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Use of resting state functional MRI to study brain development and injury in neonates

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Abstract

Advances in methodology have led to expanded application of resting state functional MRI (rs-fMRI) to the study of term and prematurely-born infants during the first years of life, providing fresh insight into the earliest forms of functional cerebral development. In this review, we detail our evolving understanding of the use of rs-fMRI for studying neonates. We initially focus on the biological processes of cortical development related to resting state network development. We then review technical issues principally affecting neonatal investigations, including the effects of subject motion during acquisition and image distortions related to magnetic susceptibility effects. We next summarize the literature in which rs-fMRI is used to study normal brain development during the early postnatal period, the effects of prematurity and the effects of cerebral injury. Finally, we review potential future directions for the field, such as the use of complementary imaging modalities and advanced analysis techniques.

INTRODUCTION

Initially described in Biswal's seminal report,[1,2] resting state functional magnetic resonance imaging (rsfMRI) investigates the temporal correlations in low frequency (<0.1 Hz) fluctuations in blood oxygen level dependent (BOLD) signal. These signal fluctuations represent the baseline neuronal activity of the brain in the absence of goal-directed activity and stimulation and are used to identify networks with synchronous, spontaneous neuronal activity, termed resting state networks (RSNs).[3,4] Investigations, initially in adults and later in older pediatric populations, have consistently identified multiple canonical RSNs located throughout the brain, including the default mode (DMN), dorsal attention (DAN), ventral attention (VAN), frontoparietal control (FPC), cinguloopercular (CO), somatomotor (SMN)

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DISCLOSURE

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and visual (VIS) networks.[5] These networks depict the functional topography of the human brain, incorporating cortical and subcortical areas known to be co-activated by tasks involving memory, language, attention, motor activity, sensation and visual performance. Use of the technique has provided novel insight into the neurobiological basis of neurological disease and neurodevelopment, with recent literature implicating network-specific disruptions in RSN architecture in pediatric disorders such as autism[6], attention deficit hyperactivity disorder[7] and Tourette syndrome.[8,9]

Early neuroimaging assessments of cerebral function in neonates were typically limited to task-based investigations defining the anatomic localization of responses to visual, auditory and motor stimuli.[10–17] Subsequently, by eliminating the need for a subject to perform a task or attend to a stimulus, rs-fMRI afforded investigators a newfound, expanded ability to study the functional cerebral architecture of the developing brain, complementing information available through modalities such as surface-based morphometry, volumetrics and diffusion tensor imaging (DTI). This lead to targeted investigation of whether RSNs, or their precursors, were detectable in term and very preterm (VPT; born ≤30 weeks gestation) infant populations, including those with cerebral injury. Beginning with the initial description of immature forms of five RSNs in a cohort of VPT infants studied at term equivalent postmenstrual age (PMA) by Fransson and colleagues,[18] use of the technique to study the earliest forms of functional cerebral development has become increasingly established. The current literature details the presence and patterns of longitudinal development of multiple RSNs located throughout the brain in varied infant populations.[18–23]

rs-fMRI acquisition and analysis methods afford many inherent advantages for studying cerebral function in neonates. Importantly, from an acquisition lasting minutes in duration, robust information regarding global connectional properties can be assessed. In addition, data can be acquired from subjects resting quietly, asleep and even under anesthesia because of the limited requirements for participation. Further, commonly used rs-fMRI acquisition and analysis methods are transferrable across institutions, with limited specific equipment requirements. Analysis techniques for identifying and addressing common sources of colored noise in rs-fMRI data in infants, such as subject motion, are now established. Finally, and perhaps most importantly, similar methods can be readily employed to study diverse patient populations, including subjects with cerebral injury, varied perinatal exposures and complicated medical courses. Cumulatively, these benefits simplify experimental procedures while broadening the nature and scope of hypotheses that can be investigated.

Consequently, the use of rs-fMRI to study infants is an expanding field. Investigations have incorporated progressively younger subjects and diverse neonatal populations of interest. Recent studies have employed state-of-the-art methodology to account for technical issues commonly problematic in neonates. Advanced analysis techniques, including novel quantitative measures, graph theoretical methods and multivariate pattern analysis, have been successfully implemented. Functional and structural measures have been investigated in tandem, providing an early view of the “neonatal connectome” and highlighting the intricacy of the dynamic relationship between structural and functional development. While

delivering novel insights into the earliest forms of cerebral connectivity, these studies raise new questions regarding the role of RSNs and their utility as a neuroimaging biomarker and/or diagnostic tool at the individual level. Further, despite these advances, questions remain regarding best practices for data acquisition, analysis and interpretation. In this review, we detail the evolving understanding of the use of rs-fMRI for studying early RSN development in neonates. We initially focus on the key biological processes underlying RSN development, review the technical issues relevant to neonatal investigations, discuss the results from infant investigations reported in the literature, and review potential future directions for the field.

THE STRUCTURAL BASIS OF RESTING STATE NETWORKS

While the precise connection between fluctuations in BOLD signal and alterations in neural activity has yet to be completely elucidated, a brief review of early brain development, from a biological standpoint, provides a framework from which to consider rs-fMRI data. Early brain development is shaped by genetics, the exigencies of establishing synaptic connections, environmental exposure and experience.[24] It should be noted that the discussion below refers to some events that occur during the first half of fetal development, but that human infants born earlier than 23 weeks gestation usually do not survive. Thus, rs-fMRI studies before 23 weeks are impractical until methods are developed to consistently perform these studies in the fetus. Further, infants born at 23 weeks gestation are typically not sufficiently clinically stable to tolerate an MRI study for several weeks, limiting very early investigations.

Neurogenesis begins within the ventricular zone of the neural tube at 5–6 weeks gestation in humans. As dividing cells differentiate, they migrate to form the preplate, which is present by approximately six weeks gestation. By seven weeks, the preplate has matured into the developing cortical plate. A separate layer, the subplate, is formed beneath the cortical plate shortly thereafter.[25] The boundaries of the subplate are initially indistinct, but are clear by 12 weeks gestation. The subplate has its greatest extent (for somatosensory and visual areas) from 26–30 weeks gestation[26] and gradually involutes thereafter, though a limited number of subplate cells may still be present as late as six months after birth.

The subplate is critical to neurodevelopment because it serves as a staging area for afferent axons that initially form transient synapses in this region at 20–23 weeks gestation. These axons subsequently extend to the developing cortical plate and form more permanent connections at 24–32 weeks gestation.[27] The number and density of synapses increases steadily throughout early brain development, peaking during the first years of life.[28] It is interesting to consider that spontaneous neural activity during early development plays a central role in establishing and maintaining neural connections.[29,30] As a result, the spontaneous neural activity described in premature infants may serve a different function than that described in adults and children. While the subplate and cortical plate are clearly distinct entities both anatomically and physiologically, the spatial resolution of a typical rs-fMRI study is not sufficient to distinguish them.[31] Thus, they have been treated as a single entity in rs-fMRI studies published to date.

The process of cortical maturation outlined above is not spatially uniform. As initially described by Conel,[32–37] cortical maturation begins in the primary motor and sensory cortices and is followed by other more distal regions. Further, it occurs earliest in areas close to the insula and radiates outward, progressing more slowly in regions more distant from the insula such as cortical association areas.[32,35,38,39] This differential maturation, described initially on the basis of histological investigation, has also been confirmed in DTI studies.[40] In addition to considering cortical maturation in terms of local structural maturation, it is also possible to consider maturation of networks and their associated connections on the basis of rs-fMRI studies. As described below, these investigations also largely confirm the histological findings.[41]

TECHNICAL ISSUES RELATED TO STUDIES OF INFANTS

rs-fMRI studies are technically demanding, and studying neonates offers unique challenges related to both data acquisition and analysis. For example, infants will typically move during data acquisition and, unfortunately, cannot be trained lie still like older children. As a result, infants are sometimes sedated.[18,19] While RSNs can be detected in sedated subjects, sedation affects results.[42–44] Thus, we recommend that studies be conducted in non-sedated infants.[45] Even without sedation, there are likely subtle differences between subjects resting quietly and those at different stages of sleep.[46] Accurately identifying the arousal state of non-sedated subjects requires simultaneous EEG monitoring, which is not yet commonly performed due to the difficulty of acquisition, particularly in infants.

Motion is a problematic issue in rs-fMRI for all investigated populations, but is particularly prevalent in infants. *A priori*, one might assume that motion would affect sensitivity for discerning networks uniformly. Unfortunately, this is not the case. While motion increases all correlation values, proximal values are increased more than distal ones. As a result, analysis of data sets with excessive motion will make connections between regions that are physically close seem stronger while making connections that are physically further apart seem relatively weaker (Fig 1). This is particularly a problem when comparing two populations for which one moves more than the other. To complicate matters further, regions in lateral orientations to one another tend to undergo greater increases in correlation values due to motion than those in other orientations.[47] Thus, motion presents a vexing problem for data analysis and interpretation. Developing approaches by which to mitigate motion effects remains an area of active investigation.

Image distortion caused by static magnetic field inhomogeneity is also a common problem in rs-fMRI and is related to the fast image acquisition methods (typically echo planar imaging) used for these studies. The effects are strongest near air-tissue interfaces such as sinuses and the nasal cavity, often prominently affecting the orbitofrontal region. While these effects are less prevalent in infants as sinuses have not yet completely formed, they still must be addressed. One way to address them is to obtain additional imaging data from each subject which can be used to generate a map of the field distortions caused by susceptibility effects.[48,49] These field maps can then be used to undo the susceptibility-induced voxel shifts, thereby creating an undistorted image. An efficient variation of this approach involves obtaining an image set in which the phase encode polarity is reversed.[50]

The distortions of the images from the original data set and the one in which phase encode polarity is reversed are essentially opposite (*i.e.*, one image is stretched where the other is compressed and vice versa). Thus, the two image sets can be used to create a single undistorted image set. Note that both of these approaches require an additional image data set on which to create the distortion correction. However, if the rs-fMRI data were collected without the necessary additional image data, it still may be possible to correct the distortions. This is because for each scanner, RF coil and subject type (*e.g.*, an infant), the magnetic susceptibility induced field distortions are consistent. As a result, an average field map derived from a group of subjects imaged with the same system can be applied to those for which no map is available.[51] Though imperfect, this approach can lead to a significant improvement in image quality (Fig 2).

Data analysis in infants also presents unique challenges, one of which is image registration. The size and cortical folding of the brain vary dramatically during early brain development, most markedly between 24 weeks and term equivalent postmenstrual age. Thus, it is important to use a gestational-age specific target atlas, not only for rs-fMRI studies, but also for studies involving tissue identification/segmentation or comparison of brain structure across groups. Such atlases are freely available from a variety of sources (*e.g.*, www.brain-development.org and sumsdb.wustl.edu).

RESTING STATE FUNCTIONAL MRI INVESTIGATIONS IN INFANTS

Gradually increasing numbers of investigations have applied rs-fMRI to study infants, beginning during the neonatal period and extending through the first two years of life.[16,17,19–23,41,52–56] These inquiries have included heterogeneous subject groups of varied sizes, investigating both healthy, term-born infants and neonatal clinical populations of interest. Studies have been both cross-sectional and longitudinal, and acquisition and analysis techniques have differed across institutions. Despite these differences in study populations and approaches to assessment of connectivity, consistent patterns have emerged in the results from these inquires. These data, complemented by that available through existing histological and neuroradiological approaches, have provided invaluable information regarding early functional cerebral development and a foundation for expanded investigation applying rs-fMRI.

RSN Development in Infants

Through use of rs-fMRI, it has become increasingly evident that multiple canonical RSNs incorporating cortical and subcortical gray matter regions and the cerebellum are present during infancy. These include RSNs located in primary motor and sensory cortices (*e.g.*, SMN, VIS, auditory) and those involving association cortices (*e.g.*, DMN, FPC, DAN, VAN). Through investigations of VPT infants (and complimented by information available through fetal fMRI investigations, *vide infra*), the foundations of these networks are identifiable at least as early 26 weeks PMA. Many of these RSNs, particularly their early forms, consist of strong interhemispheric correlations between homotopic counterparts, with intrahemispheric correlations present but quantifiably weaker. Early thalamocortical connectivity is also evident during this period.[19,23,57] The described RSN topology is consistent with results obtained in adult and older pediatric populations, though the

correlation of findings between age groups differs based upon network (Fig 3). These similarities (and differences) have now been consistently identified across multiple reports,[18–20,23] though the terminology used to describe group differences between infant and adult populations has differed (*e.g.*, 'immature', 'precursor', 'proto').

The rate at which correlations within and between RSNs develop differs by network.[19,23,41,58] It is assumed that early RSN development is dependent upon effective establishment of structural connectivity.[59–61] Two recent reports have provided rankings for RSN development in infants which closely reflect known rates of cortical development based upon histological evidence as described above.[41,58] In these studies, RSNs incorporating primary motor and sensory areas, such as the SMN or VIS, are established by term PMA, with topology and strength reflecting adult-like patterns and correlation values. These RSNs are typically located in cortical regions known to mature early (*i.e.*, areas radiating outward from the insula), demonstrate less variability between subjects[62] and are potentially less susceptible to pathology.[41] In contrast, higher-order RSNs such as the DMN and DAN are identifiable in quantifiably weaker or topographically incomplete forms at term.[18–20,23] These RSNs mature non-linearly over the first several years of life, showing greater increases in size and strength during specific developmental epochs. They are more typically located in association cortices known to mature relatively late and demonstrate greater intersubject variability in spatial and temporal patterns. Relationships between RSNs gradually evolve, with correlation between RSN pairs assuming adult-like patterns during this period.[58,63] This combination of results suggests RSN development is susceptible during critical developmental periods and/or to disruption of key structural processes.

Clinical Factors Affecting RSN Development During Infancy

A principal area of interest in the neonatal rs-fMRI literature has been the effects of prematurity on RSN development, driven by the deleterious effects of prematurity on cerebral structure identified using other neuroimaging modalities.[64,65] Early reports employing conventional RSN mapping demonstrated similar RSN topography and qualitative measures between term and VPT infants scanned at comparable PMA.[18,19,23] However, subsequent use of quantitative measures have demonstrated clear group differences in intrinsic brain activity between these populations (Fig 4).[41] Specifically, prematurity leads to RSN-specific reductions in network amplitude and dimensionality, a measure which reflects network complexity. The rs-fMRI literature suggests these RSN differences may be indicative of pathology, though the exact etiology remains undetermined.[66] Importantly, these disruptions persist into early childhood,[54] adolescence[67,68] and even early adulthood.[69] However, their long-term effects on RSN architecture and their role in adverse neurodevelopmental outcomes remains incompletely investigated.

Our evolving understanding of RSN development suggests other key clinical factors and/or environmental exposures may also affect early RSN development, either individually or cumulatively. For example, it has been shown that forms of white matter injury common in infants born prematurely, including intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (cPVL), affect RSN development in VPT infants in a manner

dependent upon injury severity and the proximity to the injury site.[56,70] In addition, RSN-specific reductions in correlation strength have been identified in prematurely-born infants at term equivalent PMA who have high exposure to stressful and/or painful procedures.[71] Finally, recent reports suggest key variables such as sex and socioeconomic status may also affect the rate and patterns of RSN development in a network-specific manner.[58] The impact of these and other clinical variables inherent to the Neonatal Intensive Care Unit environment previously linked to disruption of early cerebral development, including infection,[72] patent ductus arteriosis ligation[73] and lung disease[74], requires continued targeted investigation.

Innovative Analytic Approaches for Infant rs-fMRI Data

Recently, advanced analytic approaches have been successfully adapted from the adult literature to analyze neonatal rs-fMRI data. These include use of alternative measures of functional connectivity and application of advanced mathematical techniques. Principal among these is use of graph-theoretical analyses, which uses mathematical models to examine pairwise relationships between objects. This methodology can be applied to functional and structural neuroimaging data to characterize network topology and identify "cortical hubs" – regions critical for integration and distribution of information. Recent investigations have applied these network analysis approaches to demonstrate infants possess many of the 'small world' organizational features in network architecture reported in adults, though the location and strength of cortical hubs may differ.[55,75] A second approach to analysis involves measuring covariance. Covariance is a connectivity measure which preserves sensitivity to the magnitude of BOLD signal fluctuations, providing a more sensitive measure than correlation for detection of rs-fMRI abnormalities.[76,77] Covariance measures within and between RSNs were recently used to define group differences in infant and pediatric investigations.[41,56,76] Dimensionality estimation is another novel connectivity measure which provides a quantitative index of the complexity of intrinsic brain activity and RSN segregation.[78] This technique was also recently used to illustrate differences between term and VPT infants. Of note, best practices for applying these mathematical approaches across populations of all ages continue to evolve, with the possibility of novel information afforded by advances in methodology.[47] Even still, this combination of results emphasizes the importance of extending conventional methods comparing RSN mapping results to include quantitative analyses of rs-fMRI data that increase sensitivity for delineating individual and group differences within and between RSNs.

FUTURE DIRECTIONS

Several avenues of novel and innovative research employing rs-fMRI in infant populations are being explored. Using currently accepted acquisition and analysis techniques, these investigations center upon providing greater understanding of the dynamic relationship between structural and functional connectivity, exploring the clinical utility of rs-fMRI for predicting neurodevelopmental outcome and examining new methodological approaches and neuroimaging modalities for assessing cerebral functional connectivity.

Exploration of the Neonatal Connectome

Though differences exist, anatomical and functional connectivity are interrelated on multiple levels.[44] Recent studies suggest RSN strength and spatial characteristics at both the local and global level are dependent upon cerebral structural architecture.[79–81] Investigations combining rs-fMRI measures with those of microstructural architecture, typically assessed via measures of anisotropic water molecule diffusion using DTI,[82] have attempted to comprehensively define the "human connectome," a detailed map of the neuronal connectional matrix in the human brain.[83] Smaller-scale studies have recently reported that "connectome-like" organizational properties are also evident in prematurely-born infants.[84,85] Combining results across modalities provides increased breadth to assessments of cerebral connectivity, delivering more detailed descriptions of the heterogeneous patterns of cerebral development across the brain, including in subjects with cerebral injury and/or abnormality.[11,86–90] With both methodologies increasingly established, expanded systematic investigation combining techniques across neonatal populations of interest will provide improved comprehension of the evolving interactions between microstructural architecture and emerging functional connections.

Defining the Effects of Clinical Variables on Functional Cerebral Development

The effects of clinical variables, cerebral injury and subsequent neural plasticity on RSN development continue to be explored. As noted above, it has been demonstrated that cerebral injury (*e.g.*, stroke, IVH, cPVL) powerfully disrupts RSN development in manner dependent upon proximity to the injury site and severity of injury in both pediatric and adult populations.[56] While this study demonstrates effects local to the injury site, the widespread effects of these disruptions across networks in neonates are less clear. In adults, there is suggestion that injury in specific locations (*e.g.*, medial parietal cortex, anterior insula, superior frontal cortex and temporo-occipital cortex) may produce more potent large-scale effects.[91] Whether similar global effects occur during infancy remains to be determined. Further, the ability of disrupted RSNs to "recover" either spontaneously or via neuroprotective therapies or intensive training administered following injury during a period when the brain demonstrates a high degree of plasticity remains unknown.[30,92] These principles shape the interpretation of rs-fMRI investigations in specific infant populations known to be susceptible to cerebral injury and that face recurrent exposure to varied and potentially deleterious environmental stimuli (*i.e.*, the NICU environment). In addition, the effects of clinical variables such as sex and ethnicity on RSN development in neonates remain to be fully explored.[62,93,94] Further targeted investigation employing rs-fMRI has the potential to define the local and global effects of risk factors in neurodevelopmental outcome and the efficacy of neuroprotective interventions in fostering RSN recovery following injury.

Use of rs-fMRI Results for Prediction of Neurodevelopmental Outcomes

Significant investigation remains necessary to translate our evolving understanding of early cerebral connectivity to predictive models of developmental performance. Key to this will be prospective, longitudinal investigations correlating neonatal rs-MRI results with childhood neurodevelopmental outcomes. Investigations seeking to establish rs-fMRI as a

biomarker for brain injury and risk for subsequent neurodevelopmental delay in normal and high-risk (*e.g.*, VPT infants) neonatal populations are ongoing. Early results suggest relationships between specific connectivity and neurodevelopmental performance during the first two years of life, though no longitudinal relationships have been identified using data from the neonatal period to predict subsequent outcome.[57] Success in these endeavors will likely require use of innovative data analysis strategies such as support vector machine (SVM) multivariate pattern analysis[95–100] and its extension to SVM regression.[101] Using this global approach, large data sets, such as rs-fMRI data and outcomes for a population of VPT infants, can be used to "train" the model to identify features most relevant for predicting outcome (Fig 5). This is interesting scientifically because identification of the relevant features provides an indication of which networks are most relevant for neurodevelopmental outcomes. However, this approach also has a more practical application. In theory, it can be used to predict outcome for an individual infant on the basis of his/her rs-fMRI data. (It should be noted that other forms of clinical and/or imaging data can also potentially be incorporated into the model.) This can be helpful for identifying infants at high risk for neurodevelopmental disability who are most likely to benefit from therapy services. It could also potentially be useful for prospective trials of neuroprotective strategies.

Development of Complementary Modalities for Functional Connectivity Assessment

Development of complementary techniques for mapping early functional cerebral development is ongoing, with results validated against those obtained using concurrent rs-fMRI. Principal among these are EEG,[102,103] near infrared spectroscopy (NIRS)[104,105] and diffuse optical tomography (DOT).[106–108] High-density DOT (HD-DOT) is a portable modality which capitalizes upon recent advances in optical imaging to enable continuous, quantitative assessment of cortical RSNs at the bedside.[108,109] HD-DOT overcomes the challenges pertaining to image quality and signal discrimination faced by many optical imaging systems (*i.e.*, near infrared spectroscopy). Analysis techniques used for rs-fMRI data can also be readily employed in HD-DOT. While there are differences in spatial resolution between the techniques, HD-DOT results in term infants demonstrate strong qualitative and quantitative congruence with those obtained using rs-fMRI. Further development of this technique may enable utilization of rs-fMRI methodology in investigations of neonates unsuitable for transport to the MRI scanner due to technical and/or logistical challenges.

Aspects of rs-fMRI in Neonates Requiring Further Study

Despite numerous advances in the field, obstacles persist in the rational application and interpretation of rs-fMRI in neonatal populations. Principal among these is our incomplete understanding of the effects of cerebral growth and development on the BOLD signal on which rs-fMRI investigations are based. It has been demonstrated that the hemodynamic response to stimulation changes throughout early development, presumably as a result of dynamic changes in neurovascular coupling and cerebrovascular physiology.[11] Further, use of age appropriate hemodynamic response function models improves the accuracy of results in task-based fMRI investigations. However, normal limits for various BOLD measures in subjects of differing PMA remain to be firmly established. In addition, cerebral injury,

common in both infants born prematurely and neonatal clinical populations of interest, may induce significant changes in cerebral blood flow, and subsequently BOLD signal.[110] This lack of standardization confounds interpretation of BOLD signal correlations, often confusing interpretation of signal magnitude and leading to selection of arbitrary thresholds for analysis in neonates.[3,111] Further inquiry in this area is critical for maximizing the potential of rs-fMRI investigation in this population.

Best practices for rs-fMRI data acquisition, analysis and interpretation in neonates have become increasingly understood. As has been recently detailed, these complex procedures are critical for mitigating the introduction of colored noise due to non-neuronal signal into rs-fMRI results.[112] Despite these advances, differences persist across institutions with respect to key variables such as voxel size/slice thickness, use of sedating medications during acquisition and motion correction procedures. Further, while standardized approaches are typically used across all neonatal populations at each institution, it is uncertain whether identical scanner settings and analysis procedures accurately account for the significant differences in brain volume and cortical structure across neonates of differing PMA. In addition, test-retest reliability of results, key to establishment of normative values, has been performed on only a limited basis in this population.[79,113] Finally, methodological advances increasingly employed in adults, such as use of electroencephalography (EEG) to define subject state during acquisition, are not typically performed in this age group. As these approaches are extrapolated to neonatal populations,[114] they may provide critical information regarding key variables such as the effects of state change on rs-fMRI results.[115] The potential for artifactual discrepancies introduced into measured results by these differences in standard procedures must be considered when comparing and interpreting rs-fMRI results across investigations.

Finally, control populations for investigations of prematurely-born infants remain to be definitively identified. In tandem with increasing application of fetal MRI in clinical practice, significant strides have been reported in the application of fMRI to study human fetuses.[116–119] Targeted investigations in this field have centered upon addressing the numerous and unique technical challenges specific to this population.[116,118,120–122] With these methods increasingly established, investigators have studied fetuses during the last half of pregnancy. Early results have reported findings in fetuses similar to those reported in neonatal populations scanned at similar postmenstrual age, including primitive forms of many RSNs.[117,118] Similar to results found in neonatal populations, these RSNs demonstrate interhemispheric correlation between homotopic counterparts and increasing long-range connectivity with advancing age.[116,119] Modular organization of these networks has also been reported.[123] However, best practices for comparing fetal and neonatal data acquired and analyzed using differing approaches remain to be determined. In addition, similar to investigations of neonates, acquisition, analysis and interpretation techniques continue to evolve. With continued advances, both populations will continue to provide mutual information regarding the earliest forms of functional connectivity and the antecedents of neurological injury and neurodevelopmental disability.

CONCLUSIONS

rs-fMRI provides a novel and valuable mechanism for assessing early functional cerebral development in normal and high-risk infant populations. Advances in rs-fMRI methodology now enable consistent, robust assessment of RSN development in neonatal populations. Recent investigations in term- and prematurely-born infants have demonstrated multiple RSNs are consistently identifiable, with results bearing strong similarity to findings in older pediatric and adult populations. The rate at which these RSNs develop reflects known patterns of cortical development based upon histological investigations, with RSNs demonstrating increasing strength with advancing age. Multiple analysis approaches have recently been developed and employed to identify differences in RSNs between infant populations at the group and individual level. While the foundation for expanded investigation has been established, further exploration of the clinical utility of rs-fMRI in neonates remains necessary. Initial activities should focus upon elucidating the relationship between neonatal RSN development and childhood neurodevelopmental outcomes, efforts necessary to establish this technique as a biomarker for prediction of individual developmental outcomes.

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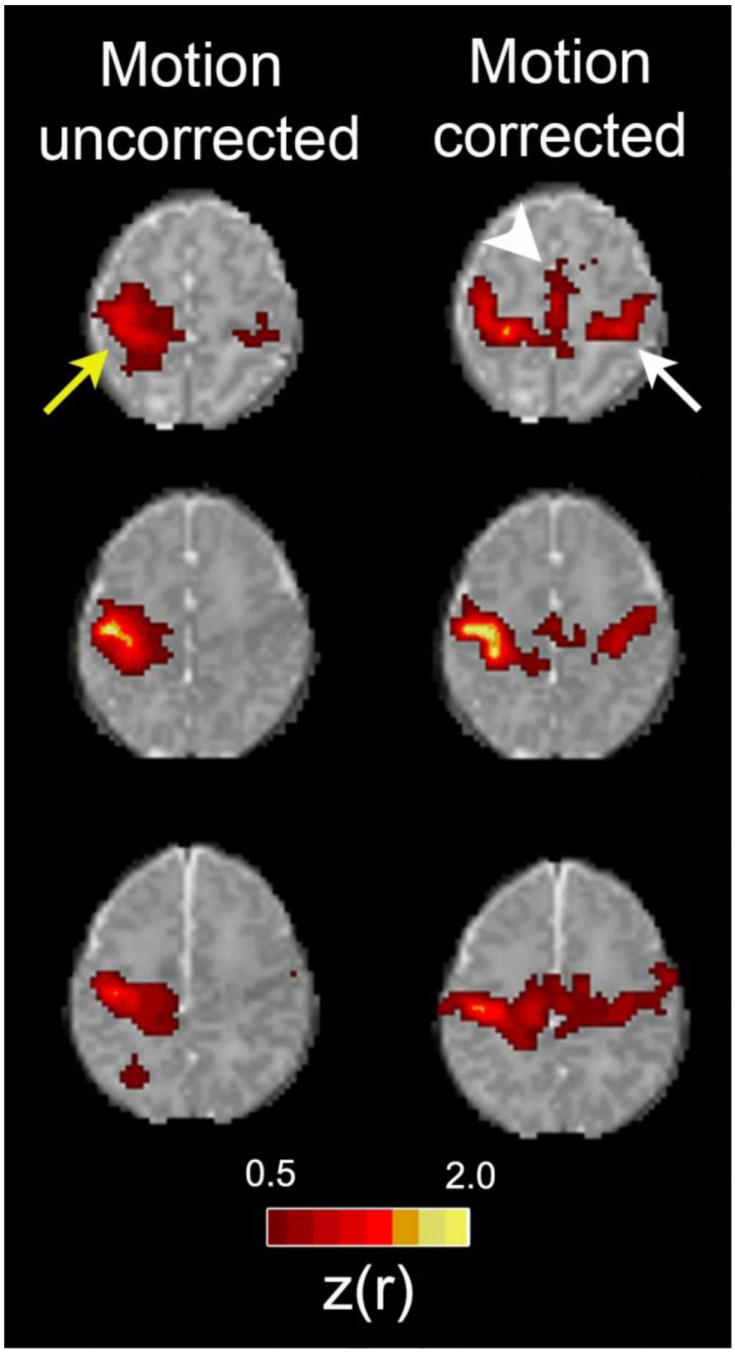

Figure 1. Improvements in rs-fMRI results using rigorous motion correction procedures

Each row shows rs-fMRI correlation maps illustrating the motor network for one of three representative healthy, term control infants. The left column shows data derived using all frames acquired during the course of all single scanning session. The right column shows data derived only from frames remaining following rigorous frame censoring procedures. For motion correction, frames were excluded if the volume-to-volume head displacement was ≥ 0.25 mm or the root mean squared BOLD signal intensity change (DVARS) was ≥ 0.3%. Images depict Fisher z-transformed correlation coefficients obtained using a left

motor cortex seed (z(r); color threshold value = 0.5). Identical slices are shown in both columns for each subject. Note the larger local area of correlation near the seed in the uncorrected data (yellow arrow). Note also that longer range connections to the contralateral motor area (white arrow) and supplemental motor area (white arrowhead) are not detected in the uncorrected data.

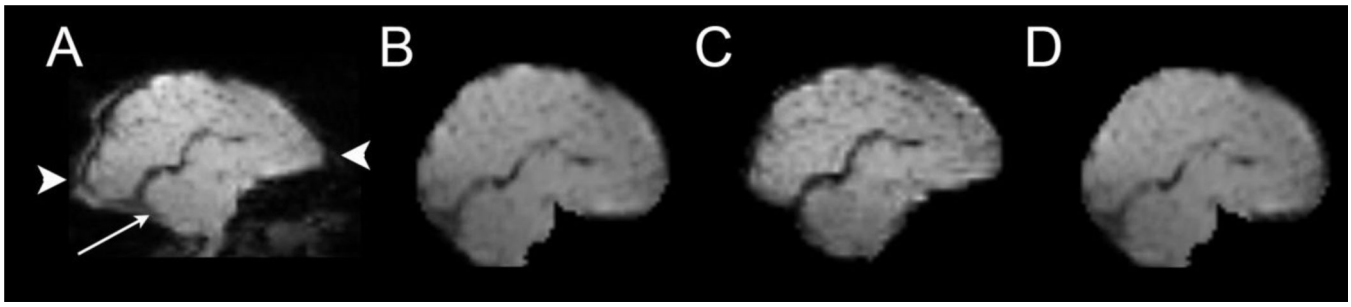

Figure 2. Multiple methods for correcting BOLD distortions due to magnetic field inhomogeneity

A parasaggital image obtained using echo-planar image acquisition. The cerebellum is indicated with an arrow. Image **(A)** is uncorrected and shows distortions due to magnetic field inhomogeneity caused by magnetic susceptibility effects. Note the stretching of the occipital and frontal lobes (arrowheads). The other images show the results of correction using **(B)** a self field map **(C)** top-down distortion correction, and **(D)** a mean field map. Note the similarity of improvement across all correction approaches.

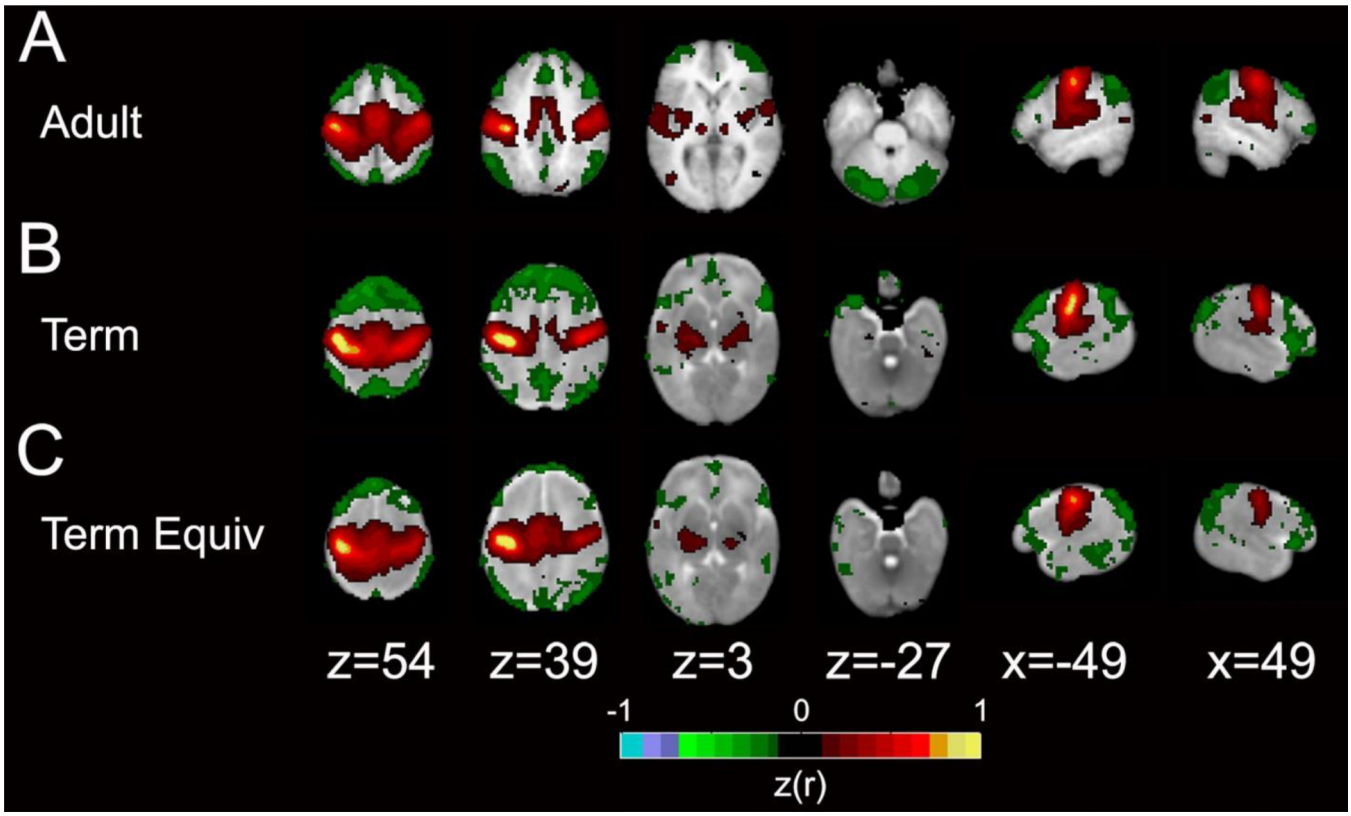

Figure 3. Motor network in adult, term and term equivalent subjects

Group mean rs-fcMRI correlation maps illustrating the motor network. The color scale is the Fisher *z*-transformed correlation coefficients (z(r); color threshold value = 0.12) obtained using a left motor cortex seed overlaid on population-specific, atlas T2-weighted images. Positive correlations are red and yellow, negative correlations are green. The images depict data from **(A)** an adult, **(B)** a term control infant and **(C)** a preterm infant at term equivalent postmenstrual age. Adapted with permission.[41]

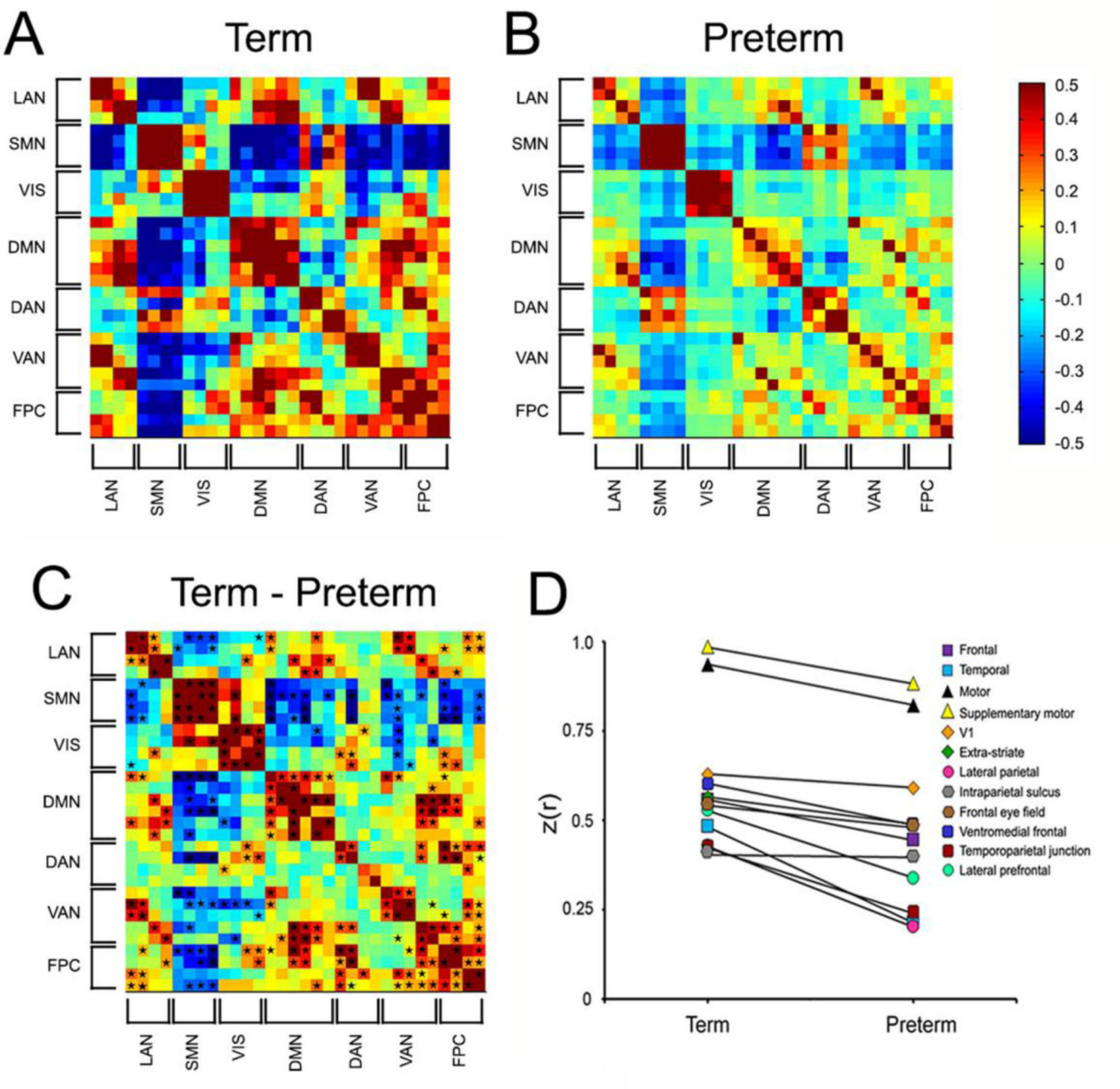

Figure 4. Term versus very preterm infant differences

Group mean covariance matrices representing multiple canonical RSNs for **(A)** term infants and **(B)** preterm infants at term equivalent postmenstrual age. **(C)** shows the difference (term minus preterm). Black stars in (C) denote cells with between group difference on two-tailed Mann-Whitney U-test ($p<0.05$; multiple comparisons uncorrected). **(D)** Group mean Fisher z-transformed correlation coefficients between homotopic ROIs pairs for term and very preterm infants. Note consistent term > preterm correlation values. Note also that areas that mature relatively early (e.g., motor and visual cortex) have higher correlation coefficients than those that mature more slowly. Adapted with permission.[41]

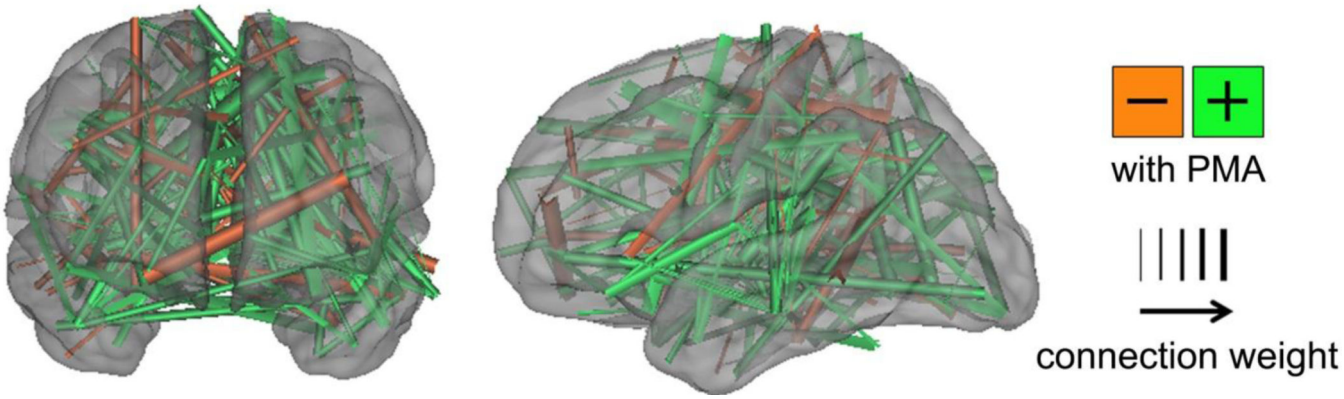

Figure 5. Support vector machine-multivariate pattern analysis demonstrating differences between term and very preterm infants

Functional connections important for differentiating term versus very preterm infants were determined using SVM. Connections stronger in term infants are shown in green; those stronger in very preterm infants are in orange. The thickness of each connection is weighted by the difference magnitude. Results were generated using 244 regions of interest located throughout the brain. Fifty infants scanned at comparable postmenstrual age with low-motion fcMRI data were included in each group. Findings are displayed on surface rendering of population-specific atlas image. Note that the differences between group are not confined to any particular area or network.