Evidence indicates there are neuroanatomical links to behaviour, in that, regions with injury tend to show similar behavioural dysfunction across subjects (Rogers et al., 2012). In the preterm infant there are several abnormalities commonly found including white and gray matter volume losses (Fischi-Gómez et al., 2015; Rogers et al., 2012). Networks often have disorganized activation, lower efficiency and weaker connectivity and generally behave poorly compared with term counterparts (Doria et al., 2010; Fischi-Gómez et al., 2015; Rogers et al., 2012) and social behaviour in preschool shows impairment. This connectivity impairment appears to be correlated with social performance in reward based behaviour, socio-emotional problems, emotional processing problems and poor prosocial behaviours with peers (Fischi-Gómez et al., 2015; Rogers et al., 2012).

Early intervention is a crucial piece of any long term success plan; cochlear implants are a good example of this (DesJardin & Eisenberg, 2007). If these specific regions show co-activation and if there is a relationship between the age of the preterm infant and their behavioral scores, fcMRI could be an early detection tool and we can put in place early interventions as a front-line defence against future social cognitive problems in the preschool aged child.

It has not been established whether the presence or strength of this social cognition network reflects social function. This study will investigate the presence and/or strength of this social cognitive network, as measured with fcMRI, and that it will be predictive of social ability, as measured through the VABS-II (2005).

Methods

Participants

Seventy-one neonates with a birth age between 24 and 41 weeks gestational age (GA) (*M* = 30.73, *SD* = 5.47) were recruited from the neonatal intensive care unit (NICU) at London Health Sciences Center, Victoria Hospital, in London, Ontario, Canada. These included infants who were born VPT or who were referred for scanning due to an adverse birth event, therefore, participants ranged from neurologically healthy to severely injured. If an infant met the inclusion criteria for this study, their parents or caregivers were asked to participate by a member of the neonatology and neurology team. If they agreed, the caregivers gave signed and informed consent. The requirements included a referral for a clinical MRI (determined by the medical team), and eligibility to be enrolled in the Canadian Neonatal Follow-Up network, which requires being born at 29 weeks gestation or less, or other events that increase the risk of neurodevelopmental complications. Infants with any contra-indications for MRI (e.g., ferromagnetic implants) were excluded from the study. Ethics approval was obtained from the Health Sciences Research Ethics Board of the University of Western Ontario.

Of the 71 neonates with fcMRI data, two infants were excluded due to MRI acquisition later than Term Equivalent Age (TEA). Fifteen infants were excluded due to normalization errors. Normalization is the process of fitting individual brain images to a template; some brain variations make this impossible. Two infants were excluded due to coregistration errors. Coregistration errors include anomalies in the brain as well as movement errors and artifacts. One infant was excluded due to unexplained missing fMRI data. Fifty-one infants remained.

Seventy-nine infants (which included the 71 from the MRI portion as well as controls) were recruited for behavioural data collection. Of the 79 infants, two were excluded due to non-TEA scans, four were lost due to infant death, eleven were excluded as controls, and twenty infants were excluded due to contact difficulty. Forty-two infants remained.

The two pools of infants were compared which resulted in 32 infants for which we had both fcMRI and behavioural data, shown in the flow chart in Figure 1.

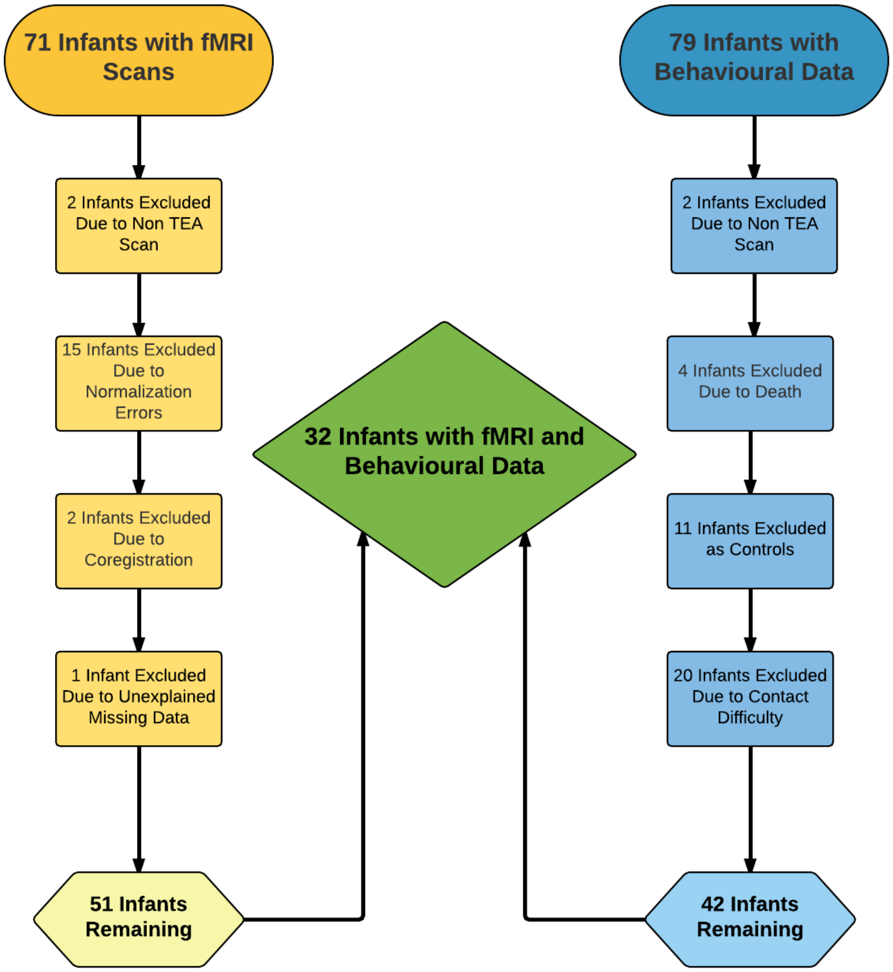

Figure 1. Flow chart showing infant exclusions

Dataset

The complete dataset included results obtained from 32 infants born between the ages of 24 and 41 weeks GA (*M* = 30.06, *SD* = 5.52) for which we had fcMRI and behavioural data. The sample included data from 22 males and 10 females. These infants ranged from being neurologically healthy to having a variety of medical diagnoses including: respiratory distress (45 infants); apnea (44 infants); IVH grades 1-5 (28 infants); sepsis (27 infants); bronchopulmonary dysplasia (22 infants); pneumonia (13 infants); cysts (12 infants); hydrocephalus (9 infants); hypoglycemia (9 infants); edema (8 infants); pulmonary hypertension (8 infants); seizures (8 infants); hypoxic-ischemic encephalopathy (7 infants); hemorrhages or hematomas (6 infants). The birth weight of the infants ranged from 490 grams to 4110 grams (*M* = 1484, *SD* = 1003.65).

For the first hypothesis, to ascertain similarity between the adult and neonate social cognition network, 51 participants were used, and included all usable infant fMRI data. Exclusions were due to: unexplained missing fMRI data (one infant); normalization errors (15 infants); coregistration errors (two infants); and non-TEA at time of scan (two infants).

MRI Acquisition

Infants were scanned at approximately term equivalent age (TEA; *M* = 38.61 weeks, *SD* = 2.31) on a 1.5 Tesla GE MR450W scanner with a 24 channel GE head coil at London Health Sciences, Victoria Hospital campus. To minimize motion during scanning, infants were securely swaddled in a vacuum cushion (Med-Vac Infant Immobilizer: http://cfimedical.com/medvac/). To protect them from the noise of the MRI scanner, they were equipped with earplugs, minimuffs (http://www.natus.com/index.cfm?page=products_1&crid=199), and ear defenders. Subjects were given a soother to comfort them during scanning, and were administered doses of sucrose to calm them if they became agitated during the session scanning. A pulse-oximeter was used to monitor the infants' heart rate and oxygen saturation while they were in the scanner, and a noise-cancelling MR-compatible microphone was used to hear the infant during the scan. A NICU trained nurse was present during the entirety of the session.

Infants first underwent a clinical scanning protocol that included T1- and T2-weighted structural images and diffusion imaging. After the successful acquisition of all clinical MR images, the research protocol consisting of four functional MRI runs was administered. Each fMRI run was approximately seven and half minutes long, and consisted of 220 volumes. fMRI volumes were gradient-echo echo planar images (EPIs) with the following parameters: repetition time (TR) 1920 ms; echo time (TE) 60 ms; flip angle 70 degrees; matrix size 44 x 44; field of view 9.075 x 9.075 cm^2; voxel size in-plane 2.0625 x 2.0625 mm^2; slice thickness 3.8 mm, with no slice gap; and 22 slices per volume acquired in an ascending order. Acquisition was oblique, angled away from the eyes, and covered the whole brain in most cases; for participants that did not fit within the 22 slices, the volume was positioned to exclude the top of the parietal lobe.

fMRI Data Pre-Processing and Analysis

MRI data were processed using automaticananalysis (version 4.1;(Cusack et al., 2014): a MRI data processing and analysis pipeline that integrates commonly used software packages (e.g., SPM8; Wellcome Centre for Neuroimaging, London, UK) with custom Matlab code. Pre-processing steps included: 1) rigid realignment of each EPI volume to the first of the session, and generation of a mean EPI image; 2) co-registration of the structural (T2) image to mean EPI; 3) estimation of the non-rigid registration (normalization) between the structural image and a neonatal template image (University of North Carolina (UNC) 40wk neonate template; (F. Shi et al., 2011) using SPM8's unified segmentation routine; and, 4) band-pass filtering from 0.01 to 0.1 Hz. No smoothing was applied to the fMRI data. The quality of the normalization was inspected by eye, and participants were excluded on the basis of subjective "bad" normalization. The non-rigid transformations were used to warp the regions of interest (ROIs; see below) to the individual subjects' space.

Regions of Interest (ROIs)

Regions of interest were created using Neurosynth (www.neurosynth.org; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) - a large-scale meta-analytic tool with access to 11,406 fMRI studies of adult data – to identify brain regions that are involved in social cognition processes. First, Latent Dirichlet Allocation (LDA; (Blei, Ng, & Jordan, 2003) analysis – a standard modeling approach to parsing texts, such as scientific abstracts and articles – was used to find topics of related (i.e., co-occurring) terms in the Neurosynth database (Poldrack et al., 2012). One of these, Topic #17, was characterized by the top-loading terms: social, empathy, person, mentalizing, mental, people, cognition and mind. Neurosynth provided a reverse inference map of brain areas in which activation would suggest a high likelihood that a study contained one or more of those terms – that is, areas that were *specifically* activated in fMRI studies that contained words related to "social".

We used an adaptive thresholding technique to parcellate this continuous z-score map into discrete brain regions of interest; this process yielded 12 ROIs. Figure 2 shows these regions on the UNC neonatal template and the typical adult brain template. These regions included the Supplementary Motor Area (SMA), Medial Superior Frontal Gyrus, Left and Right Angular Gyrus (including the TPJ), Precuneus, Superior Frontal Gyrus Medial Orbital, Left and Right Anterior Pole, Left and Right Inferior Frontal Gyrus, and the Left and Right Cerebellum.

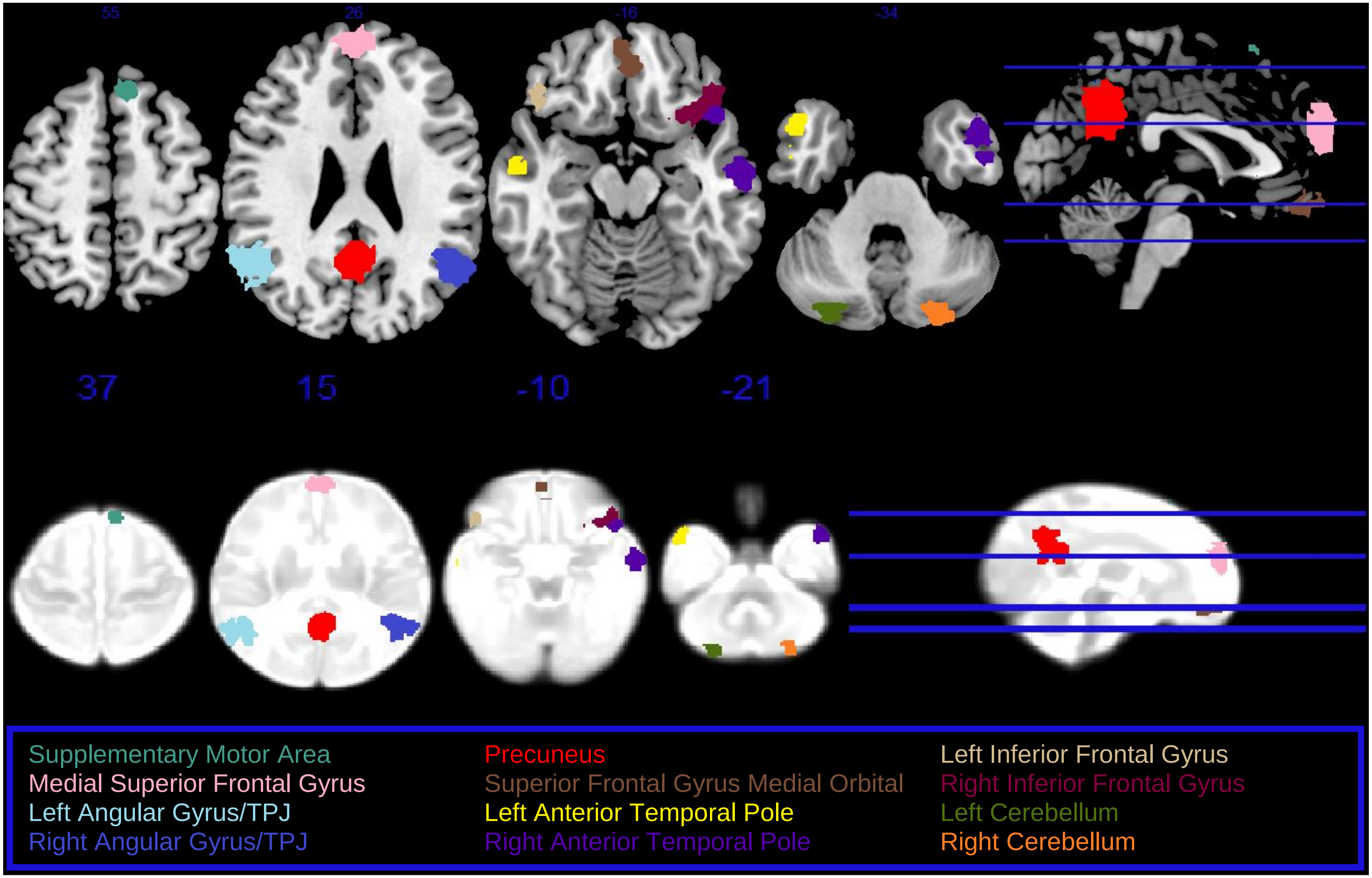

Figure 2. Twelve Regions of Interest (ROIs) plotted on the adult and corresponding neonate templates. TPJ (temporoparietal junction) and other abbreviations found on page vii.

Functional Connectivity Analysis

Functional connectivity matrices, representing the strength of the functional connections among the nodes of the social cognition network, were created for each participant and session. First, the time series of fMRI activity was extracted from each ROI by averaging across all voxels in the ROI at each point in time. Then the correlations between all pairs of regions were calculated. Realignment parameters (produced by the rigid realignment pre-processing stage) were bandpass filtered and partialled out of the correlation calculation to control for the confounding effects of motion. Finally, the connectivity matrices were averaged across sessions to yield one matrix per participant. An adult connectivity matrix was obtained in the same manner from 16 adult scans available in the Cusack lab at Western University. The neonatal matrices were then compared to the adult mean functional connectivity matrix, by correlating the two matrices, to provide an estimation of the network "similarity". A higher similarity score (i.e., correlation value) would suggest that the pattern of network connectivity for a neonate looked adult-like, whereas a value closer to zero would suggest that the pattern of network connectivity looked quite different from the adult network.

Behavioural Data Collection

Social development was assessed behaviourally using the Vineland-II Adaptive Behavior Scales (Sparrow et al., 2005). The VABS-II assesses four categories of behaviour – motor, social, self-care, and language skills – and has been used to assess cognitive abilities for decades since the first version in 1953 and is internationally accepted as the gold standard measurement for anyone from birth to age 90 with a potential cognitive deficit (Scattone, Raggio, & May, 2011). There were a total of 99 questions in the social category, made up of three sub-categories: interaction, play, and coping. For the purposes of this study, the social behaviour results, specifically the social interaction portion, were isolated and the other categories were excluded. Example questions a parent or caregiver might be asked include: “Reaches for familiar person when person holds out arms to him or her”; and “Shows interest in where he or she is (for example, looks or moves around, touches objects or people, etc.)” (Sparrow et al., 2005). Question responses were limited to the options: usually, sometimes or partially, never, or, don’t know. The VABS-II was administered by telephone by researchers in our lab when the participants were of corrected ages 3, 6, 9 and 12 months and scored by researchers in the Cusack Lab at Western University. To collect the data, an appointment was made with a parent or caregiver of the participant for a future date within 30 days of the participant’s term equivalent age of 3, 6, 9 and 12 months. Each appointment ran anywhere from 30 minutes to 1 hour depending on the age and developmental level of the subject. Questions were asked until the participants’ parent/caregiver answered ‘no’ four times in a row, at which point the VABS-II criteria was met. All participants were coded so that scoring was anonymous; scoring was completed by someone other than the interviewer. There were missing time points of behavioural data; therefore z scores were calculated for each participant at each time point; then scores for 3 and 6 months were collapsed and averaged, as were 9 and 12 months, resulting in one set of behavioural scores for the first half year and another for the second half year, to correlate with fcMRI data.

Results

Results show a significant positive correlation between the fcMRI adult social cognition network and the fcMRI neonate social cognition network, $r(64) = .59$, $p < .0001$. Figures 3 and 4 show the mean adult connectivity matrix and the mean neonate connectivity matrix respectively. To statistically test whether the neonatal functional connectivity matrix is similar to the adult

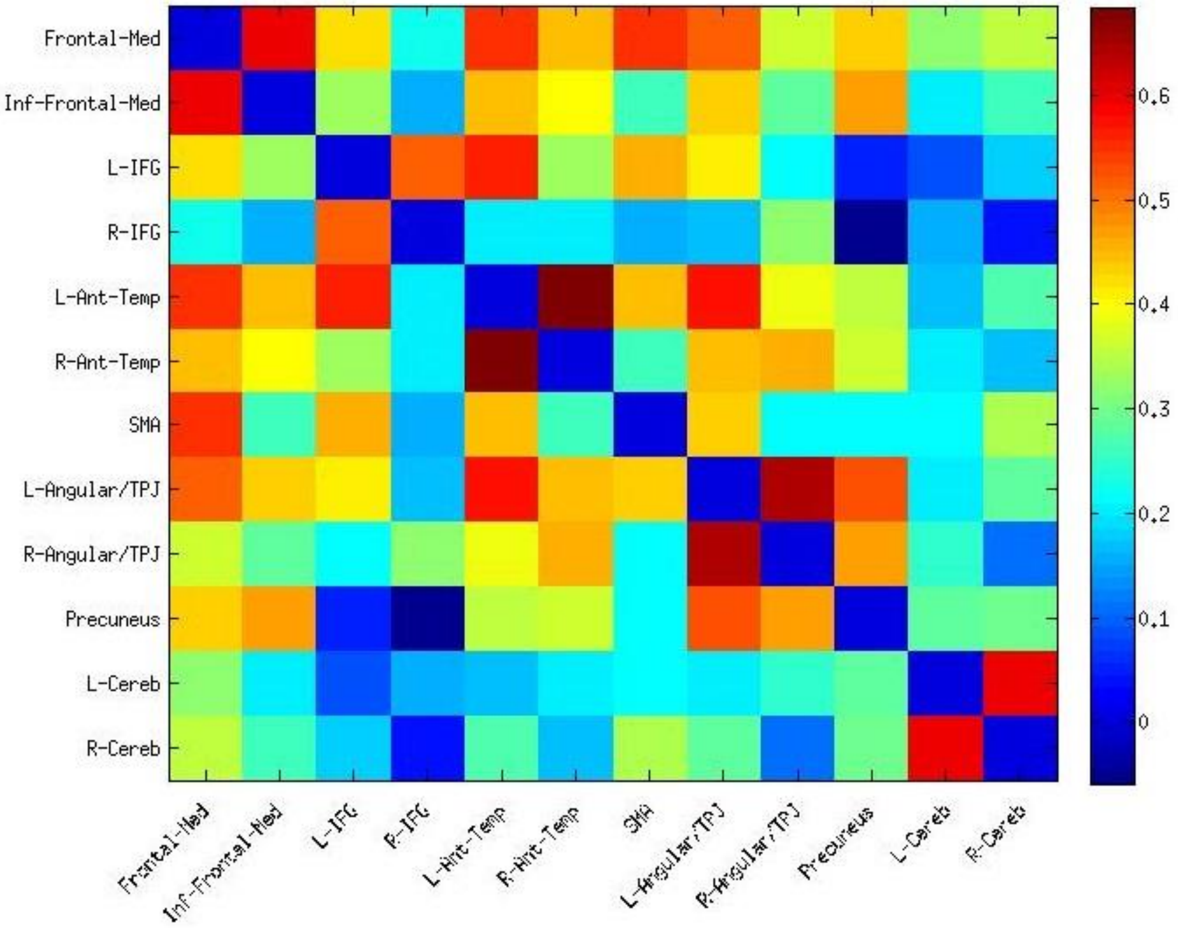

Figure 3. Mean adult functional connectivity matrix of a social cognition network (N=16). Higher correlations between regions are darker red with weak correlations as dark blue. The 1.0 diagonal correlations have been zeroed out to avoid distraction. Brain region abbreviations can be found on page vii.

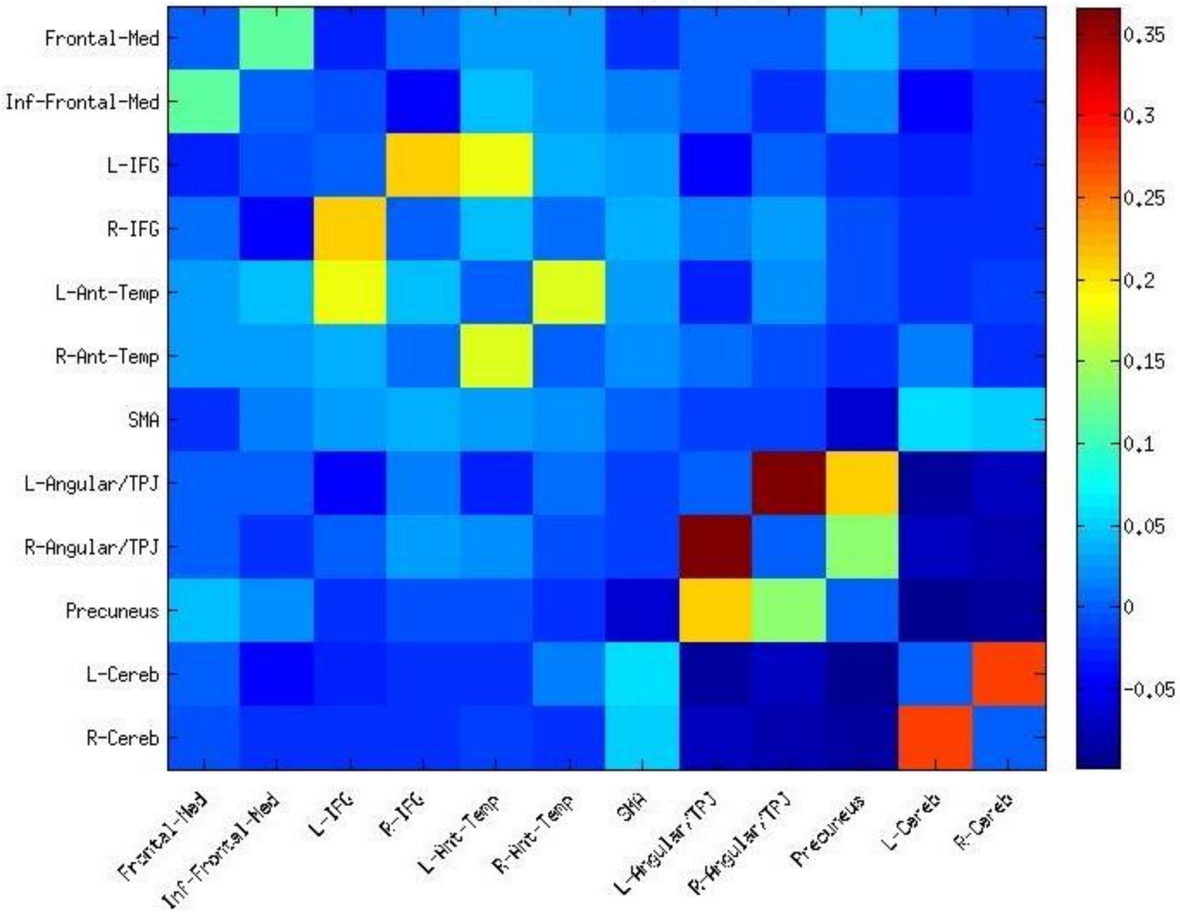

Figure 4. Mean neonatal connectivity matrix of a social cognition network (N=51). Higher correlations between regions are darker red with weak correlations as dark blue. The 1.0 diagonal correlations have been zeroed out to avoid distraction. Brain region abbreviations can be found on page vii.

functional connectivity matrix, we first calculated the Pearson correlation between the off-diagonal elements of the mean neonatal matrix and the off-diagonal elements of the mean adult matrix. This yielded a correlation value of 0.591. Next, we performed a permutation test in which we calculated the correlation between 10,000 randomly scrambled versions of the mean connectivity matrices. These correlations represent the similarity between matrices which have no correspondence; that is, they represent the null hypothesis that the pattern of functional connectivity in the neonatal social cognition network does not correspond to the adult pattern of connectivity. The distribution of these null correlations is shown in Figure 5. The real correlation ($r = 0.591$) is greater than every single one of these null correlations (Figure 5; red line), and so we can conclude that the patterns of functional connectivity are more similar than one would expect due to chance ($p < 0.0001$).

A paired-samples t-test was conducted to compare the VABS-II social interaction scores between the first six months and the second six months. There was a significant difference in the scores for the first six months ($M = -0.28$, $SD = 0.95$) and second six months ($M = 0.41$, $SD = 0.86$) social interaction scores; $t(16) = -2.86$, $p = 0.01$ (Figure 6).

A paired-samples t-test was conducted to compare the VABS-II social play scores between the first six months and the second six months. There was no significant difference in the scores for the first six months ($M = -0.17$, $SD = 0.97$) and second six months ($M = 0.08$, $SD = 1.28$) social play scores; $t(17) = -0.85$, $p = 0.41$ (Figure 6).

Results show no correlation between fcMRI scores of neonates and the Vineland Adaptive Behavior Scales-II test scores for Social Interaction at Ages 3 and 6 months collapsed, $r(30) = .17$, $p > .05$). Results also show no correlation between fcMRI scores of neonates and

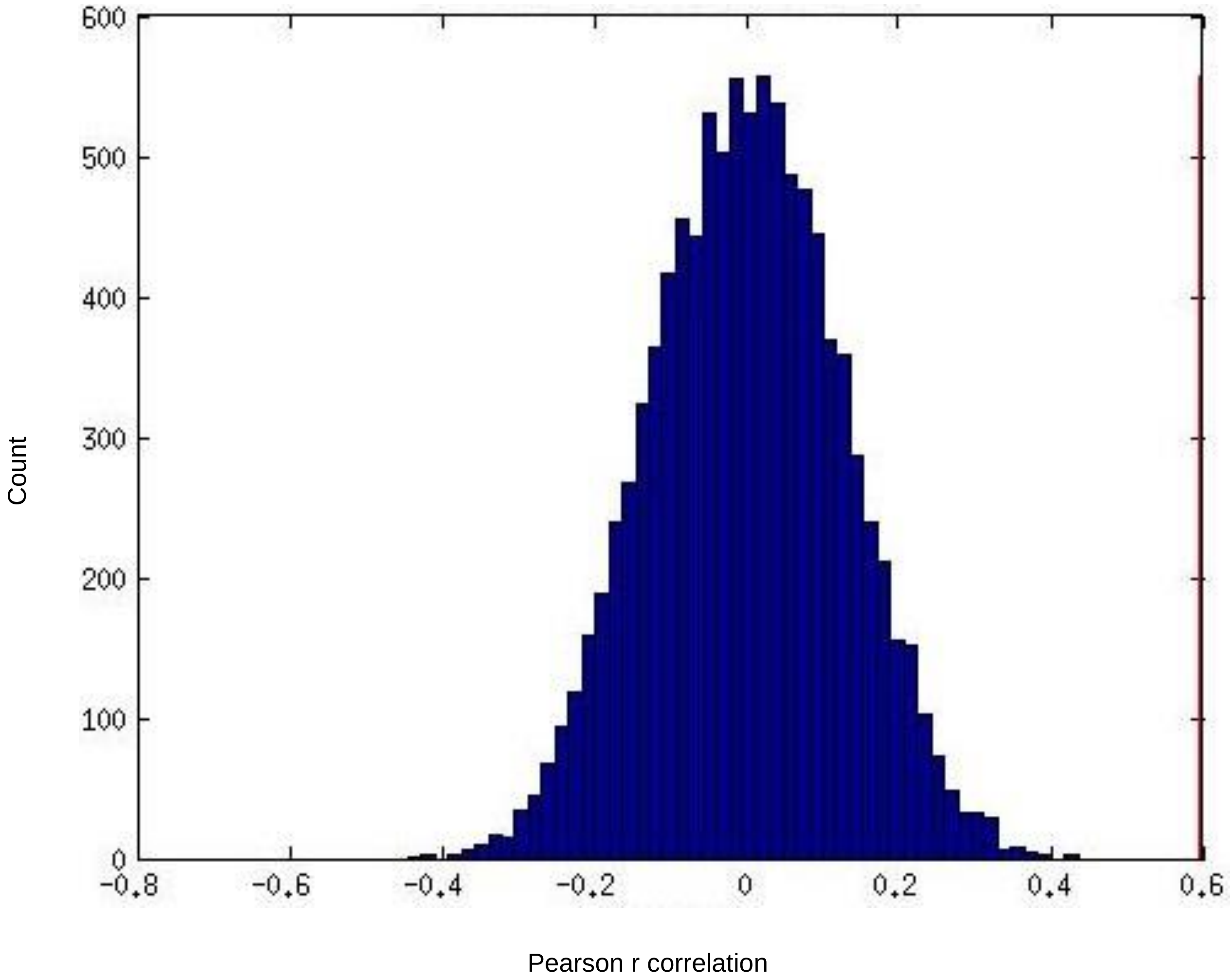

Figure 5. Distribution of null hypotheses for 10,000 permutations of randomly scrambled mean connectivity matrices.

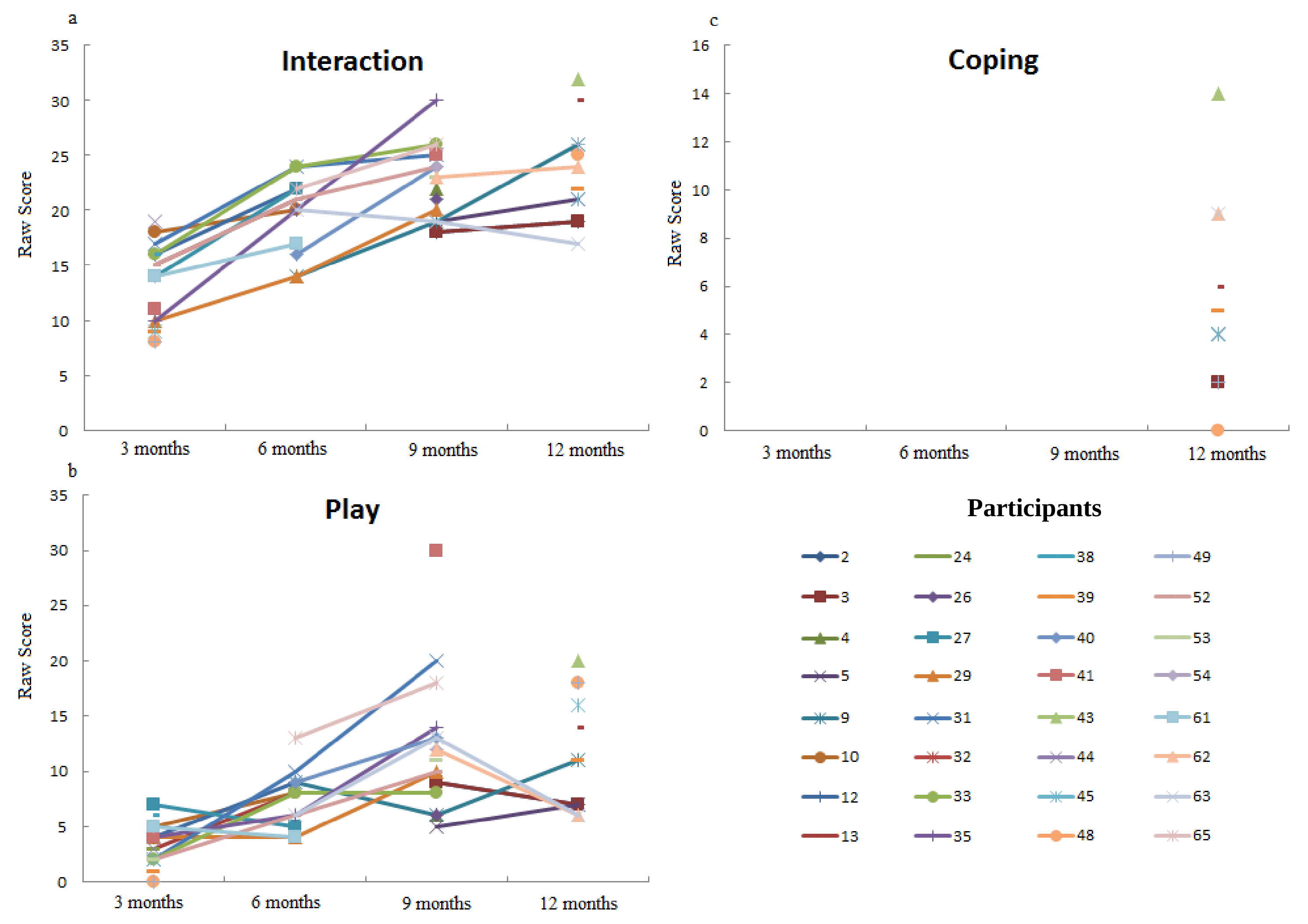

Figure 6. Raw scores of the VABS-II for 32 infants at each time point of 3, 6, 9 and 12 months for three subcategories of socialization: a) interaction; b) play; and c) coping.

the VABS-II test scores for Social Interaction at Ages 9 and 12 months collapsed, $r(30) = .09$, $p > .05$. Results are shown in Figure 6.

Results show no correlation between fcMRI scores of neonates and gestational age, $r(30) = .20$, $p > .05$, nor birth weight, $r(30) = .22$, $p > .05$). Results are shown in Figure 7.

Discussion

There is ample evidence for Resting State Networks in newborn infants (Biswal, Yetkin, Haughton, & Hyde, 1995; Doria et al., 2010; Smyser & Neil, 2015). Studies have largely focused on motor and somatosensory networks, vision network, auditory networks, and the default mode network (Doria et al., 2010, 2014; Smyser & Neil, 2015; Smyser et al., 2010, 2011). There is very little functional connectivity research on a social cognition network of infants and this study offers evidence that supports the hypothesis that this network not only exists in infants but that infants are born with this network already in place. It would seem intuitive that there would be connectivity between paired regions in the hemispheres, both left and right tempo-parietal junction, for example, but connectivity is seen throughout more than just homologous pairs of regions. Results show a correlation between the mean adult resting state social cognition network and the mean infant resting state social cognition network, even in our preterm and neurologically impaired dataset. This result could mean that this system is a vital component to early social development of children.

Future study of the social cognition network could look at more region-specific information; it may be more informative to identify fewer regions that play a larger role in social cognition for comparison and prediction. It is important to note that there are similarities in the social cognition network and the default mode network (thought to be involved with our inner

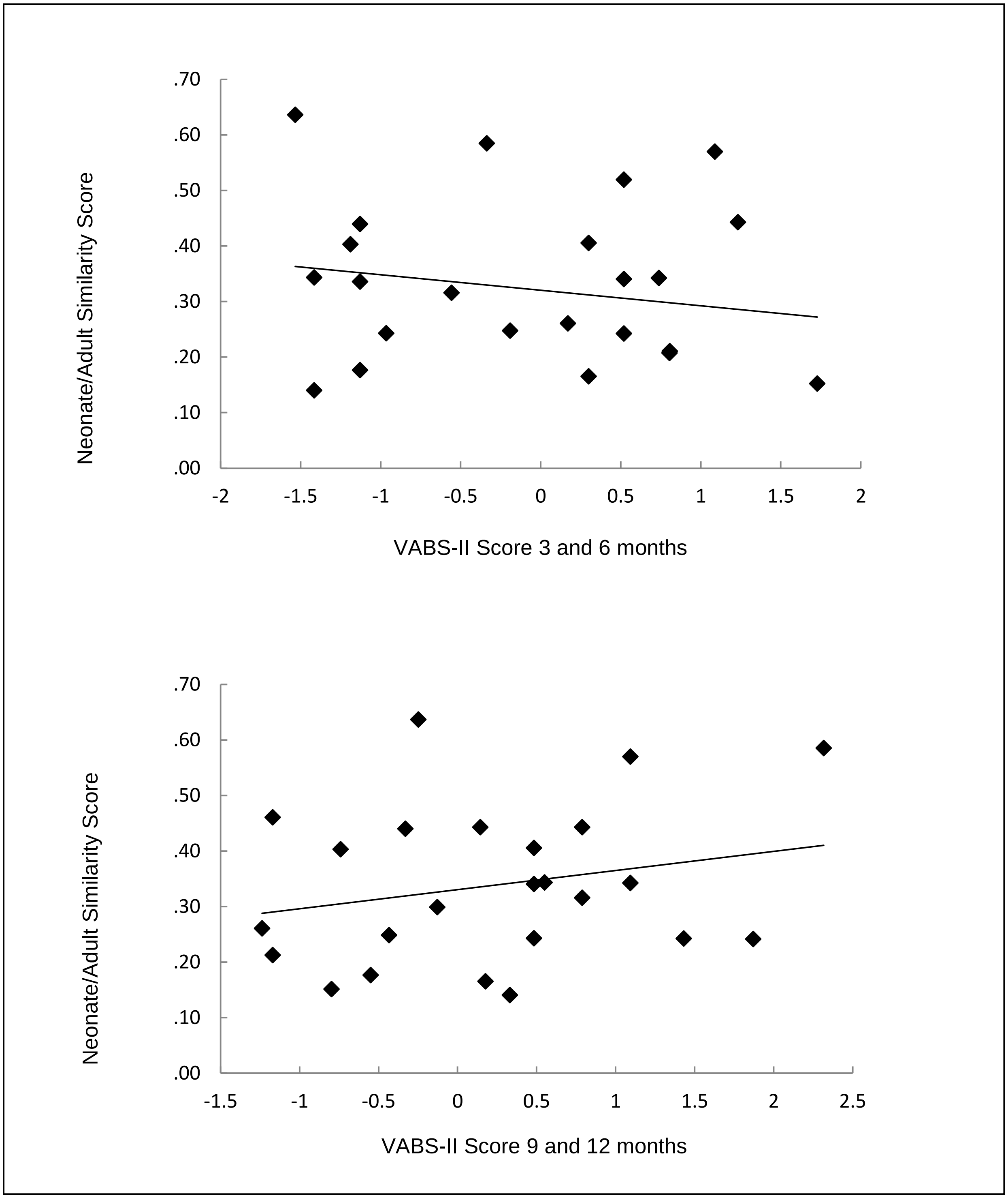

Figure 7. a) VABS-II and fcMRI similarity score correlation 3 and 6 months collapsed, and b) VABS-II and fcMRI similarity score correlation 9 and 12 months collapsed.

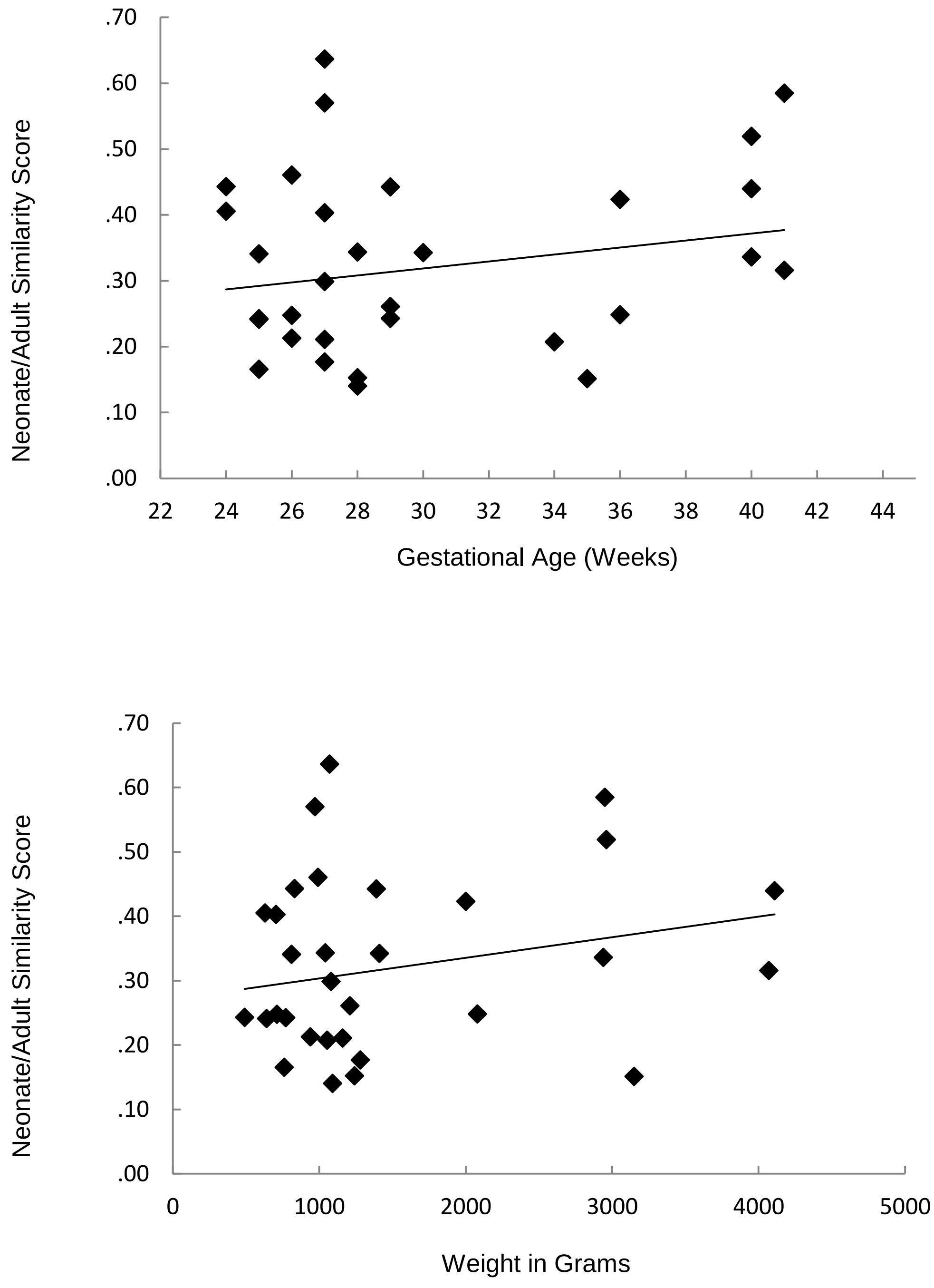

Figure 7. a) Gestational age and fcMRI similarity score correlation, and b) Birth weight and fcMRI similarity score correlation.

monologue and self-reflection) but there are also significant differences between the two networks. The default mode network has been shown to include activity in the hippocampus, posterior cingulate, prefrontal cortex and the parietal opercular cortex (Doria et al., 2010; Smyser et al., 2010). While there is some overlap with the social cognition network, including the prefrontal cortex, cerebellum and smaller parietal regions, the differences indicate the possibility of a separate network for social cognition. Further study in identifying these differences could help us delineate the separate networks and their function to enable us to be more specific in our predictions of future problems in preterm populations.

With the establishment of a social cognition network, the question then became, could this social cognition network be predictive of social ability within the first year of life? If this network were predictive, then it would be a valuable tool for identifying which preterm infants might have a social deficit later in life. To test this, the fcMRI similarity scores for each infant were compared to VABS-II scores from the first 6 months and the second 6 months of life. Results showed no correlation between fcMRI similarity score and averaged scores of VABS-II in either the first six months or the second six months. There were also no correlations between fcMRI scores and birth weight, or gestational age. One possible explanation could be that medical diagnoses were more likely to be indicative of behavioural scores; infants in our study had varying birth weights and varying behavioural scores but there didn’t appear to be a pattern with behavioural measures. An infant may have been born with a low birth weight or VPT but that did not necessarily mean that the infant had any more tendency to have problematic diagnoses, nor did age and birth weight indicate severity of diagnosis. Our sample was also too small to separate infants into specific diagnoses to look for relationships between diagnosis and behaviour.

Another reason we may not have found a correlation is that our 12 regions were too broad. It is possible that further research will show that the social cognition network is better described with fewer regions and that this concise grouping would give us different results. It is important to further study the specific regions to delineate specific roles for the various brain regions. Further research should also investigate the connectivity in this network and how it relates to social cognition in infants; it might be possible to stimulate this network in infants using a visual gaze based paradigm to see if activity in this region follows a pattern of connectivity similar to the 12 regions identified for this study.

The VABS-II is an excellent tool for assessing neurological competence. There are four broad categories (motor skills, daily living skills, language and socialization) present and for the purpose of this study we focused on the socialization subset. The social category of the VABS-II, purported to test three things: interaction; play; and coping. Our infants were given the full VABS-II but all scores for the coping portion were zeroes for children 12 months and younger, and the data for play were not significant between the first six month scores and the second six month scores. Questions for the 3 month portion are very limited and it is difficult to get a measure of social scores for this young population. As such, the behavioural scores for the 3 and 6 month VABS-II were collapsed, as were the 9 and 12 month scores for each infant. Due to these limitations, particularly for the 3 and 6 month infants, we may not have obtained a precise measurement of the infants' social ability.

It is difficult to accurately determine what noise is in our data; our sample included infants with neurological diagnoses, some quite severe. In a healthy term population, a correlation could potentially be found with the VABS-II. It is also possible there might not be a relationship between fcMRI similarity scores and social behaviour scores, but we do see similarity in the network of our neonate sample and the adult network, and we also see VABS-II social scores increasing over time, and there is good variability in both scores. To better understand these relationships, further study, particularly replicating this study with a neurologically healthy sample, could give us more information to help make connections for the purposes of prediction.

The VABS-II gives us better information as the child ages. It is fair to say that the scores for VABS-II for a 24 month-old infant are likely more informative compared with the scores for a 3-month-old infant. It is possible that there are other, more precise, measurement tools to assess social cognition development and deficit in this younger population. Further research could look at other testing measures to compare with fcMRI similarity scores to see if there really is a correlation. Testing of older children, Ages 3 and 4, for example, could show a correlation to fcMRI similarity scores. The VABS-II was designed to test from infancy through to elderly participants with impairment; it could be that this test is too broad to specifically test social cognition competence in infants. Further, it might be possible that this young population cannot accurately be tested at all. Infants at 3 months cannot tell us when or what they are thinking nor can they respond to verbal requests; their motor skills are not developed sufficiently to be able to point or make a choice between stimuli such as in a typical social cognition paradigm. Researchers need to utilize some creative measure that could work in lieu of these natural infant limitations.

As the similarity scores did not correlate with the VABS-II scores, we compared the similarity score with both gestational age at birth and birth weight. Results of the correlation between gestational age at birth and fcMRI scores were surprising. It would seem intuitive that the more an infant was premature, the more they should be ill and the more they should show lower behavioural scores; however, our data did not show this.

The infant social cognition network needs more research. Our study was partly an exploratory study to see if we could find this network in infants as in previous adult studies. Since we do see a similar pattern of connectivity between neonates and adults this is a good indication that there is potential for a resting state network we could call the social cognition network. The connectivity in this network appears to be present at 40 weeks GA in our sample of infants ranging from neurologically healthy to neurologically impaired; we need to study a neurologically healthy population to reduce the number of discreet regions and to come up with a model of what a typical infant connectivity matrix should look like during resting state. This would give us a good way to compare individual infant data to a model so that we can predict which infants are likely to have social difficulties by school-age. Larger samples of specific medical diagnoses in infants should also be studied to see if there are links between specific illnesses and social behaviour. Prediction is the main goal. If we can predict which children would benefit the most from intervention, this would have vast implications for where we put our funding in medical care, educational testing and support, and improve the quality of life for children and their families.

Until recently little research has looked at the human brain close to the time of birth and what systems or networks are present at this point. This study provides support that a social cognition network might be present even weeks before birth. This network joins a growing list of networks thought to be present from a very early age. The presence of a social cognition network that is similar to what we see in adults underscores how important early social contact is for young infants. Further exploration of this network in infants and young children could help us to understand how we come to recognize and interpret the vast array of social interactions.

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Curriculum Vitae

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