Social-Cognitive Development in Infants Born Preterm

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Angela Fenoglio

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Chapter 1: Introduction

Preterm Birth

According to recent estimates from the Centers for Disease Control, approximately 1 in 10 infants born in the United States is delivered prior to 37 weeks of gestational age (GA) (Martin et al., 2015). Worldwide, complications related to preterm (PT) birth are the leading cause of death in the neonatal period (Liu et al., 2014). In the U.S., prematurity accounts for 35% of all infant deaths, and is a principal cause of neurological disabilities in children (Mathews, Macdorman, & Thoma, 2015). Medical advances in recent decades have contributed to an increased survival rate in preterm infants (Philip, 2005), but this decreased mortality has been accompanied by an increase in morbidity (Horbar et al., 2002). In addition to medical complications (Ancel et al., 2015; Glass et al., 2015), infants born preterm are at an increased risk for a variety of adverse neurologic, psychiatric, and cognitive outcomes (P. Anderson & Doyle, 2003; D'Onofrio et al., 2013).

Recent decades have seen an increasing emphasis on the pivotal role of early brain development for subsequent psychological functioning, and the recognized sensitive period has gradually shifted to encompass not only the infant and toddler years but also the time from conception to birth. Developmental science has long focused on the themes of "experience-expectant" and "experience-dependent" plasticity (Greenough, Black, & Wallace, 1987). In this framework, experience-expectant plasticity refers to the idea that the human brain has evolved to expect certain inputs in order to select appropriate subsets of synaptic connections. In turn, a lack of these expected inputs (or inappropriate timing for these inputs) may lead to abnormal brain development. Experience-dependent

plasticity, on the other hand, refers to the brain's incorporation of environmental experiences unique to the individual. These inputs can occur throughout the lifespan and the nervous system is presumed to organize or specialize in response. Ostensibly, preterm birth can lead to alterations in both experience-expectant and experience-dependent development. Borrowing terminology from Luciana (Luciana, 2003), PT-born infants are exposed to both "events of commission," in the form of neurological or medical insult, and "events of omission," in the form of less time spent in utero (accompanied by early exposure to the extra-uterine environment).

Age Adjustment

Given these atypical inputs, it is somewhat surprising that the majority of infants born PT develop various psychological capacities within the normal range, at least as measured by the off-the-shelf standardized measures that are frequently employed. Determining an appropriate "normal range" for comparison is complicated, however. Most often, PT-born infants and toddlers are compared to full-term (FT)-born children of the same "corrected" or "adjusted" age. These terms refer to postnatal age, corrected for degree of prematurity (e.g. an infant who was born at 32 weeks and is now 14 months old would be compared to an infant who was born at 40 weeks and is now 12 months old). Skills in some domains, such as sequences of gross motor development (Allen & Alexander, 1990; Lems, Hopkins, & Samsom, 1993; Palisano, 1986) appear to map to postmenstrual age (PMA; that is, gestational age (GA) plus postnatal age), which suggests a large degree of intrinsic developmental programming. However, in other domains, such as language comprehension (Gonzalez-Gomez & Nazzi, 2012), binocular vision (Jando et al., 2012), and some aspects of recognition memory (DeRegnier, Wewerka, Georgieff, Mattia, &

Nelson, 2002), preterm (albeit healthy) infants seem to show some advancements relative to those born full-term. These differences in performance between preterm and full-term infants of the same adjusted age point to the importance of experience dependent learning in these domains, and it is readily conceivable that experience may be paramount when it comes to capacities that are highly dependent on social interaction.

The Social Brain

Critically, impaired social functioning is observed across a wide range of psychiatric and neurological disorders, including those that appear to be disproportionately prevalent in the preterm population. As conceptualized by Kennedy and Adolphs (Kennedy & Adolphs, 2012), the observable social interactions between individuals are termed "social behavior," while "social functioning" refers to entrenched or consolidated patterns of interacting with others. In this schema, "social cognition" refers to the psychological processes underpinning social behavior, and the "social brain" comprises the brain regions that underlie social cognition. This putative "social brain" (see Table 1) encompasses a collection of highly distributed structures, circuits, and networks (including the amygdala, medial prefrontal cortex, the corpus callosum, the anterior and posterior cingulate cortex, and various regions within the temporal lobe) that have been identified as necessary for processing social information through various methodologies including lesion studies, neuroimaging, and behavioral assays. These areas have been consistently implicated in a number of neurological and psychiatric conditions, from schizophrenia (Russell et al., 2000; Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007) and depression (Pezawas et al., 2005) to autism (Kleinhans et al., 2008) and other neurodevelopmental disorders (Schumann, Bauman, & Amaral, 2011), and may be especially vulnerable to prematurity

due to their topographical architecture and the temporal dynamics of emerging brain connectivity.

Table 1.

Selected Social Brain Structures and Networks.

Region/Network	Associated structures	Review	Associated social function/behavior
Amygdala		Adolphs [2010]	Recognizing emotional expressions, social behavior towards conspecifics, reward learning
Default mode network	Posterior cingulate, medial prefrontal cortex, medial temporal lobe	Mars et al. [2012]	Self-referential processing, self-projection, mentalizing/ theory of mind
Corpus callosum		Paul et al. [134]	Social competence, introspection, judgment, planning, emotional communication
Uncinate fasciculus	Anterior temporal lobe, lateral orbitofrontal cortex, anterior frontal lobe	Olson et al. [2015] Von Der Heide et al. [2013]	Social-emotional processing, social valuation

Outcomes Associated with Preterm Birth

Altered Social Brain Circuitry and Prematurity.

An accumulating body of work has investigated atypical structural and functional brain development in infants born preterm. In a recent study of 325 infants born prior to 32 weeks of gestation or with a birth weight of less than 1250 grams, approximately one third showed some form of brain injury, with approximately 10% showing evidence of severe brain injury (Kidokoro et al., 2014). Meanwhile, estimates of the rate of neurobehavioral impairment in a similarly-sized cohort of PT and extremely low birth weight infants are closer to 50% (Hutchinson, De Luca, Doyle, Roberts, & Anderson,

2013). Thus, the occurrence of detectable brain injury does not fully account for the incidence of adverse neurodevelopmental outcomes seen in the PT population. Traditionally, studies have focused on the increased prevalence of injury in the PT-born population. More recently, however, there is growing recognition that the altered developmental trajectories observed in this group are not fully accounted for by "events of commission" (such as white matter injury) but may also hinge on "events of omission" in the form of a lack of typical environmental inputs, suggesting the body's neurodevelopmental processes may be programmed to expect 40 weeks in the womb. In other words, these atypicalities are likely influenced by a complex interplay of biology (in the form of developmental programming) and experience (in the form of early exposure to the ex-utero environment).

Altered gray and white matter volumes in social brain regions.

Magnetic resonance imaging (MRI) studies show that the most common structural observations in PT infants include diffuse white matter (WM) and gray matter (GM) abnormalities. Periventricular leukomalacia (PVL) is characterized by both focal and diffuse lesions to white matter in the brain's motor areas. Inder et al. (T E Inder et al., 1999) collected quantitative volumetric MRI in preterm infants (birth GA <32 weeks) with prior evidence of PVL. At term, these infants displayed a reduction in cerebral cortical (but not subcortical) gray matter, along with a reduction in the volume of total brain myelinated (but not unmyelinated) white matter. PVL was, until recently, the most commonly diagnosed brain injury in PT infants. The recent decrease in the prevalence of cystic PVL is thought to be associated with several factors, including reductions in the duration of mechanical ventilation and the incidence of bacterial sepsis (Hamrick et al., 2004). It has

since been recognized, however, that white matter damage often occurs in the absence of the cystic regions of necrosis seen in classic PVL (Miller & Ferriero, 2009; Volpe, 2009). A later study (Terrie E Inder, Warfield, Wang, Hüppi, & Volpe, 2005) reported reduced cerebral cortical gray matter volume and deep nuclear gray matter volume in 119 preterm infants (birth GA ≤32 weeks, birth weight ≤1500 g), as compared to 21 full-term infants, and found that these abnormalities correlated with moderate to severe neurodevelopmental disability at one year of age. Brown et al. (Brown et al., 2009) imaged a cohort of very preterm (VPT, birth GA < 30 weeks or birth weight < 1250 g) infants and found that lower composite neurobehavioral scores at term were related to the degree of white matter abnormality observed via MRI, and correlated most strongly to abnormal WM signal and reduced WM volumes, rather than the grade of GM abnormality. In aggregate, these findings suggest atypical gray and white matter development and associated behavioral abnormalities occur even in PT infants who do not meet criteria for canonical insults such as PVL. Neurodevelopmental research has traditionally been focused on infants with identifiable anatomic injury or severe symptomatology, but there is increasing recognition of the need to identify infants who may manifest more subtle impairments.

The brain undergoes rapid and dynamic development during the latter two trimesters. In terms of gross structure, total brain volume increases and ventricle size decreases during the second trimester, and while major fissures begin to emerge, the cerebral surface remains largely smooth until the end of the second trimester (Huang et al., 2009). A small amount of cortical folding occurs by 25 weeks, and folding intensifies in the third trimester (Battin et al., 1998). This folding occurs in an orderly fashion, with many primary sulci forming during the second trimester, and tertiary sulci appearing during the third trimester and after

term (Stiles & Jernigan, 2010). Sulci and fissures emerge in a posterior to anterior fashion: the parieto-occipital, calcerine, and cingulate sulci around 20-22 weeks GA; the central, interparietal, and superior temporal sulci by 25 weeks GA, and the precentral, post-central, superior frontal and middle temporal sulci around 24-28 weeks (Huisman, Martin, Kubik-Huch, & Marincek, 2002). Between 18 and 40 weeks GA, fetal white matter volume shows a 22-fold increase, along with a 21-fold increase in cortical gray matter and a 10-fold increase in deep subcortical structures (Andescavage et al., 2016). Presumably, birth prior to 40 weeks may disturb the typical progression of neural circuit organization. Structural MRI studies have indeed shown abnormalities in specific structures and regions in the preterm brain, including areas associated with the putative social brain. The majority of these studies have imaged former PT infants at school age or later. This later-stage imaging introduces difficulties in interpretation – while this body of work suggests lifelong consequences for a portion of the PT-born population, the substantial interim between birth and assessment introduces difficulty in specifying the contributions of prematurity, per se, as opposed to potential downstream or tangential effects. For this reason, this portion of the review will focus on data collected during infancy, rather than imaging acquired later in childhood or in adulthood.

As mentioned above, the set of structures associated with social cognition is widely distributed, and emerging evidence suggests that prematurity is associated with altered brain volumes in many of these regions. Thompson et al. (Thompson et al., 2007) compared 202 preterm (birth GA <30 weeks and/or birth weight < 1250 g) and 36 term infants (scanned at term equivalent age, TEA) and found that PT infants showed reduced cortical gray matter and unmyelinated WM volumes in orbitofrontal regions. Similarly, Ball et al.

(Gareth Ball et al., 2012) collected scans from 71 preterm (birth GA <36 weeks) infants at TEA and found that degree of prematurity was associated with volume reduction in the orbitofrontal lobe. The orbitofrontal cortex seems to be key for self-monitoring (Beer, John, Scabini, & Knight, 2006) and emotional self-regulation (Cicerone & Tanenbaum, 1997), amongst many other behaviors.

In the parietal region, Ball et al. (Gareth Ball et al., 2012) also found that increasing prematurity was associated with reduced posterior cingulate cortex (PCC) volume. This finding was echoed by Gousias et al. (Gousias et al., 2012), who compared scans from 15 PT infants (<36 weeks GA, imaged at TEA) and 5 FT infants and also found that PT infants had relatively smaller PCC volumes. The PCC is thought to play a crucial role in the so-called "default mode network" (Fransson & Marrelec, 2008). This network includes the PCC, medial prefrontal cortex (mPFC), and medial temporal lobe (MTL) and several studies have pointed to its role in social-cognitive processing (Harrison et al., 2008; Spreng & Grady, 2010).

Significant volumetric differences have also been observed in the occipital region in the brains of PT infants. Peterson et al. (Peterson et al., 2003) scanned 10 PT (birth GA not specified) and 14 term infants once between 34 and 42 weeks GA, and calculated volumes for cortical gray and white matter parcellated into 8 subregions. In this study, PT infants were observed to have reduced GM volumes in the parieto-occipital and inferior occipital cortices. Similarly, Thompson et al. (Thompson et al., 2007) found that PT infants showed reduced deep nuclear gray matter in the parieto-occipital region. The extrastriate body area and occipital face area, which would likely be captured in the "inferior occipital" subdivision, have been implicated in perceiving human bodies and body parts (Urgesi,

Candidi, Ionta, & Aglioti, 2007) and accurate face perception (Pitcher, Walsh, & Duchaine, 2011), respectively. The area designated as "parieto-occipital" in these studies also may have been large enough to capture the temporoparietal junction, an area associated with numerous aspects of social cognition including theory of mind (Samson, Apperly, Chiavarino, & Humphreys, 2004), empathy (Jackson, Brunet, Meltzoff, & Decety, 2006), and moral judgments (Young et al., 2010).

Many of the structures associated with the "social brain" are concentrated in the temporal lobe, including the amygdala (A. K. Anderson & Phelps, 2001), the superior temporal sulcus (Pelphrey, Morris, & McCarthy, 2004) and superior temporal gyrus (Zahn et al., 2007), the fusiform face area (Kanwisher, McDermott, & Chun, 1997), and the temporal pole (Zahn et al., 2007), amongst others. In Gousias' study (Gousias et al., 2012), several significant differences were pinpointed in the temporal region. Here, PT infants had relatively smaller volumes in the middle and inferior temporal gyri, as well as the anterior temporal lobe. Interestingly, in this sample the PT group (as compared to the FT group) showed larger volumes in the amygdala, as well as the left superior temporal gyrus (though it should be noted that none of these group differences remained significant after correcting for multiple hypothesis testing). The amygdala is one region consistently implicated in processing social information, including emotional responses (Morris et al., 1996), detection of socially salient information (A. K. Anderson & Phelps, 2001), and social affiliative behavior (R Adolphs, Tranel, & Damasio, 1998) (see (Ralph Adolphs, 2010) for a review of amygdala function). The temporal lobe has also been a region of strong interest in follow-up imaging conducted after infancy (see Box 1).

While volumetric findings can admittedly be difficult to interpret, the research reviewed above suggests that preterm birth is associated with atypical cortical and subcortical development. This altered development could be a result of disruptions to the typical developmental processes occurring during the second and third trimesters. These alterations in both gray and white matter appear in several brain regions believed to underlie processing of social information.

Abnormalities in social brain microstructure

Much of the most recent work on preterm brain development has used a method called diffusion weighted imaging (DWI) to investigate microstructural development. Diffusion weighted imaging (DWI) measures the restricted diffusion of water molecules. The rate of diffusion is affected by tissue structures. For example, water moves more readily *along* axonal bundles than *perpendicular* to them and diffuses isotropically in cerebrospinal fluid. The directionality of anisotropic diffusion of any given voxel can be characterized by applying a tensor model (i.e., diffusion tensor imaging or DTI). By providing information about the spatial distribution of water diffusion in a given voxel, diffusion imaging can serve as a tool for quantitatively characterizing brain microstructure. Common diffusion metrics include axial diffusivity, radial diffusivity, and mean diffusivity. Axial diffusivity (AD) refers to diffusion parallel to the principle eigenvector of the three-dimensional voxel, while radial diffusivity (RD) denotes diffusion in the direction orthogonal to the principle eigenvector. Mean diffusivity (MD) or apparent diffusion coefficient (ADC) represent the average of the two Fractional anisotropy (FA) reflects the degree of diffusion along the principle axis relative to the other directions. FA is a scalar metric with values ranging from 0 (unrestrained or

"isotropic" diffusion) to 1 (completely constrained or "anisotropic" diffusion). Opinions differ somewhat as to which aspects of the brain's microstructural architecture are reflected best by each measure. It is thought that MD is most closely related to overall water content in the brain (Neil et al., 1998), while FA represents an index of the brain's microarchitecture that is influenced by axonal density, axonal diameter, cell membrane and microtubule composition, myelination, and dendritic cytoarchitecture (Gareth Ball et al., 2013; McKinstry, Mathur, & Miller, 2002; Mukherjee et al., 2002; Neil et al., 1998).

In terms of gray matter, postmortem studies of fetal brains show an increase in regional cortical FA from 15 to 28 weeks of gestation, followed by a decrease through 36 weeks (Gupta et al., 2005). This finding is consistent with the migration of neurons from the germinal matrix, as it is thought that the bulk of cortical neurons migrate along radially organized glial fibers early in gestation (Rakic, 1988, 2003; Rakic & Kornack, 2001; as cited in (Gupta et al., 2005)), perhaps contributing to the increased cortical FA observed prior to 27 weeks. At this point these glial cells retract (Volpe, 2001; Rakic 2003; as cited in (Gupta et al., 2005)), ostensibly resulting in a decline in cortical FA. Thus, gray matter microstructure undergoes significant change during the period of gestation disrupted by preterm birth.

McKinstry et al. (McKinstry et al., 2002) attempted to characterize water diffusion in vivo in neonatal cortical gray matter by imaging 24 PT and FT infants (birth GA 26 – 41 weeks) in the first 36 hours of life. These studies found that (similar to Huang et al. (Huang et al., 2009)) the cerebral cortex shows a pronounced radial organization by 26 weeks of gestation, but this radial organization disappears by term, as evidenced by a decrease in averaged water diffusion coefficient. Ball et al. (Gareth Ball et al., 2013) imaged preterm

infants (birth GA 23-35 weeks), 47 of whom were scanned once, and nine of whom were scanned twice. Between 27 and 46 weeks post-conception, a decrease in cortical FA was observed until week 38. Higher initial FA values and rates of change were seen in gyri, frontal and temporal poles, and parietal cortex, with lower values and rates of change in sulcal, perirolandic, and medial occipital cortex. Kersbergen et al. (2014) looked at longitudinal change in FA in 122 distinct regions of the brain in infants between 30 and 40 weeks of postmenstrual age. The sample included infants born prior to 28 weeks of gestation and was limited to individuals without cerebral injury and with a normal neurodevelopmental outcome (as characterized at 15 months of age with the Griffiths Mental Development Scales), who were scanned longitudinally around 30 weeks of gestation and again at term equivalent age. In cortical brain areas, frontal areas showed a slight increase in FA, while temporal-occipital areas exhibited a slight decrease in FA. The majority of brain regions showed a clear decrease in mean, radial, and axial diffusivity, though the degree of decrease was heterogeneous across regions. Similar to the pattern of FA change, increases in MD, AD, and RD were seen in the occipital, temporal, and frontal regions. As described above in the context of structural imaging, the putative "social brain" encompasses cortical areas spread across the brain. As such, microstructural alterations in these areas (as indexed, in this case, by altered diffusion metrics) might contribute to atypical patterns of social cognitive development.

White matter has been of particular interest in the realm of preterm brain development, for multiple reasons. As described earlier, it appears to be acutely vulnerable to insult. DWI provides especially important information about white matter development during the perinatal period in the early stages of myelination (Hermoye et al., 2006). Studies of

postmortem fetal brains suggest that white matter fibers transition from a dominant radial organization around 15 weeks of gestational age to a more laminar and radial architecture through the duration of the second trimester (Huang et al., 2009), Meanwhile, white matter tracts considered crucial to early social-cognitive behaviors (including the corpus callosum, the uncinate, and the inferior longitudinal fasciculus) undergo rapid change from 13 to 22 weeks of gestation (Huang et al., 2009). More generally, imaging from fetal brain specimens and full-term neonates (Huang et al., 2009, 2006) indicates that limbic fibers (including the stria terminalis, fornix, and cingulum) are well formed by 19 weeks of gestational age. Association fibers (including the uncinate fasciculus, inferior fronto-occipital fasciculus, and superior and inferior longitudinal fasciculi) seem to develop relatively more slowly (Huang et al., 2009). Based on three-dimensionally reconstructed WM tracts of fetal specimens, the uncinate is visible by 15 weeks of gestation but the superior longitudinal fasciculus is still not prominent by term (Huang et al., 2009). White matter FA appears to increase rapidly from term through the first two years of life, at which point it slows but continues to increase through childhood (Hermoye et al., 2006; Provenzale, Liang, DeLong, & White, 2007).

Critically, several of the tracts developing largely in the second and third trimesters have been consistently implicated in various aspects of social processing. The corpus callosum is visible in rudimentary form by the twelfth week of gestation (Kier & Truwit, 1996), but undergoes exuberant proliferation during the third trimester followed by a period of axonal pruning until the second month post-term (Clarke, Kraftsik, Van der Loos, & Innocenti, 1989). Much of the work investigating the role of the corpus callosum in social functioning comes from studies of individuals in whom the fibers of the corpus callosum

fail to develop, a condition known as agenesis of the corpus callosum (AgCC). Parents of children with AgCC report impairments in social competence, introspection, social judgment and planning, and poor emotional communication (Paul et al., 2007). Abnormalities of the corpus callosum have also been associated with the range of social deficits observed in autism, specifically measures of social responsiveness (Alexander et al., 2007). One study of corpus callosum diffusion at TEA in 58 PT infants (divided into groups of 23-25, 26-29, and 30-33 weeks birth GA, all without apparent WM lesions) found that lower birth GA was associated with lower FA in the posterior corpus callosum, such that FA decreased linearly with birth GA (Hasegawa et al., 2011). Another study using DTI in 44 PT (birth weight between 600 and 1250 g) and 41 FT adolescents found that prematurity was associated with lower FA in multiple regions including the splenium of the corpus callosum (K. M. Mullen et al., 2011). Eikenes et al. also found reduced FA in the corpus callosum of 49 VLBW (birth weight < 1500 g) PT-born 12-year-olds, when compared to 59 term-born controls (Eikenes, Løhaugen, Brubakk, Skranes, & Håberg, 2011). A recent meta-analysis (Li et al., 2014) incorporated 232 original studies, for a total of 513 PT-born children, adolescents, and young adults and 309 healthy controls. The analysis used an activation likelihood estimate (ALE) procedure to identify regions of abnormal FA in the corpus callosum. The ALE analysis yielded 11 regions of decreased white matter FA in the PT versus FT group, including the bilateral splenium of the corpus callosum, the bilateral external capsule, the left superior fronto-occipital fasciculus, the left posterior thalamic radiation, the right superior longitudinal fasciculus, the genu of the corpus callosum, the left cingulum, the left posterior corona radiata, and the left posterior limb of the internal capsule (also seen in (Arzoumanian et al., 2003)). Four regions of

increased FA were observed, including the bilateral posterior corona radiata and the anterior corona radiata. The authors interpret these findings to mean that the mechanisms underlying alterations in FA in the preterm brain may vary during different stages of white matter development. The areas of increased FA were smaller than the areas of decreased FA (192 voxels and 4360 voxels, respectively), and the authors note that the findings of decreased FA are more consistent with prior work. The regions of increased FA seem harder to explain; it is suggested that these increases may in fact be due to differences in methodology between studies.

The uncinate is a bidirectional long-range pathway that extends from the anterior temporal lobes and amygdala to the lateral orbitofrontal cortex (Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). While the exact function of the uncinate is under debate (Von Der Heide et al., 2013), it serves to connect areas believed to be vital to various social-cognitive functions, and has been associated with behaviors such as joint attention (Elison et al., 2013) and sensitivity to social rewards (Bjornebekk, Westlye, Fjell, Grydeland, & Walhovd, 2012). Abnormalities in the uncinate have been associated with various psychiatric disorders (see Olson et al., 2015 for a review) and it has been hypothesized that the slow time course of uncinate development may make it particularly susceptible to perturbation contributing to social-emotional problems. There has been little investigation of the uncinate in PT infants, but in addition to their findings related to the corpus callosum, Eikenes et al. (Eikenes et al., 2011) and Mullen et al. (K. M. Mullen et al., 2011) found reduced FA in the uncinate of adolescents born preterm.

Recent years have seen a striking increase in work investigating diffusion in the PT brain, and as of yet there is little consensus as to the precise structures or circuits most often

affected by prematurity. As Li (Li et al., 2014) notes, this may be due at least in part to differences in methodology, including the population of interest, the time at which images are collected, and the manner in which brains are segmented into regions or networks. What is clear is that even uninjured PT-born infants show differences in brain connectivity, both structurally and functionally (as described below).

Altered functional connectivity.

One burgeoning area of research involves functional imaging in preterm infants. The bulk of this work has been conducted with adolescents or adults born preterm, in which case it is challenging to draw specific conclusions given the amount of time lapsed, but some groups have attempted to characterize functional activity closer to the time of birth. As described in the diffusion imaging section, prematurity has been found to be associated with alterations in the brain's connectomic architecture. Another way to characterize the development of the brain's neural circuitry is to examine functional connectivity through methods such as resting state fMRI. Echoing the aforementioned findings related to structural brain changes in the third trimester, this is also a time of great change in the organization and connections in the brain's functional networks. In a cohort of 40 preterm and full-term infants (birth GA 25 to 41 weeks) imaged between 31 and 42 weeks PMA, higher PMA was associated with greater functional connectivity (Cao et al., 2016). There were also regional differences, such that age-dependent increases in connectivity were greater in primary sensory and motor regions and lesser in default mode and executive-control regions. Doria et al. (2010) collected resting state fMRI (rs-fMRI) data in 70 infants born between 29 and 43 weeks of gestation. Several networks (visual, auditory, somatosensory, default mode, frontoparietal, and executive control) were examined and

appeared to emerge at differing rates, though all showed rapid change during the period from 30 to 40 weeks PMA. Similarly, van den Heuvel et al. (van den Heuvel et al., 2015) imaged 27 PT infants (birth GA 24 – 29 weeks) at 30 and/or 40 weeks PMA and found evidence of resting state networks by 30 weeks PMA. He and Parikh (He & Parikh, 2016) also observed significant increases in functional connectivity strength in a large set of resting-state networks between 32 and 52 weeks PMA in a sample of 34 VPT infants (birth GA $\leq$ 32 weeks). Prematurity is associated with widespread alterations in functional connectivity (see (Doria, Arichi, & Edwards, 2014; Kwon et al., 2016; Lee, Morgan, Shroff, Sled, & Taylor, 2013) for comprehensive review). Findings reveal impaired cerebral lateralization (Kwon et al., 2015; Scheinost et al., 2014), atypical thalamocortical connectivity (Toulmin et al., 2015), and reduced connectivity between "rich " nodes, a set of cortical regions which are typically highly connected (Scheinost et al., 2016). These findings are supported by machine learning studies which have used whole-brain functional connectivity to successfully classify infants as either preterm or full-term (G. Ball et al., 2016), and even to estimate birth GA (Smyser et al., 2016).

One focus of functional research has been the aforementioned "default mode network," (DMN) which has been consistently implicated in higher-order social cognitive behaviors such as self-referential processing and self-projection (Mars et al., 2012). Fransson et al. (2007) collected resting state data around term age from twelve preterm (between 24 weeks and 27 weeks birth GA) and did not find evidence of an infant equivalent of the default-mode network. It is worth noting, however, that this study did not include a comparison group of FT-born infants. Smyser et al. (2010) observed precursors to the DMN in 10 FT but not 53 VPT (birth GA 26 – 28 weeks) infants, scanned longitudinally from 26 to 40

weeks PMA. A later study (Smyser et al., 2016) included resting state data from 50 PT-born (23-29 weeks birth GA, without moderate-sever brain injury) compared to 50 FT-born infants, all scanned at TEA. Using machine learning algorithms and 214 regions of interest, they were able to distinguish PT and FT-born infants with 84% accuracy. Here, the default mode network contributed to successful categorization, suggesting that preterm birth contributes to altered functional connectivity even in the absence of brain injury. Similar results have been found with PT-born individuals later in life: at 36 months of age, PT-born children show relatively weaker connectivity between resting state networks including the DMN (Damaraju et al., 2010). One recent study also examined functional connectivity in the amygdala of 65 FT (birth GA > 36 weeks) and 57 PT (birth GA < 30 weeks) infants imaged at TEA (Rogers et al., 2016). Here, functional connectivity patterns in the PT and FT groups were similar to those of older children and adults, though prematurity was associated with reduced magnitude of activation.

Collectively, these imaging findings suggest an array of maturational changes throughout the brain during the second and third trimesters that might be interrupted or altered by preterm birth. These results indicate two potential sources for the unique vulnerability of the PT brain. First, prematurity is associated with an increased risk of specific brain insults such as intraventricular hemorrhage, white matter damage, and hypoxic-ischemic injury. Secondly, and perhaps more critically, the PT brain shows atypicalities in the extensive network connectivity seen by term, and atypical early life experience -- even in the form of early exposure to the extra-uterine environment -- may result in these connections forming abnormally. Prematurity appears to be associated with altered brain architecture and connectivity in a variety of cortical and subcortical brain

regions, including areas and networks traditionally implicated in social-cognitive processing. However, there are few (if any) biomarkers relating specific brain abnormalities to the long-term cognitive, psychiatric, or social outcomes for which preterm infants are at an increased risk.

Social Impairment in Psychiatric Outcomes.

Preterm infants are at an increased risk for maladaptive or clinically concerning behavioral problems consistent with various psychiatric classifications. As previously mentioned, dysfunction within the putative social brain has been associated with a vast range of psychiatric disorders, from schizophrenia (Russell et al., 2000; Shamay-Tsoory et al., 2007) to depression (Pezawas et al., 2005). According to one recent estimate (Treyvaud et al., 2013), children born very PT had three times the odds of meeting criteria for any psychiatric diagnosis by age seven when compared to full-term children. In this study, the most common diagnoses were anxiety disorders, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). Similarly, Johnson et al. (Johnson et al., 2010b) followed up a sample of 307 children born prior to 26 weeks of gestation. At 11 years of age, parent and teacher reports suggested that VPT children had a threefold greater risk of showing symptoms consistent with a psychiatric disorder when compared to term classmates, with the most common disorders being ADHD, emotional disorders, anxiety disorders, and ASD.

While social impairment is widely recognized as a central component of ASD (as discussed in the following section), even ADHD is known to have associated social deficits. Some DSM criteria for ADHD directly implicate social functioning, such as "interrupting or intruding on others," (American Psychiatric Association, 2013) and

researchers have long observed impaired peer relationships (Becker et al., 2006; Coghill et al., 2006), friendships (Hoza et al., 2005), and social communication skills (Klimkeit et al., 2006) in children and adolescents with ADHD. It is sometimes hypothesized that these social difficulties may be more closely tied to comorbid disorders (such as oppositional defiant or conduct disorder) than to ADHD itself (Nijmeijer et al., 2008). Although studies specific to social cognition are sparse, some evidence suggests that ADHD is associated with impairments in both complex social cognitive processes, such as theory of mind (Sodian, Hulsken, & Thoermer, 2003), and more basic processes, such as emotional face perception (Cadesky, Mota, & Schachar, 2000; Sinzig, Morsch, & Lehmkuhl, 2008; Uekermann et al., 2010). If there are social brain circuits that are particularly vulnerable to prematurity, identification of the developmental trajectories associated with these circuits may help to predict or prevent psychiatric symptoms.

Autism Spectrum Disorders and Prematurity.

Impaired social functioning (including deficits in social-emotional reciprocity, nonverbal communicative behaviors, and interpersonal relationships) represents a core feature of autism, and several studies have investigated a reputed link between preterm birth and ASD. Johnson et al. (Johnson et al., 2010a) assessed 219 survivors of birth prior to 26 weeks GA, as well as 153 FT classmates. At 11 years of age, parents completed a measure of ASD symptoms (the Social Communication Questionnaire, SCQ) followed by a semi-structured diagnostic interview to diagnose ASD (the Development and Well Being Assessment, DAWBA). VPT children had a significantly higher frequency of ASD symptoms (as measured by the SCQ). After controlling for IQ, the PT cohort still showed significantly more impairment than the control group for social interaction,

communication, and total scores, but not repetitive/stereotyped behavior. Sixteen (or approximately 7%) of the PT children and none of the FT children were diagnosed with ASD by 11 years. For comparison, a 2012 estimate places the prevalence of ASD in the general U.S. population at about 1.5% (Centers for Disease Control and Prevention [CDC], 2016), while the prevalence in siblings of children with ASD is estimated at approximately 11% (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010).

The majority of the work pointing to an increased risk of ASD in the PT population has been limited to the use of screening measures (such as the SCQ and Modified Checklist for Autism in Toddlers, MCHAT), which are intended to identify all high-risk individuals; as such, these measures may overestimate the prevalence of ASD. For example, Limperopoulos et al. (2008) investigated the prevalence of ASD in PT/VLBW infants at around two years of age, using a parent report checklist designed to screen for ASD symptoms (the MCHAT), a standardized measure of functional status (the Vineland Adaptive Behavior Scale, VABS), and the Child Behavior Checklist (CBCL). In this study, 26 percent of PT infants were flagged by the MCHAT, and abnormal scores on that measure correlated with internalizing behavior problems (via the CBCL) as well as social and communication deficits (based on the VABS). Lower birth weight and gestational age were significantly correlated with abnormal MCHAT scores, though it should be noted that no FT infants were assessed. A few recent studies have used instruments designed specifically for diagnostic classification, rather than those designed to screen for risk. The Autism Diagnostic Observation Schedule (ADOS) is a direct, standardized, semi-structured observational assessment of the diagnostic features that define autism (Falkmer, Anderson, Falkmer, & Horlin, 2013; C Lord et al., 2000). Pritchard et al. (Pritchard et al.,

2016) administered the M-CHAT and ADOS to groups of 2- and 4-year-old children born prior to 29 weeks GA. Of 169 individuals, 22 (13%) screened positive based on the M-CHAT, while only 3 (1.8%) met ASD criteria based on the ADOS.

There are several potential explanations for this notable discrepancy. As noted by Yaari et al. (2016), parent-report questionnaires may index "developmental difficulties of the preterm phenotype" – in other words, the behaviors targeted by these questionnaires may indeed be symptoms of ASD, but some of them may also be related to medical conditions associated with prematurity, such as infection or neonatal illness (Hofheimer, Sheinkopf, & Eyler, 2014). Indeed, in a 2016 study (Kim et al., 2016) that used the M-CHAT at two years of age and the ADOS and ADI at ten years of age in 827 extremely preterm (EPT) infants (birth GA < 28 weeks), the positive predictive value of the M-CHAT was approximately 20%. In other words, only one in five of the children who screened positive on the M-CHAT at age two had a diagnosis of ASD at age ten. In addition, impairments in vision and hearing were associated with higher misclassification rates. As the authors note, the sensory, motor, and cognitive impairments that are prevalent in the preterm population can all affect the validity of the M-CHAT. Additionally, use of the ADOS alone provides poorer *specificity* for ASD than its use in conjunction with the Autism Diagnostic Interview—Revised (ADI-R) (Catherine Lord, Rutter, & Le Couteur, 1994). The use of the ADOS and ADI-R in combination provides improved diagnostic validity than use of the ADOS alone (Kim & Lord, 2012).

All of this is to say that it remains unclear whether there is truly an increased prevalence of autism in the PT-born population. Nonetheless, these data support a rapidly expanding body of evidence suggestive of the etiologic heterogeneity of autism and raise interesting

questions such as whether the proximal pathological mechanisms that result in the autistic-like symptoms in some preterm children are similar to or different form the proximal neural mechanisms that cause idiopathic autism. Again, clarity on this front requires further investigation of the effects of prematurity on the social brain.

Social-Emotional Development and Prematurity.

While autism presents a case with a clear emphasis on atypical social functioning, a number of recent studies indicate an association between preterm birth and atypical social-emotional development. In a study of 188 VPT (birth GA < 30 weeks or birth weight < 1250 g) and 70 FT (birth GA ≥ 37 weeks), parents of PT two-year-olds reported significantly higher levels of internalizing behaviors and dysregulation, and lower social competence scores (as measured with the Infant-Toddler Social and Emotional Assessment, ITSEA). Similarly, Cosentino-Rocha, Klein, and Linhares (2014) asked mothers of 18-36 month-old children born PT (n = 44, birth GA < 37 weeks) and FT (n=36, birth GA ≥ 38 weeks) to assess their children's temperament (using the Early Childhood Behavior Questionnaire, ECBQ) and behavioral problems (using the CBCL). PT children had significantly higher scores than the FT group on measures of high-intensity pleasure, perceptual sensitivity, and attention problems, and lower scores on discomfort, cuddliness, and attentional focusing. These social-emotional differences extend to deficits in the quality of parent-child interactions between preterm infants and their mothers, from comparatively lessened infant activity and responsivity (Crnic et al., 1983) to reactions between infant irritability and maternal responsiveness (Beckwith & Rodning, 1996) and lower levels of maternal involvement (Barnard, Bee, & Hammond, 1984).

Rogers et al. (Rogers et al., 2012) attempted to relate this increased risk of social-emotional issues to specific brain circuits, and found that social-emotional difficulties (as measured by the Strengths and Difficulties Questionnaire) at age 5 correlated with higher apparent diffusion coefficient (ADC; see below for explanation of diffusion MRI) in the right orbitofrontal cortex. This is a brain region that has been associated with social regulation and social cognition (Vollm et al., 2006), and ADC typically decreases during development (Hermoye et al., 2006; Mukherjee et al., 2002), suggesting that a higher ADC may be representative of less mature white matter fiber bundles. Hille and Dorrepaal (Hille & Dorrepaal, 2008) assessed young adults born PT or VLBW as compared to peers from the general population. At around 19 years of age, the PT sample participated in less risk-taking behavior than their peers and did not report a higher rate of psychopathology, but males from the PT group did appear to have more difficulty establishing relationships. Critically, Ritchie et al. (Ritchie, Bora, & Woodward, 2015) conducted a systematic meta-analysis and concluded that children born VPT exhibit more peer problems, greater social withdrawal, and poorer social skills. The findings regarding prosocial behavior were mixed but the authors point out numerous limitations in the extant literature on social competence in children born PT, including the lack of longitudinal data, child or peer report, and conceptual models.

In summary there is increasing evidence of prematurity's specific effects on social behavior. As with the other domains discussed in this paper, the complex behavioral patterns involved in social competence as adolescents or adults have developmental roots in (and share neural circuitry with) early emerging social cognition.

Social-Cognitive Development and Prematurity.

Despite evidence of the close ties between cognitive, behavioral, social development, remarkably little research has been conducted on the topic of social-cognitive development in children born preterm. The capacity to deftly navigate the complex dynamics of social interaction, as observed in typical adults, has developmental roots in early social communication behaviors. This includes joint attention and reciprocal social behaviors that depend on rapid and efficient processing of social contingencies. Recent research has begun to map individual differences in these behaviors to individual differences in specific social brain circuits during the infant period (Elison et al., 2013).

Several groups have found evidence of early impairments in social development in infants born PT. In one study, PT infants averted gaze more frequently during social interactions at both 4 and 6 months (De Schuymer, De Groote, Desoete, & Roeyers, 2012). In another study, PT infants performed more poorly than FT infants on measures of gaze following, joint attention, and behavioral requests at 14 months (De Schuymer, De Groote, Beyers, Striano, & Roeyers, 2011). Telford et al. (2016) tracked the gaze of PT-born (birth GA < 33 weeks) and FT 7-month-olds while viewing photographs of natural faces, natural face and scrambled face images vs. nonsocial images (phones, cars, birds), and real-world scenes containing social or non-social content. The dependent measures were time to first fixation and looking time in areas of interest. The PT-born group showed shorter looking time durations to social content in all three tasks, suggesting less preferential attention for these stimuli.

One early behavior considered a cornerstone for social communication and later social-emotional development is joint attention (JA), which refers to the capacity to coordinate

attention on an object with another person. In full-term infants, the abilities to respond to joint attention (RJA) and initiate joint attention (IJA) show specific patterns of age-related growth between 9 and 18 months of age. Additionally, RJA at 12 months and IJA at 18 months predicted language abilities at 24 months, after controlling for cognitive development (Mundy et al., 2007). These skills also underpin other higher order competencies such as theory of mind (Nelson, Adamson, & Bakeman, 2008). Some of these studies have found significant sex differences in early joint attention behaviors (Mundy et al., 2007; Saxon & Reilly, 1999) and other related early social communicative behaviors (Leeb & Rejskind, 2004; Olafsen et al., 2006).

One early study investigating joint attention behaviors in PT and full-term six-month-olds (Landry, 1986) found no significant differences between groups. However, the experimental context, a two-minute videotaped naturalistic interaction between mother and infant, was fairly uncontrolled. Further, the timing of this assessment may not have been ideal for detecting differences given that relevant joint attention behaviors tend to emerge later in life, between 6 and 9 months. Another more recent study (Pena, Arias, & Dehaene-Lambertz, 2014) compared gaze following (a critical precursor to joint attention) in groups of PT-born 7-month-olds, PT-born 10-month olds, FT-born 4-month-olds, and FT-born 7-month-olds. Thus, individuals in the PT cohort could be matched to FT infants on either postmenstrual age (time in utero + time ex utero) or on chronological age (time ex utero). The impetus for this comparison was the idea that a longer duration of exposure to the rich ex utero social environment could potentially accelerate social development in infants born PT. Gaze following was measured in two contexts: in one, adults cued the infant to orient their gaze to one toy or another using both head and eye movements, and one in which the

adult cued using eye movements alone. The 7-month-old PT infants performed like 7-month-old FT infants (with whom they shared chronological but not postmenstrual age) in both tasks, suggesting that time functioning in the social world, and not just time since conception, might affect the development of social behavior.

Illness Severity

Preterm infants are an inherently complex population, and studies of prematurity have struggled to incorporate this complexity, rather than taking advantage of the opportunity for a type of dose-response approach. Many studies restrict sampling to a particular gestational age range, such as "very preterm" infants born prior to 30 weeks of GA or "moderate and late" preterm infants born between 32 and 36 weeks GA. These preterm samples are then compared to full-term samples in a dichotomous manner, grouping all PT infants together. Studies of preterm development typically incorporate some clinical characterization of PT samples, including information such as birth weight, duration of intubation, and diagnosed neurological injury. Most often, however, this information is either reported posthoc or used as exclusionary criteria. One key imaging study (Bonifacio et al., 2010) found that the association between extreme prematurity and white matter microstructure was no longer significant when neonatal comorbidities associated with extreme prematurity (such as mechanical ventilation, patent ductus arteriosis, and necrotizing enterocolitis) were added to the model. This introduces several methodological concerns, as studies of PT brain and behavioral development often focus on the very preterm very low birth weight population without quantitatively addressing medical status.

One potential method for dealing with this heterogeneity is to characterize medical comorbidities or illness severity in a continuous manner, rather than dichotomously, and

to build that information into the statistical models. Several scoring systems for neonatal illness severity have been proposed (see Dorling, Field, & Manktelow, 2005 for a review). There are a few common variables across systems, such as birth weight, that have been found to have predictive value for later outcomes. In general, however, these systems are designed for specific purposes which guide the nature of the information to be included. Unsurprisingly, there is no widely-known illness severity scoring system designed to predict social cognitive outcomes. Most systems were created to predict mortality, including the two most widely known neonatal scoring systems, the Clinical Risk Index for Babies (The International Neonatal Network, 1993) and its update, the CRIB-II (Parry, Tucker, & Tarnow-Mordi, 2003), and the Score for Neonatal Acute Physiology (SNAP) and its perinatal extension (SNAPPE) (Richardson, Gray, McCormick, Workman, & Goldmann, 1993) and their updates, SNAP-II and SNAPPE-II (Richardson, Corcoran, Escobar, & Lee, 2001). As with many other systems, the CRIB and SNAP scores were designed to predict neonatal mortality but have been used to predict other outcomes. Both systems contain similar information, but the CRIB-II is relatively easier to collect from medical records. Neither have been used to predict social developmental outcomes, but the CRIB has been used to predict neurodevelopmental outcomes at age three (Lodha, Sauvé, Chen, Tang, & Christianson, 2009).

These findings, typically conceptualized as disparate in nature, collectively point to the possibility that alterations in the development of social brain circuitry may help to account for the atypical outcomes observed in the preterm population. This, in turn, implicates the putative prognostic value of assessing social behaviors and social brain circuits during infancy. Preterm birth serves as one common instantiating event linked to a variety of

adverse outcomes, and strategic mental health intervention necessitates the comprehensive characterization of both adaptive and maladaptive neurodevelopmental trajectories. This work is crucial with regard to clinical questions -- the "typical" trajectory of preterm social cognitive development must be characterized before it will be possible to identify atypical trajectories that might predict subsequent impairment. In addition, these studies will contribute to knowledge of more basic principles of neural plasticity, as they provide a unique opportunity to investigate the relative contributions of developmental programming and exposure to the social world.

Conclusions

The first years after conception are a critical period of development, showing rapid change in both brain and behavior. In-vivo and ex-vivo imaging studies suggest that the third trimester is a critical period for brain development, and preterm birth is associated with alterations in brain structure, function, and connectivity. PT-born infants show atypical cortical and subcortical development, presumably resulting from disruptions to typical maturational processes across the brain, including several of the regions implicated in social processing. These neural anomalies have been linked to abnormal cognitive development in the PT population in infancy as well as childhood and early adulthood. PT-born individuals also appear to be at an increased risk of adverse neurobehavioral outcomes, from a relatively higher incidence of anxiety disorders and attentional impairment to abnormal social-emotional development and a putative increased risk of autism. The social brain plays a crucial role in all of these domains of impairment, yet little work has been done to investigate whether and how these neural circuits may be especially sensitive to both the events of omission and events of commission associated with the

premature brain. Thus, in order to do justice to the complexity of development, research must incorporate both brain measures and assessment of social-cognitive behavior.

This begs the question of how and why research into social-cognitive development in the PT population fell so far behind studies of development in other domains. One explanation might be that social processes are more difficult to localize in the brain, but as detailed in this paper our knowledge of the relevant neural circuitry has expanded greatly in the past decade. Another justification might be that social-cognitive development is harder to assess across time. Indeed, specific and informative measures of social behaviors have lagged behind those in the purely cognitive domain, but this social cognitive toolbox is growing. More broadly, there seems to be a fundamental failure to understand how social impairments or delays, particularly in the presence of normal IQ, can compromise quality of life for both children and adults. Our knowledge is limited to the extent that we cannot address something as basic as whether social-cognitive milestones are mediated more by postmenstrual or postnatal age. It is possible, in fact, that different areas of the same circuit may be driven by postnatal and postmenstrual age. In this case, prematurity could lead to a disconnect in maturation rates between these areas. Such brain "dysmaturity" (Scher, Johnson, Ludington, & Loparo, 2011) may be one cause of the adverse neurodevelopmental outcomes observed in the PT population.

While much effort has been invested into characterizing adverse neurobehavioral outcomes in the PT population, there are few biomarkers relating specific brain abnormalities to the adverse outcomes for which preterm infants are at an increased risk. Many of these outcomes may have developmental antecedents in early emerging social cognition, which in turn may reflect abnormal social brain circuit function. More broadly,

we do not fully understand how individual differences in social functioning map to individual differences in development of the neural circuitry of the "social brain," and preterm infants may serve as a model population for characterizing these associations.

Chapter 2: The Current Study

Aims

The primary goal of this project was to use a combination of direct behavioral assessments and parent-report questionnaires to characterize early social development in a cohort of infants ranging in gestational age and medical status.

Aim 1. *To test the hypothesis that greater neonatal illness severity will be associated with lower joint attention in the preterm sample.*

I hypothesize that medical adversity in the newborn period (as indexed by the CRIB-II) will be associated with performance on a measure of responses to joint attention (as measured by average scores on the Dimensional Joint Attention Assessment, DJAA) in the preterm group, such that higher CRIB scores will be associated with lower average DJAA scores, after controlling for sex, study sample, and adjusted age at the time of DJAA.

Aim 2. *To test the hypothesis that preterm infants will show higher joint attention when compared to full-term infants of the same adjusted age.*

I hypothesize that, after controlling for sex, study sample, and adjusted age at the time of the DJAA, infants born preterm will exhibit higher average DJAA scores than full-term infants.

Aim 3*. Lower joint attention performance in the preterm sample will be associated with more clinically concerning behaviors as indicated by parent report measures****.***

I hypothesize that, after controlling for sex , study sample, and adjusted age at the time of assessment, lower average DJAA scores will be associated with higher rates of clinically concerning behaviors at 12 and/or 18 months of age as measured by the Vineland Adaptive Behavior Scales, the Repetitive Behavior Scales—Early Childhood version, the Infant-Toddler Social Emotional Assessment, and the Video-Referenced Rating of Reciprocal Social Behavior.

Methods

Participants.

Preterm infants were recruited from a newborn intensive care unit (NICU) follow-up clinic at the University of Minnesota Children's Hospital and from a departmental research participant registry. Infants who were inpatient in the NICU are referred to the follow-up clinic if they were born prior to 32 weeks of gestational age and/or exhibited significant medical comorbidities. Every infant is scheduled for a visit at 12 months of adjusted age; some infants with particularly complex medical issues are also seen at 8 months of adjusted age. With approval from the medical team on a case-by-case basis, families of infants attending their 8- or 12-month visit were approached and offered the option to participate in the study. 118 families were approached in clinic and 105 infants were enrolled. Of these 105 infants, 66 completed the direct behavioral assessment of joint attention at 12 months of age, and 9 full-term infants who completed 12-month behavioral assessment were excluded from analyses as the nature of their medical comorbidities differs clinically from preterm birth, the focus of the present study. A second sample of 49 moderate and late preterm infants (born between 32 and 36 weeks of gestational age) were recruited from a department-maintained participant pool. 48 of these infants completed the 12-month direct

behavioral assessment of joint attention. Data from 149 full-term infants came from other studies conducted in the lab and did not require enrollment or assessment under this protocol.

The study was approved by the University of Minnesota Human Research Protection Program and institutional review board (#1504P69101), and parents of all participants provided informed consent and permission for their child to participate in this research study. Exclusion criteria included (a) vision concerns such that the infant would be unable to see the experimenter and (b) motor impairment such that the infant would be unable to turn his or her head in order to make an orienting response. See Table 2 for demographic information on the preterm and full-term samples.

The "social brain" networks discussed in Part 1 (see Table 1 for a summary of relevant brain areas) are dispersed across the brain and develop at different times and rates. Perhaps the development of coherent and efficient brain circuitry relies on carefully timed development of constituent networks, and this process could be perturbed by abnormally timed or unexpected events such as preterm birth and/or accompanying neonatal illness. If the response to joint attention, for example, depends on connectivity between regions in the temporal and prefrontal areas, and medical conditions associated with prematurity (such as bronchopulmonary dysplasia) are associated with diffuse white matter injury, it stands to reason that such neonatal illness might affect the development of such social behavior. Presumably, these networks may also vary in their responsiveness in terms of experience-expectancy and experience dependency. It is largely unknown whether the development of these circuits is tied more closely to post-conceptional or postnatal age, so the question of timing is critical.

The 12 month adjusted age time point was selected because: (1) it falls within a window of maximal individual differences in responses to joint attention (Carpenter, Nagell, Tomasello, & Butterworth, 1998; Elison et al., 2013), (2) it is a time point at which infants are routinely seen in the NICU follow-up clinic, and (3) it falls within the age range for several parent report questionnaires measuring facets of social and adaptive behavior. This is also a conceptually compelling time, as the second half of the first year of life is a time period crucial for the emergence of social behavior, from attentional bias to threat (Peltola, Leppänen, Vogel-Farley, Hietanen, & Nelson, 2009) to attributing intentions to others (Gergely, Nádasdy, Csibra, & Bíró, 1995) and categorization of species and race information (Pascalis, de Haan, Nelson, Haan, & Nelson, 2002).

Session timeline.

For infants from the NICU Follow-Up Clinic, direct behavioral assessment was conducted at the end of their clinic visits and consisted of a brief joint attention assessment. These infants also completed a 12-month neurodevelopmental assessment as part of their clinical visit. Infants from the departmental registry were invited to the lab to complete the joint attention assessment as well as a 12-month neurodevelopmental assessment, a set of eye tracking tasks, and a videotaped parent-child interaction. All parents were asked to fill out 12-month questionnaires online and over the phone, including demographic information and measures of their child's adaptive function, restricted and repetitive behaviors, temperament, and language. At approximately 18 months of adjusted age, parents were contacted and asked to complete a second set of online and phone questionnaires assessing their child's adaptive function, language, restricted and repetitive behaviors, reciprocal social behaviors, and social and emotional functioning,

Table 2.

Demographic Information for the Full (Preterm and Full Term) Samples.

Variable	Preterm, Clinic (n=57)	Preterm, Registry (n=48)	Full term (n=149)
Mean DJAA score	2.1 (SD = .93)	2.49 (SD = .97)	2.28 (SD = 1.03)
Adjusted age (months)	12.78 (SD = 1.09)	12.32 (SD = 1.26)	11.98 (SD = 1.77)
Nonverbal DQ at 12 months	104 (SD = 21.80)	113 (SD = 13.59)	111.26 (SD = 16.01)
Sex			
Male	27 (47.4%)	23 (48.0%)	71 (47.7%)
Female	30 (52.6%)	25 (52.0%)	78 (52.3%)
Gestational age at birth (weeks)	29.31 (SD = 3.3)	34.28 (SD = 1.18)	39.78 (SD = 1.15)
Race			
White	44 (77.2%)	38 (79.2%)	102 (68.5%)
American Indian/Alaska Native	0 (0%)	1 (2.1%)	0 (0%)
Asian	1 (1.7%)	1 (2.1%)	0 (0%)
Black/African American	3 (5.3%)	1 (2.1%)	0 (0%)
Native Hawaiian/Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)
More Than One Race	9 (15.8%)	6 (12.5%)	15 (10.0%)
Unknown/Not Reported	0 0%)	1 (2.1%)	24 (16.1%)
Ethnicity			
Hispanic	2 (3.5%)	6 (12.5%)	11 (7.4%)
Non-Hispanic	54 (94.7%)	38 (79.2%)	112 (75.2%)
Unknown/Not Reported	1 (1.8%)	4 (8.3%)	24 (16.1%)
Household income			
$24,999	2 (3.5%)	0 (0%)	0 (0%)
$25-34,999	5 (8.8%)	0 (0%)	5 (3.3%)
$35-49,999	7 (12.3%)	3 (6.3%)	8 (5.4%)
$50-74,999	4 (7.0%)	5 (10.4%)	26 (17.4%)
$75-99,999	8 (14.0%)	8 (16.7%))	36 (24.1%)
$100-149,999	14 (24.6%)	19 (39.6%)	38 (25.5%)
$150-199,999	7 (12.3%)	7 (14.6%)	13 (8.7%)
>$200,000	3 (5.3%)	6 (12.5%)	12 (8.0)
Unknown/Not Reported	7 (12.3%)	0 (0%)	11 (7.4%)
Maternal education			
Junior high	0 (0%)	0 (0%)	
High school degree	6 (10.5%)	1 (2.1%)	2 (1.3%)
Some college/2-year degree	9 (15.8%)	6 (12.5%)	13 (8.7%)
College degree	19 (33.3%)	19 (39.6%)	60 (4.0%)
Some graduate school	1 (1.8%)	5 (10.4%)	9 (6.0%)
Graduate degree	15 (26.3%)	17 (35.4%)	53 (35.6%)
Unknown/Not Reported	7 (12.3%)	0 (0%)	12 (8.1%)
Maternal age at birth (years)			
<25	9 (15.7%)	0 (0%)	4 (2.7%)
25-29.9	13 (22.8%)	7 (46.1%)	41 (27.5%)
30-34.9	21 (36.8%)	26 (54.2%)	70 (47.0%)
35-39.9	9 (15.7%)	11 (22.9%)	23 (15.4%)
40-44.9	1 (1.8%)	4 (8.3%)	5 (3.3%)
≥45	3 (5.3%)	0 (0%)	3 (2.0%)
Unknown/Not Reported	1 (1.8%)	0 (0%)	1 (.7%)

Measures.

Joint attention. The Dimensional Joint Attention Assessment (DJAA) was conducted at approximately 12 months of adjusted age. This procedure was developed by the applicant's primary mentor (Elison 2013) and informed directly by seminal work in the field (Carpenter 1998; Presmanes 2007). The primary goal of the procedure is to characterize a dimensional rating of responding to joint attention (RJA) that reflects individual differences in RJA performance. The context of the assessment is designed to elicit naturalistic play-based social interaction between the infant and the examiner. After a warm-up period, the experimenter proceeds through 4 series of hierarchically organized sets of cues, varying in the modality (e.g. gaze vs. verbal vs. pointing cues) designed to elicit RJA. Each series consists of 4 presses that vary in cue redundancy and are hierarchically ordered from least redundant to most redundant. Scoring of the responses are scaled to reflect the sophistication by which an infant responds to cues to share joint attention on an object in the distal visual field. Scoring of the responses is scaled to reflect the sophistication by which an infant responds to bids or cues to share joint attention on an object in the distal visual field. In each of the 4 series, a child is given a score of 0-4 (e.g., no response to any of the 4 prompt types = 0; response to gaze shift, head turn, point, and verbal cue = 1; response to gaze shift, head turn, and point = 2; response to gaze shift, head turn, and verbal cue = 3; response to gaze shift and head turn = 4). Total scores range from 0-16, with 0 indicating no response to any of the 4 prompts and 16 indicating gaze shift and head turn on all 4 prompts. Scores are averaged across trials to provide a mean RJA score between 0 and 4. Preliminary data suggests that this task elicits robust and dimensional individual differences in 9-15 month old infants (see Elison 2013, Fig. 5).

Clinically concerning behaviors. The *Vineland Adaptive Behavior Scales (VABS-II)* assesses child adaptive behavior in the communication, socialization, daily living skills, and motor domains. The Survey Interview (age range: 0 to 90 years) is administered to a parent using a semi-structured interview. The first edition of this scale had excellent reliability and validity (Carter et al., 1998). Similar psychometrics are available on this updated version. This measure is commonly used in studies of autism and developmental disabilities, has strong psychometric support, and is used in clinical settings to establish an individual's degree of functional impairment. In addition, the behaviors measured by the Vineland can be assessed relatively early in development, and the communication, socialization, and motor skills subscales are particularly relevant to adaptive function in this age range (Estes et al., 2015). This measure has been used in children born preterm, and prior studies have found associations between preterm birth and impairments in composite scores (Hack et al., 1994) and scores on the social competence subscale (Alduncin, Huffman, Feldman, & Loe, 2014). The VABS-II was collected at the 12- and 18-month time points; the current analysis uses only the 12-month data as the 18-month data is still being scored.

The *Repetitive Behavioral Scales – Early Childhood Supplement (RBS-ECS)* is 34-item parent-report questionnaire that is a modified version of the Repetitive Behavior Scales-Revised (RBS-R) (Bodfish 2000), which is a measure covering a broad range of repetitive behaviors. Subscales include stereotypical, self-injurious, compulsive, ritualistic, sameness, and restricted behaviors. Parents base ratings upon observations of their child's behavior over the previous month. The RBS provides total and subscale scores using two scales: an inventory or items-endorsed score and a weighted score, which reflects degree

of severity. It has shown good evidence of validity and reliability (Wolff, Boyd, & Elison, 2016), and prior work has demonstrated an association between birth weight percentile for gestation duration and the restricted and repetitive behavior scores from the RBS-ECS (Sifre et al., 2018). Parents completed this questionnaire for the 12- and 18-month visits. The current analysis uses only the 12-month data.

The *Video-Referenced Rating of Reciprocal Social Behavior (vrRSB)* is a 48-item downward extension of the Social Responsiveness Scale – Preschool, a parent-report questionnaire designed to provide a dimensional index of social functioning. Parents report on their child's social awareness, social information processing, reciprocal communication, social anxiety or avoidance, and preschool relevant preoccupations. Higher scores are evidence of greater social impairment. Reciprocal social behavior scores have also been associated with birthweight percentile for gestation duration (Sifre et al., 2018). Parents completed the vrRSB as part of the 18-month follow-up battery.

The *Infant-Toddler Social and Emotional Assessment (ITSEA)* is a 166-item parent report questionnaire that assesses 4 primary domains of dimensional functioning that include externalizing behaviors, internalizing behaviors, dysregulation, and competencies. The assessment also captures low base-rate, clinically relevant, social behaviors that include maladaptive behaviors, atypical behaviors, and social relatedness (Carter 2003). Two prior studies have shown lower social competence scores in preterm as compared to full-term children (Alduncin et al., 2014; Spittle et al., 2009).

Illness severity. In order to assess medical status, families granted authorization to access children's relevant medical records. For patients from the UMMC NICU Follow-Up Clinic or those seen within the Fairview system, records were accessed digitally. For

all other participants, signed authorization forms requesting full hospitalization records were faxed to any hospital where participants were seen for delivery and/or follow-up newborn care, such as NICUs, special care nurseries, or stepdown clinics. Records were then received in either digital or paper form and abstracted for relevant clinical information.

Medical records were abstracted to estimate each individual's severity of neonatal illness, based on the *Clinical Risk Index for Babies-II* (Parry 2003). The CRIB score was designed to predict mortality for infants born prior to 32 weeks of GA. The authors used logistic regression to identify a set of six variables most predictive of mortality. The CRIB-II was designed to improve predictions for smaller and more premature infants, and incorporates measures from the first 12 hours after ICU admission including gender, gestational age at birth, birth weight (in grams), body temperature at admission, and base deficit from arterial blood gas, and computes a score between 0 and 27 (with 27 representing the most severe neonatal illness). For infants who were missing either blood gas or admission body temperature but were otherwise healthy (scores of 1 or below) based on all other clinical variables, that missing variable was assumed to be within the normal range (as per Reid, Bajuk, Lui, & Sullivan, 2015).

Additional information collected.

In order to estimate general developmental level, infants were assessed using either the *Bayley Scales of Infant and Toddler Development (Bayley)* or the *Mullen Scales of Early Learning (MSEL)*. Both the Bayley (Bayley, 2006) and the Mullen (Mullen, 1995) are standardized developmental assessments that yield age equivalent scores in several domains of cognitive development. Both of these measures are frequently used to estimate overall developmental level as well as predict developmental outcomes.

The Bayley is commonly conducted in clinical settings, and infants being seen in the NICU FU are routinely assessed at approximately 12 mo. using this measure. The Bayley has 5 scales (Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior). The Mullen Scales of Early Learning provide a comprehensive assessment of language, motor, and perceptual abilities for children of all ability levels, ages birth to 68 months. The revised and updated version provides subscales to assess five developmental areas: (a) Gross Motor; (b) Fine Motor; (c) Visual Reception; (d) Expressive Language; and (e) Receptive Language. It yields standard scores, percentile ranks, and age equivalents. The MSEL was administered to infants from the participant registry at approximately 12 months of adjusted age. Full-term control participants were also administered the MSEL. A nonverbal developmental quotient (DQ) was calculated for each individual by dividing the child's age equivalent from the cognitive domain (from the Bayley) or the average of the child's age equivalents from the visual reception and fine motor domains by the child's adjusted age and multiplying by 100.

The *Infant Behavior Questionnaire-Revised (IBQ-R)* is a parent-report questionnaire designed to assess different dimensions of temperament: activity level, distress to limitations, approach, fear, duration of orienting, smiling and laughter, vocal reactivity, sadness, perceptual sensitivity, high intensity pleasure, low intensity pleasure, cuddliness, soothability, and falling reactivity. Parents completed the IBQ for the 12-month visit.

The *MacArthur-Bates Communicative Development Inventories (M-CDI)* is a widely used parent-report questionnaire designed to index expressive language, receptive language, and communicative gesture use. An advantage of this parent report measure is the avoidance of situational and temperamental factors that may interfere with test

performance. Parents completed the MCDI for the 12- and 18-month visits.

Participants from the departmental registry, who completed visits in the lab, also completed a 5-10 minutes unstructured play session with their caregiver, which could be coded for measures such as caregiver-infant interaction (i.e. maternal sensitive responsiveness and non-directiveness, infant attentiveness to caregiver, positive affect, and liveliness, and dyadic mutuality and intensity of engagement).

Data Analytic Plan.

Aim 1. To determine whether greater neonatal illness severity (in the form of higher CRIB-II scores) in preterm infants was associated with lower 12-month RJA (as measured by average score across series on the DJAA), a hierarchical multiple regression was conducted using SPSS. Only the preterm samples were included in this analysis, as medical records were not available for the full-term infants. RJA scores were entered as the outcome variable; Sex and adjusted age were entered as step 1 control predictors. Sex was dummy coded (0 = male, 1 = female) and adjusted age at the time of assessment was a continuous measure. Given that the preterm samples from the follow-up clinic and the sample from the participant registry showed significant differences on both 12-month RJA scores and some demographic variables (see Table 2), a dummy-coded "preterm study sample" variable was also entered as a control predictor (0 = PT sample recruited from the departmental registry, 1 = PT sample recruited from the clinic). Next, CRIB score was entered as a step 2 predictor to determine the portion of variance in RJA accounted for above and beyond the step 1 control predictors.

Aim 2.

To determine whether infants in the preterm samples showed higher 12-month RJA scores than full-term infants of the same adjusted age, a hierarchical multiple regression was conducted. RJA scores were entered as the outcome variable. Sex (dummy coded) such that 0=male and 1= female) and adjusted age (continuous) were entered as step 1 control predictors. Study sample (full-term, preterm clinic sample, preterm registry sample) was dummy coded into 2 new variables (Preterm Clinic vs. Full-Term, Preterm Registry vs. Full-Term) and those variables were entered as the step 2 predictors in order to determine the portion of variance in RJA accounted for above and beyond the step 1 control predictors.

Aim 3. To determine whether lower 12-month RJA was associated with higher levels of clinically concerning behaviors at 12 and 18 months, 5 series of hierarchical multiple multivariable regression analyses were conducted, with one regression for each outcome of interest. Only preterm infants were included in this analysis, as the assessment time points for several of the measures of interest differed in the full-term sample.

For each regression, sex (dummy coded), adjusted age at time of DJAA, and preterm study sample (dummy coded) were entered as step 1 control predictors. Adjusted age was excluded for VABS ABC and socialization, as these scores are already standardized by adjusted age. Next, 12-month RJA score was entered as the step 2 predictor to determine the portion of variance accounted for above and beyond the step 1 control predictors.

For the 12-month VABS, regressions were conducted for both the socialization subscale score and the adaptive behavior composite score. For the 12-month RBS-EC, one hierarchical regression was conducted for the composite score. For the 18-month ITSEA, one regression was conducted for the social competence subscale. For the 18-month

vrRSB, one regression was conducted for the total score. P values were not adjusted for multiple comparisons as no one dependent variable was being tested more than once.

Results

Illness Severity. Descriptive statistics and bivariate correlations are presented in Table 3; regression results are presented in Table 4.

A hierarchical regression was conducted to examine the relationship between neonatal illness severity and 12-month RJA in the two preterm samples, after controlling for sex, adjusted age at time of assessment, and study sample. Preliminary analyses were conducted to ensure no violations to the assumptions of normality, linearity, and homoscedasticity. Additionally, the correlations amongst the predictor variables were examined. All correlations were weak to moderate; positive correlations ranged between $r = .00$ and $r = .23$ and negative correlations ranged from $r = -.25$ to $r = -.62$. This indicates that multicollinearity was unlikely to present an issue in the models. RJA was significantly and positively correlated with adjusted age ($r = .23$, $p < .05$), and significantly negatively correlated with preterm study sample ($r = -.25$, $p < .05$), but was not significantly correlated with sex or neonatal illness severity. Study sample was also significantly positively correlated with adjusted age ($r = -.20$, $p < .05$) and negatively correlated with illness severity ($r = -.62$, $p < .01$).

Table 3.

Descriptive Statistics and Bivariate Associations for Variables Predicting 12-Month Response to Joint Attention in a Preterm Sample.

Variable	1. Mean DJAA Score	2. Study Sample	3. Sex	4. Adjusted Age	5. CRIB-II Score
1. Mean DJAA Score	1.00				
2. Preterm Study Sample[a] (Clinic)	-.25*	1.00			
3. Sex[b] (Female)	.02	.00	1.00		
4. Adjusted Age (Months)	.23*	.20*	.02	1.00	
5. CRIB-II Score	-.10	-.62**	.00	.05	1.00
Mean (% if binary)	2.27	54%	52%	12.57	4.68
Standard Deviation	.97	--	--	1.19	4.78
Minimum to maximum	.38-4.00	--	--	9.53-16.13	0-20

Note. CRIB-II = Clinical Risk Index for Babies-II.
[a] Study sample was coded as 0 = registry, 1 = clinic. [b] Sex was coded as 0 = male, 1 = female.
*$p < .05$. **$p < .01$.

In the first step of hierarchical multiple regression, three control predictors were entered: sex, adjusted age, and preterm

. This model was statistically significant ($F (3,88) = 4.78$; $p < .01$) and explained approximately 14% of the variance in RJA. After the addition of illness severity, the model as a whole explained 14.8% of the variance in RJA ($F (4, 87) = 3.18$, $p < .01$). Illness severity explained an additional .8% of the variance in RJA, which was not a significant contribution ($\Delta R2 = .01$; $F (1,87) = .36$, $p > .05$).

In the final model, two out of four predictor variables were statistically significant, with preterm study sample serving as the best predictor ($\beta = -.38$, $p < .01$), followed by adjusted age ($\beta = .30$, $p < .01$). Neither sex nor illness severity were statistically significant, $\beta = .02$, $p > .05$ and $\beta = .12$, $p > .05$, respectively. On average, preterm infants from the

clinic sample had RJA scores .73 points lower than those from the registry sample, after controlling for sex, adjusted age, and illness severity. A single standard deviation increase in adjusted age (which would be equivalent to 1.19 months) is associated with a .30 standard deviation increase in average RJA score, equal to a .29-point score increase.

Table 4.

Hierarchical Regression Analysis for Variables Predicting 12-Month Response to Joint Attention in a Preterm Sample.

	Model 1			Model 2		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Sex[a]	.03	.19	.02	.03	.19	.02
Adjusted Age	.24	.08	.29**	.24	.08	.30**
Preterm Study Sample[b]	-.58	.20	-.30**	-.72	.25	-.38*
CRIB-II Score				.02	.02	.117
R^2		.14			.15	
F for change in R^2		4.78**			.84	

Note. N = 105. CRIB-II = Clinical Risk Index for Babies-II.
[a] Sex was coded as 0 = male, 1 = female. [b] Study sample was coded as 0 = registry, 1 = clinic.
*$p < .05$. **$p < .01$.

Preterm Versus Full-Term Samples.

Bivariate correlations and descriptive statistics are presented in Table 5; regression results are presented in Table 6. A hierarchical regression was conducted to examine the relationship between preterm birth and 12-month RJA, after controlling for sex and adjusted age at time of assessment, Preliminary analyses were conducted to ensure no violations to the assumptions of normality, linearity, and homoscedasticity. Additionally, the correlations amongst the predictor variables were examined. All correlations were weak to moderate; positive correlations ranged between r = .00 and r = .39 and negative correlations ranged from r = -.12 to r = -.26. This indicates that multicollinearity was unlikely to present an issue in the models. RJA was significantly and positively correlated with adjusted age (r = .39, p < .01). Adjusted age was also significantly positively

correlated with Preterm Clinic vs. Full-Term ($r = .19$, $p < .01$) and significantly negatively correlated with Preterm Registry vs. Full-Term ($r = -.26$, $p < .01$).

Table 5.

Descriptive Statistics and Bivariate Associations for Variables Predicting 12-Month Response to Joint Attention in the Preterm Versus Full-Term Samples.

Variable	1	2	3	4	5
1. Mean DJAA Score	1.00				
2. Sex[a]	.12	1.00			
3. Adjusted Age (Months)	.39**	.05	1.00		
4. Preterm Clinic vs. Full-Term[b]	-.12	.00	.19**	1.00	
5. Preterm Registry vs. Full-Term[c]	.12	.00	.03	-.26**	1.00
Mean (% if binary)	2.28	52%	12.22	22%	19%
Standard Deviation	1.00	--	1.58	--	--
Minimum to maximum	.13-4.00	--	8.60-16.13	--	--

Note.
[a] Sex was coded as 0 = male, 1 = female. [b] Preterm Clinic vs. Full-Term was coded as 0 = Full-Term, 1 = Preterm Clinic. [c] Preterm Registry vs. Full-Term was coded as 0 = Full-Term, 1 = Preterm Registry.
*$p < .05$. **$p < .01$.

In the first step of the hierarchical multiple regression, two control predictors were entered: sex and adjusted age. This model was statistically significant ($F (2,251) = 24.50$; $p < .01$) and explained 16.3% of the variance in RJA. After the addition of the Preterm Clinic vs. Full-Term and Preterm Registry vs. Full-Term variables, the model as a whole was still significant and explained 20.6% of the variance in RJA ($F (4, 249) = 16.11$, $p < .01$). The addition of the Preterm Clinic vs. Full-Term and Preterm Registry vs. Full-Term contrasts explained an additional 4.2% of the variance in RJA, which was a significant contribution ($\Delta R2 = .04$; $F (2,249) = 6.61$, $p < .01$).

In the final model, two out of four predictor variables were statistically significant,

with adjusted age again serving as the best predictor of RJA (β = .42, p < .01), followed by Preterm Clinic vs. Full-Term (β = -.18, p < .01). Neither sex (β = .11, p > .05) nor Preterm Registry vs. Full-Term (β = .06, p >.05) were statistically significant. A single standard deviation increase in adjusted age (which would be equivalent to 1.58 months) is associated with a .42 standard deviation increase in average RJA score, equal to a .42 point score increase. On average, preterm infants from the clinic sample had RJA scores .44 points lower than those from the full-term sample, after controlling for sex and adjusted age. Preterm infants from the registry sample averaged joint attention scores .16 points lower than those in the full-term sample, but this difference was not significant.

Table 6.

Hierarchical Regression Analysis for Variables Predicting 12-Month Response to Joint Attention in the Preterm Versus Full-Term Samples.

	Model 1			Model 2		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Sex[a]	.20	.12	.10	.20	.11	.10
Adjusted Age	.25**	.04	.39	.27**	.04	.42
Study Sample						
Preterm Clinic vs. Full-Term[b]				-.44**	.14	-.18
Preterm Registry vs. Full-Term[c]				.16	.15	.06
R^2		.16			.21	
F for change in R^2		24.50**			6.61**	

Note. N = 254.
[a] Sex was coded as 0 = male, 1 = female. [b] Preterm Clinic vs. Full-Term was coded as 0 = Full-Term, 1 = Preterm Clinic. [c] Preterm Registry vs. Full-Term was coded as 0 = Full-Term, 1 = Preterm Registry.
*p < .05. **p < .01.

Clinically Concerning Behaviors.

A summary of the hierarchical regression results is shown in Table 7 (descriptive statistics and bivariate correlations are presented in Table 8 in the Appendix).

Table 7.

Summary of Hierarchical Regression Analyses for Clinically Concerning Behaviors in the Preterm Sample.

		Model 1		Model 2			
Key Parameters	*N*	R^2	*P*	β	ΔR^2	*F*	*P*
VABS Socialization†	79	.05	.16	.00	.00	.00	.97
VABS Composite†	79	.05	.14	.05	.00	.21	.64
RBS-EC Composite	90	.02	.61	-.01	.00	.01	.90
ITSEA Competence	60	.09	.14	-.07	.01	.29	.59
vrRSB Total Score	60	.02	.80	-.07	.01	.26	.61

Note: VABS = Vineland Adaptive Behavior Scales. RBS-EC = Repetitive Behavior Scales -- Early Childhood Supplement. ITSEA = Infant Toddler Social and Emotional Assessment. vrRSB = Video Referenced Rating of Reciprocal Social Behavior.
ΔR^2 and P values are reported for Step 1 models, which included the control variables (sex, adjusted age, and preterm study sample). Step 2 regression statistics are reported for the β value for RJA score, as well as the ΔR^2 from the Step 1 model, and corresponding F and P values from comparison with Step 1 Model.
† Does not include adjusted age, as scores are already standardized by adjusted age.
*$p \leq .05$. **$p < .01$.

12-month Vineland socialization domain standard score. In the first step of the hierarchical multiple regression, two control predictors were entered: sex and preterm study sample. This model was not statistically significant (F (2,76) = 1.90; p >.05) and explained 4.8% of the variance in Vineland socialization score. After the addition of 12-month RJA score, the model as a whole explained 4.8% of the variance in socialization (F (3, 75) = 1.25, p > .05). RJA explained an additional 0.0% of the variance in socialization, which was not a significant contribution (ΔR2 = .00; F (1,75) = .00, p > .05). In the final

model, neither sex, preterm study sample, nor RJA were statistically significant predictors ($\beta = .02$, $p > .05$; $\beta = .22$, $p > .05$; $\beta = .00$, $p > .05$, respectively).

12-month Vineland adaptive behavior composite (ABC) score. In the first step of the hierarchical multiple regression, two control predictors were entered: sex and preterm study sample. This model was not statistically significant ($F(2,76) = 1.99$; $p > .05$) and explained 5.0% of the variance in adaptive behavior. After the addition of 12-month RJA score, the model as a whole explained 5.3% of the variance in adaptive behavior ($F(3, 75) = 1.39$, $p > .05$). RJA explained an additional 0.3% of the variance in adaptive behavior, which was not a significant contribution ($\Delta R2 = .00$; $F(1,75) = .21$, $p > .05$). In the final model, only preterm study sample was a significant predictor of adaptive behavior, $\beta = .24$, $p < .05$. Neither sex nor RJA were statistically significant predictors, $\beta = .00$, $p > .05$; $\beta = .05$, $p > .05$, respectively.

12-month RBS-ECS items endorsed composite score. In the first step of the hierarchical multiple regression, three control predictors were entered: sex, adjusted age at time of assessment, preterm study sample. This model was not statistically significant ($F(3,86) = .60$, $p > .05$) and explained 2.1% of the variance in RBS composite score. After the addition of 12-month RJA score, the model as a whole explained 2.1% of the variance in composite score ($F(4, 85) = .45$, $p > .05$). RJA explained an additional .00% of the variance in composite score, which was not a significant contribution ($\Delta R2 = .00$; $F(1,85) = .00$, $p > .05$). In the final model, none of the four predictor variables were statistically significant. Neither sex, adjusted age, preterm study sample, nor RJA were statistically significant ($\beta = .06$, $p > .05$; $\beta = -.01$, $p > .05$; $\beta = .14$, $p > .05$; $\beta = .01$, $p > .05$, respectively).

18-month ITSEA competence domain score. In the first step of the hierarchical multiple regression, three control predictors were entered: sex, adjusted age at time of 18-month assessment, and preterm study sample. This model was not statistically significant ($F(3,56) = 1.92$, $p > .05$) and explained 9.3% of the variance in competence. After the addition of 12-month RJA score, the model as a whole explained 9.8% of the variance in competence ($F(4, 55) = 4.50$, $p > .05$). 12-month RJA explained an additional .5% of the variance in competence, which was not a significant contribution ($\Delta R2 = .01$; $F(1,55) = .29$, $p > .05$). In the final model, none of the four predictors (sex, adjusted age, preterm study sample, RJA) were statistically significant ($\beta = .11$, $p > .05$; $\beta = .25$, $p > .05$; $\beta = -.23$, $p > .05$; $\beta = -.07$, $p > .05$, respectively).

18-month vrRSB total score. In the first step of the hierarchical multiple regression, three control predictors were entered: sex, adjusted age at time of 18-month assessment, and preterm study sample. This model was not statistically significant ($F(3,56) = .33$, $p > .05$) and explained 1.8% of the variance in competence. After the addition of 12-month RJA score, the model as a whole explained 2.2% of the variance in competence ($F(4, 55) = .31$, $p > .05$). 12-month RJA explained an additional .5% of the variance in competence, which was not a significant contribution ($\Delta R2 = .01$; $F(1,55) = .26$, $p > .05$). In the final model, none of the four predictors (sex, adjusted age, preterm study sample, RJA) were statistically significant ($\beta = -.03$, $p > .05$; $\beta = -.09$, $p > .05$; $\beta = -.09$, $p > .05$; $\beta = -.07$, $p > .05$, respectively).

Chapter 3: Discussion & Future Directions

The overall goal of these analyses was to characterize early social-cognitive development in a cohort of infants ranging in both degree of prematurity and neonatal

illness severity. The analytical approach was threefold. The first analysis aimed to investigate the relationship between illness severity and RJA in two samples of preterm infants. The second analysis incorporated an additional group of healthy full-term infants, in order to address questions about the possible benefit accrued to infants by virtue of additional experience. The third analysis dove into the predictive value of early joint attention behaviors in preterm infants, evaluating its relationship to various measures of clinically concerning behaviors from an array of parent report questionnaires.

Discussion

Illness Severity

The hypothesis for the first analysis was that infants with greater neonatal illness severity would show lower RJA scores at 12 months of adjusted age. Sex was included as a control variable because prior work has shown some sex differences in joint attention behaviors in this age range, though there were no significant correlations between sex and RJA or any of the other predictors in this model. Adjusted age was incorporated as a covariate for two reasons: first, infants in this age range are typically assessed and evaluated based on their adjusted age range, lending to ease of comparison. Secondly, preliminary visual inspection of the data (including correlation matrices and scatter plots) suggested a substantial correlation between adjusted age and RJA. Indeed, adjusted age was significantly correlated with RJA, such that higher adjusted age was associated with higher average joint attention scores. Preterm sample group was added as a control variable after careful inspection of the raw data distributions and comparison of demographic variables that differed between the samples enrolled from the clinic and the departmental registry. RJA was also significantly correlated with study sample, such that infants

recruited from the departmental registry showed higher average joint attention scores than those recruited from the clinic.

As is often the case with studies of the preterm population, this sample contains a significant number of multiple births (approximately 38% of the preterm sample). Basic a priori inspection of the data set failed to reveal any significant correlations between multiple birth and any of the outcomes of interest, but as a basic check this regression was re-run after excluding all multiples (even those whose siblings were not assessed). The observed effects (see Table 9 in the Appendix) were similar to those in the primary regression, except that the control model was no longer significant. Study sample was still the best predictor of RJA, followed by adjusted age.

In the primary regression analysis for aim 1, the control model incorporating sex, adjusted age, and study sample was significant. Contrary to the stated hypothesis, however, illness severity (as indexed by CRIB score) did not prove significant in terms of its contribution to explaining variance in RJA.

One potential explanation for this finding lies with the illness severity measure itself. While CRIB score was chosen for its dimensionality, and at least one study has attempted to use it to predict neurodevelopment, it was designed to predict mortality. This is somewhat evident when viewing the raw distribution of CRIB scores within the preterm sample: there is a significant right skew, such that a large number of infants have a score of 0 or 1 and the tail extends out to the right with a few scattered infants showing scores closer to the maximum (27). As such, it may only provide meaningful information within a subset of infants who faced significant early illness. In a cursory investigation of this hypothesis, the same hierarchical regression was run excluding infants with a CRIB score

of 0 or 1. Illness severity score still didn't contribute significantly to accounting for the variance in RJA above and beyond the control variables, but the sample size was also lessened drastically, reducing the power to detect such an association if it does indeed exist.

A related explanation would be that while CRIB score accurately captures illness severity in the first 12 hours of life, that time period may not represent the peak sensitive period for developing capacities related to later joint attention behaviors. Perhaps, instead, it is sustained medical adversity that takes a toll on this type of development, and that type of medical comorbidity isn't captured by the CRIB score or any of the similar scoring systems. In addition, illnesses that develop after this initial period may have distinct and measurable effects on brain development. For example, proinflammatory conditions such as bronchopulmonary dysplasia and necrotizing enterocolitis often develop weeks or even months after birth and are associated with structural brain abnormalities (Gagliardi, Bellù, Zanini, & Dammann, 2009; Merhar, Ramos, Meinzen-Derr, & Kline-Fath, 2014) and adverse effects on neurodevelopment (P. J. Anderson & Doyle, 2006; Walsh, Kliegman, & Hack, 1989). These scoring systems typically rely on medical data collected only in the first (or very early) days of hospitalization, which relies on the assumption that developmental risk is a result of a discrete and early insult. There is an alternate argument to be made, that the sum effect of early medical adversity is more of an "area under the curve" across early hospitalization and likely into follow-up (for example, via continued growth restriction after discharge, e.g. Dusick, Poindexter, Ehrenkranz, & Lemons, 2003).

One future analysis that could be done with this existing data set would look at duration of NICU stay, rather than or in conjunction with illness in the first day of life. Perhaps, on the other hand, this very early illness does have an effect on early social cognitive

behaviors, but that effect becomes harder to detect over time. The characterization of such an early effect would require assessment earlier in infancy, perhaps using assessments tailored to younger infants such as eye tracking tasks investigating gaze following. One further possibility is that the impaired social competence associated with the "preterm phenotype" is rooted in alterations to more basic capacities such as visual or perceptual processing, that manifest in nuanced ways later in development.

While the hypothesized effect of illness severity was not evident in this analysis, even the control model itself is informative. Interestingly, study sample was a stronger predictor of 12-month response to joint attention than was adjusted age. The samples recruited from the NICU follow-up clinic and the departmental participant registry were enrolled based on adjusted age, and the samples were similar in terms of race, ethnicity, and sex. The samples were not merged, however, because they differed significantly across multiple demographic dimensions, including gestational age at birth, family income, maternal education level, and maternal age at birth. There were also significant differences between the two preterm samples in terms of response to joint attention and nonverbal developmental quotient at 12 months. The relationship between preterm birth, demographic variables, and this type of joint attention behavior was outside the scope of this project but certainly merits further exploration.

Preterm vs. Full-Term Samples

The hypothesis for the second analysis was that preterm infants might show some advancement in early social cognition, as indexed by higher RJA scores when compared to full-term infants (while controlling for sex and adjusted age). Were this the case, it would support the idea that preterm infants may benefit from additional "on-planet experience,"

at least in the domain of social cognition. The original analytic strategy incorporated illness severity, as well, but given its lack of effect in the preterm samples it was dropped from this analysis.

Once again, the model containing just the control predictors (sex and adjusted age) was significant. This, in and of itself, is a somewhat compelling finding. In both the initial and final models, adjusted age was once again the strongest predictor of RJA. This suggests that the relationship between adjusted age (again, time since conception) and joint attention is robust across a sample of infants varying greatly in both prematurity and medical status. If RJA is in fact tied very closely to adjusted age, that might imply that some early social-communicative behaviors are developmentally programmed to proceed in a somewhat similar fashion regardless of events such as preterm birth.

The final model, which also incorporated variables contrasting each preterm sample with the full-term sample, was also significant. While adjusted age was the strongest predictor of RJA, the Preterm Clinic vs. Full-Term contrast variable was also a significant predictor, while the Preterm Registry vs. Full-Term contrast was not significant. So, after controlling for sex and adjusted age, preterm infants recruited from the follow-up clinic had significantly lower average joint attention scores than the infants in the full-term sample; the same was not true for preterm infants recruited from the departmental registry. This is likely related to the differences between these preterm study samples, as discussed above. Above and beyond variations between the preterm groups in demographic variables such as maternal age at childbirth or family income, or perhaps in conjunction with those differences, there may be qualitative or quantitative effects of birth gestational age and

subsequent alterations in experience that differentially affect the development of early social communicative behaviors.

Once again, this regression was re-run after excluding all multiples (even those whose siblings were not assessed). Again, observed effects were very similar (see Table 10 in the Appendix).

Clinically Concerning Behaviors

The third analysis consisted of a series of hierarchical multiple regressions relating 12-month RJA to various measures of clinically concerning behaviors at both 12 and 18 months of adjusted age, including measures of adaptive function and socialization from the 12-month VABS, an index of restricted and repetitive behaviors via the 12-month RBS-ECS, the social competence domain score from the 18-month ITSEA, and a composite score of reciprocal social behaviors from the 18-month vrRSB. Previous studies have found associations between preterm birth and measures from the VABS and ITSEA; the models involving the RBS-ECS and vrRSB were more exploratory. They were included, however, as an exploratory investigation that might relate to the studies of autism risk in this population.

None of the models in this set of regressions were significant. It's curious that 12-month RJA didn't predict either the 12-month socialization scores from the VABS or the 18-month competence scores from the ITSEA, given the large degree of overlap between the behaviors tapped in those measures. In addition, at least two prior studies (Alduncin et al., 2014; Hack et al., 1994) have found differences in VABS socialization scores in children born preterm, though the Hack study only found differences for infants with a

birth eight under 750 grams, which is an effect that could also be tested in the current sample.

One potential limitation of this analysis was that 12-month RJA were being tested for its association with 18-month measures of the ITSEA and vrRSB. Perhaps any effects of RJA on the ITSEA and vrRSB would have become difficult to detect over this amount of time. Another limitation of the current analysis is that it only incorporates parent report data from the PT sample. This was done as an exploratory analysis, but the question might be further informed by including the same questionnaire data from the FT sample (which has been collected, albeit not at the exact same time points). In addition, a subset of outcomes was chosen for this exploratory analysis, but many of the other subscales from the VABS, RBS-ECS, ITSEA, and vrRSB are conceptually relevant to this population.

General Discussion

One potential limitation to the study as a whole is that the demographics of the study sample don't necessarily reflect the demographics of those at increased risk of preterm birth (and of adverse outcomes as a result of preterm birth). The overall sample (preterm and full-term) was 72% white, with a mean family income $75,000-$99,999 a year and a mean maternal education level of some graduate school. It would be valuable to enrich the study sample for socioeconomic risk, which to some extent goes hand in hand with risk of preterm birth.

It is important to acknowledge the confounds inherent in studying the PT population; there is no "normal" PT infant and many researchers have dedicated significant time and effort to investigating the ideal way to characterize and subdivide this population. However, given the incidence of PT birth and its associated adverse outcomes,

characterizing PT development is increasingly critical. Given the mixed findings as to impairment and advancement in the PT population in various domains of development, it is not entirely surprising that the stated hypotheses were not supported. Regardless, this study has yielded a rich and meaningful dataset with the potential to contribute to the body of knowledge about joint attention and more broadly about social competence in the preterm population. Given the questions surrounding age adjustment and its potential domain specificity, the strong contribution of adjusted age to RJA provides some support for domain general adjustment.

Future Directions

Following the research reviewed here, there are a number of areas ripe for exploration. While more and more research groups are working to image the brain during infancy, much of the work linking specific biomarkers (such a structural or functional brain abnormalities) to behaviors (such as language delay, or externalizing behaviors) focus on outcomes measured after interludes of years or even decades. Developmental scientists have a number of tools that can be used to measure both brain and behavior in infancy, which could help to disentangle potential cascading effects. This is not to say that measurement at a single time point is ideal; rather, the ability to characterize developmental trajectories hinges on a need for longitudinal data. In addition, the identification of atypical trajectories requires knowledge of the *typical* trajectory of preterm development, which pinpoints another gap in the field: there is currently a paucity of data from the "normative" PT population. Little work has been done to characterize brain and behavioral development in lower-risk PT infants and children, such as those born moderate to late preterm. Rather,

most of the studies of preterm development draw from samples of the very preterm and/or very low birth weight. On a somewhat similar note, the majority of these analyses looked only at the preterm sample. While there are certainly some risks that are relatively increased in infants born preterm, questions of the role of experience and developmental programming might be better suited by incorporating the full gestational range. This would also include full-term infants who spent time in the NICU; a small set of these patients were enrolled in the current study but were excluded due to sample size. A dataset enriched with full-term infants who experience high levels of neonatal illness might help to characterize the role of illness severity vs. age in early social cognitive development. This would, in turn, enhance our understanding of the "preterm phenotype" by helping to pinpoint factors or profiles unique to the PT population.

The PT brain is not only quantitatively but also qualitatively different from the brain of a FT infant. Researchers now have the means, the numbers, and certainly the rationale to study the social brain in infants born PT. Future work should make use of behavioral measures of social functioning linked to specific neural circuitry in order to identify the specific brain circuits that are at risk following PT birth and may benefit from targeted behavioral interventions. Such work will allow for the characterization of differential trajectories of social cognitive and brain development in infants born preterm, and the identification of early social cognitive behaviors and brain signatures related to later emerging clinical impairment. Ultimately, targeted assessment of the social brain in infancy has the potential to improve the lives of a substantial proportion of infants born preterm.

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Appendix

Table 8.

Descriptive Statistics and Bivariate Associations for Clinically Concerning Behaviors in the Preterm Sample.

Variable	1	2	3	4	5	6	7	8	9	10
1. 12mo Mean DJAA Score	1.00									
2. Sex (Female)	.02	1.00								
3. 12mo Adjusted Age (Months)	.23*	.02	1.00							
4. Preterm Study Sample[a] (Clinic)	-.25*	.01	-.27**	1.00						
5. 12mo VABS Socialization	-.06	.02	-.05	.22	1.00					
6. 12mo VABS Composite	0	0	.04	.22*	.91**	1.00				
7. 12mo RBS-EC Composite	-.02	.06	.02	.13	.08	.07	1.00			
8. 18mo Adjusted Age (Months)	.14	.07	.26*	.19	-.13	-.03	.05	1.00		
9. 18mo ITSEA Competence	.02	.13	-.08	-.16	-.03	-.04	-.02	-.20	1.00	
10. 18mo vrRSB Total Score	-.06	-.04	.10	-.08	-.09	-.06	.04	-.11	-.57**	1.00
N	105	105	105	105	79	79	90	61	60	60
Mean (% if binary)	2.27	52%	16.13	54%	104.66	100.42	14.34	18.31	40.25	24.32
Standard Deviation	.97	--	1.19	--	13.98	15.21	5.74	.65	8.41	6.99
Minimum to maximum	.38-4.00	--	9.53-16.13	--	87-152	74-150	1-29	17.50-20.18	22-55	10-49

Note. N= 105. VABS = Vineland Adaptive Behavior Scales. RBS-EC = Repetitive Behavior Scales -- Early Childhood Supplement. ITSEA = Infant Toddler Social and Emotional Assessment. vrRSB = Video Referenced Rating of Reciprocal Social Behavior.

[a] Sex was coded as 0 = male, 1 = female. [b] Preterm study sample was coded as 0 = registry, 1 = clinic.

*$p < .05$. **$p < .01$.

Table 9.

Hierarchical Regression Analysis for Variables Predicting 12-Month Response to Joint Attention in a Preterm Sample, Excluding Multiple Births.

	Model 1			Model 2		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Sex[a]	-.04	.25	-.02	-.06	.25	-.03
Adjusted Age	.25	.12	.29*	.25	.12	.30*
Preterm Study Sample[b]	-.45	.26	-.23	-.71	.34	-.37*
CRIB-II Score				.04	.03	.20
R^2		.096			.117	
F for change in R^2		1.939			1.333	

Note. N = 65. CRIB-II = Clinical Risk Index for Babies-II.
[a] Sex was coded as 0 = male, 1 = female. [b] Preterm study sample was coded as 0 = registry, 1 = clinic.
*$p < .05$. **$p < .01$.

Table 10.

Hierarchical Regression Analysis for Variables Predicting 12-Month Response to Joint Attention in the Preterm Versus Full-Term Samples, Excluding Multiple Births.

	Model 1			Model 2		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Sex[a]	.20	.13	.10	.21	.13	.11
Adjusted Age	.26**	.04	.40	.27**	.04	.43
Study Sample						
Preterm Clinic vs. Full-Term[b]				-.37*	.17	-.14
Preterm Registry vs. Full-Term[c]				.11	.19	.04
R^2		.18			.21	
F for change in R^2		23.80**			2.83	

Note. N = 65.
[a] Sex was coded as 0 = male, 1 = female. [b] Preterm Clinic vs. Full-Term was coded as 0 = Full-Term, 1 = Preterm Clinic. [c] Preterm Registry vs. Full-Term was coded as 0 = Full-Term, 1 = Preterm Registry.
*$p < .05$. **$p < .01$.