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Using fcMRI to Measure Brain Connectivity in Preterm Infants

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Abstract

Background—The use of functional connectivity magnetic resonance imaging (fcMRI) in research involving preterm infants is relatively new and its feasibility in this population is not fully established. However, fcMRI images reveal functional neural connections that may be useful in establishing the mechanisms of neuroprotective interventions in preterm infants.

Objective—To determine the feasibility of using fcMRI to measure differences in functional neural connections in nursing intervention studies.

Methods—A pilot study was conducted as part of a longitudinal, randomized controlled trial testing the effect of a feeding intervention on neurodevelopmental and clinical outcomes of preterm infants randomly assigned to one of two groups: a patterned feeding experience (PFE) group and a usual feeding care group (UFC). The fcMRIs were done at term equivalent age (TEA). Visual, motor, and default mode networks were analyzed.

Results—Seven infants were studied (four were in the PFE group and three were in the UFC group). Participants were selected sequentially from the parent RCT. Clear images were obtained from all participants. Differences were noted among PFE and UFC infants: Infants receiving PFE were hyperconnective in the default mode (caudate, anterior cingulate cortex, and precuneus) and motor networks (middle temporal and middle occipital areas) and hypoconnective in others areas of the default mode (hippocampal and lingual regions) and motor networks (precentral and superior frontal cortices) relative to UFC infants. No differences were noted in visual networks.

Discussion—The feasibility of using fcMRI at TEA in preterm infants who participated in an RCT on the effect of a nursing intervention was demonstrated. Differences in connectivity among infants by group were detected. Further research is needed to demonstrate the benefit of fcMRI in studies of preterm infants given the costs of the procedure, as well as the uncertain relationship of this early outcome measure to long-term neurodevelopment.

Keywords

fMRI; infant development; neuroprotection; preterm infant

Functional connectivity magnetic resonance imaging (fcMRI) is beginning to be more widely used. This procedure may reveal information about early neural connectivity that correlates with later developmental outcomes in high-risk infants such as those born preterm (Lee, Morgan, Shroff, Sled, & Taylor, 2013), although relationships between fcMRI results and long-term developmental outcomes have not been reported.

Magnetic resonance imaging (MRI) is a highly versatile imaging technique, frequently used in the diagnosis of a variety of health conditions. Although general MRI has been used to

obtain information about brain structures, functional MRI (fMRI), a newer technique, is used to understand how different areas of the brain respond to external stimuli or to passive activity during a resting state. While MRI measures hydrogen nuclei activity, fMRI measures changes in magnetization between oxygen-rich and oxygen-poor blood in the brain (blood oxygenation level dependent [BOLD] signal). Following collection of images, statistical methods are used to construct a "map" of the brain indicating the brain regions that demonstrate significant changes in activity. fMRI can localize activity to within millimeters of its source and show the connectivity between brain regions.

More specifically, fcMRI can show temporal relationships between spatially remote neurophysiological events, expressed as a deviation from statistical independence, in both resting state and task-state studies. While functional connectivity can refer to correlations across subjects, runs, blocks, trials, or individual timepoints, resting state functional connectivity focuses on neural interactions across individual BOLD timepoints when the subject is not performing a specific task such as reading or looking at an object. Functional connectivity appears to represent the network behavior underlying cognitive function in part because unlike structural connectivity, functional connectivity can change quickly and can be measured as a change in the ratio of oxyhemoglobin and deoxyhemoglobin. Thus, fcMRI —a noninvasive measure—allows for the characterization of the neural substrate of behavior by locations of the brain that are engaged (the amount of brain tissue involved) and the strength of the response (Greve, Brown, Mueller, Glover, & Liu, 2013). Table 1 provides brief definitions of MRI-related terms.

The techniques of fcMRI are well developed for infants (Alcauter et al., 2014; Gao, Lin, Grewen, & Gilmore, 2016; Smyser et al., 2010), but no published reports exist relating functional connectivity in infants to specific developmental interventions in the neonatal intensive care unit (NICU). The mismatch between the NICU environment and the preterm infant's developing brain and neurologic system increases the risk for poor developmental outcomes, including cognitive, motor, and sensory abnormalities (Gorzilio, Garrido, Gaspardo, Martinez, & Linhares, 2015). The importance of matching the environment with the brain's "expectations" for sensory input in order to form neural synapses—which are the structural substrate of the brain—during critical periods of development has been demonstrated (Als et al., 2004). Ways to measure the effects of NICU interventions have generally included behavioral observations and, more recently, head ultrasounds (Symington & Pinelli, 2006). The fcMRI approach may be useful for more definitive assessment of outcomes following interventions in preterm infants.

Purpose

The purpose of this pilot study was to assess the feasibility of using fcMRI to examine differences in functional connectivity networks in a subsample of preterm infants who participated in a larger study testing the effectiveness of a neuroprotective intervention provided with feeding care in the NICU. We were particularly interested in determining the feasibility of detecting brain connectivity in areas associated with early development including the default mode network (DMN) (Raichle et al., 2001): A network of interconnected and anatomically defined brain regions that preferentially activates when the

brain is at rest and not engaged in a task such as looking at an object. The DMN is negatively correlated with brain systems focused on external visual signals; it is one of the most studied resting state networks and is one of the most easily visualized. Other resting state networks included in our feasibility assessment were the sensory/motor and visual networks. These resting-state networks consist of anatomically separate, but functionally connected, regions displaying a high level of low-frequency correlated BOLD signal activity. Importantly, they represent known functional networks in brain regions documented to share and support cognitive functions (Fox & Greicius, 2010).

Methods

Design, Setting, Sample

We conducted this feasibility study in concert with a longitudinal, randomized control trial of preterm infants ≤ 32 weeks gestation (Pickler, Wetzel, Meinzen-Derr, Tubbs-Cooley, & Moore, 2015b). The patterned feeding experience (PFE) intervention involved tactile experiences starting with the first gavage feeding on first or second day of life, and continuing through the transition to oral feeding and discharge. The PFE intervention was based on neurologic, developmentally dependent brain expectations for holding during feedings for human infants. For the fcMRI pilot study, we sequentially enrolled seven preterm infants from the parent study: four from the intervention and three from the usual care group. The fcMRIs were completed at term equivalent age (TEA; about 40 weeks post-menstrual age), following hospital discharge and consistent with prior research; fcMRI results obtained at TEA can be compared to existing infant brain atlases for determination of network patterns. The study was approved by the Institutional Review Board and carried out in accordance with the ethical standards set forth in the Helsinki Declaration of 1975 as revised in 2013.

MRIs were completed at the Imaging Research Center at Cincinnati Children's Hospital Medical Center using a Philips Achieva 3.0T X-series scanner with a 32 channel head coil using a pre-established MRI imaging protocol (Merhar et al., 2016). Infants were medically and thermally stable, and MRI was performed without sedation using the "feed and swaddle" method (Mather, Neil, McKinstry, & Inder, 2008; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; 2013). Ear plugs and Minimuffs were applied for hearing protection, and additional padding was used to minimize movement. The MRI research assistant and study research nurse were present during the imaging, which lasted 45–60 minutes. Following MRI acquisition, images were examined by a clinical radiologist; clinical abnormalities were reported to the parents and primary care physician.

Analysis

The fcMRI data were analyzed at the Biomedical Research Imaging Center (BRIC) at the University of North Carolina-Chapel Hill (UNC-CH) by analysts blinded to group assignment; researchers at the BRIC have a well-established history of assessing brain networks including comparison of results with their infant brain atlas (Li, Wang, Shi, Gilmore, Lin, & Shen, 2015). The BRIC standard preprocessing steps were implemented using the Analysis of Functional NeuroImages software suite (AFNI version

2011-12-21-1014) (Cox, 1996). Briefly, the first three timepoints of resting state fcMRI (rsfcMRI) data were excluded to ensure magnetization equilibrium. Next, the data were motion-corrected using standard volume registration (AFNI 3dvolreg). Subsequently, the rsfcMRI data were coregistered [AFNI 3dAllineate "-EPI"] to the UNC neonatal template (Shi et al., 2011), and then filtered in both the spatial and temporal domains (AFNI 3dBandpass: frequency range 0.01–0.1 Hz, nuisance variables: global signal plus motion parameters, and smoothing kernel: 6 mm). Seed-based, whole-brain, functional connectivity analyses were conducted using the postcentral gyrus (PoCG) (Biswal, Yetkin, Haughton, & Hyde, 1995), posterior-cingulate gyrus (PCG), and calcarine cortices (CAL) as seed-regions (Shi et. al, 2011) yielding motor, default-mode, and visual networks, respectively. Whole brain analyses were generated separately for left and right hemisphere seed regions and then averaged to yield single networks (AFNI 3dNetCorr) (Taylor & Saad, 2013). Correlation measures were normalized using Fisher's Z-transformation. Finally, voxel-wise t-tests (AFNI 3dttest++) were used to generate within and between group functional connectivity maps. Functional connectivity measures were visualized on a surface model constructed using the UNC-CH neonate template (Van Essen et al., 2001) and subjected to qualitative analysis.

Results

Sample infants were similar in birth gestation, weight, and morbidity; Table 2 provides a summary of infant characteristics. Whole brain, functional connectivity maps corresponding to the default mode, motor, and visual networks were generated for each infant followed by development of connectivity maps by group, as shown in Figure 1. Qualitative differences between groups were noted. Specifically, images from infants in the PFE group showed hyperconnectivity in the default mode network at the caudate (CAU), anterior cingulate gyrus (ACG), and precuneus (PCUN), and in the motor network at the middle temporal gyrus (MTG) and middle occipital gyrus (MOG). Regions of PFE-related hypoconnectivity were also detected in the default mode at the hippocampus (HIPP) and lingual gyrus (LING), and in the motor network at the precentral gyrus (PreCG) and superior frontal gyrus, dorsal subdivision (SFGdor).

Discussion

We assessed the feasibility of using fcMRI to evaluate functional network connections in the visual, motor, and default mode networks in preterm infants who were part of a randomized clinical trial aimed at testing the effect of a patterned feeding experience on developmental outcomes. We chose these networks based on our prior research where infants in an oral feeding intervention group achieved full oral feedings sooner, and were discharged sooner, than those in a control group—a finding associated with improved neurodevelopmental functioning (Pickler, Best, Reyna, Wetzel, & Gutcher, 2005; Pickler, Reyna, Wetzel, & Lewis, 2015a; Pickler, Best, & Crosson, 2009).

Research supports that human brain development involves a continuous, dynamic maturation of functional brain networks (Gao et. al, 2016). Preterm infants are vulnerable to altered brain development resulting in abnormal neural connectivity. Specific targeted interventions

in the NICU may promote a more normal developmental trajectory of neural networks in preterm infants. However, there are few objective physiological measures to assess actual changes in the brain following these interventions. Our pilot study demonstrated the feasibility of using fcMRI to measure brain connectivity following intervention in the NICU; clear images were obtained from all study participants and qualitative analysis showed differences between groups in both hyper- and hypoconnectivity in the default mode and motor networks. Although these results are interesting, we are quite cautious in our interpretation of these results due to sample size; the pilot study was not designed to measure effectiveness. However, among these preliminary findings, there are signs of delayed development for infants receiving UFC compared with PFE; the known connectivity between PCG and ACG within the default-mode network was decreased (negative) in UFC group (Figure 1) suggesting that it may take longer for infants in the UFC group to establish this connectivity. Moreover, because our intervention—delivered as part of routine care—is very simple, inexpensive, and theoretically driven, we are encouraged to continue tests of its effectiveness using fcMRI in larger samples and extended over time.

Limitations

The fcMRI approach is not without limitations. The cost of fcMRI is high and include $700–$1200 for the MRI itself, plus costs for analysis of the images, which requires highly trained and specialized analysts. Nurse researchers will generally need to collaborate with healthcare researchers who are experienced in obtaining research fcMRIs; clinical readings of the MRI results should be included in the protocol with abnormal results reported to the primary care providers for their follow-up with families. Nurse researchers will also need to collaborate with neuroscientists for the analysis of fcMRIs; not all clinical centers will have scientists who are qualified to complete the complex qualitative and statistical analysis that is necessary to test intervention effectiveness. These experts can also provide guidance on areas of the brain to focus on for analysis based on how an intervention is hypothesized to affect outcomes (i.e., cognition vs. motor development).

An fcMRI is rarely ordered for routine care (Melbourne et al., 2016). Thus, fcMRI is generally obtained only under a research protocol. IRBs rarely allow sedation for nonmedically indicated MRI studies. Thus, techniques such as feed-and-swaddle—which we used in this pilot study—are required. These techniques need skillful practitioners and patience in order to assure that images are as motion free as possible in order to reduce signal “noise”—a common problem reported in fcMRI studies (Greve et al., 2013). We had very little noise signal, although we also took steps to insure that analyzed images were indeed motion free, as described above. Although fcMRI holds great promise as a measure of intervention effectiveness (Parikh, 2016), most nurse researchers will need significant funding and strong collaborators in order to obtain sufficient data to make results meaningful.

Conclusion

Interventions that promote more normal development of the preterm brain—and perhaps ameliorate the deleterious effect of the NICU environment on subsequent developmental outcomes—are needed. Improved understanding of how these interventions affect the brain

will advance general knowledge of the effects of NICU caregiving on brain development, plasticity and injury, and inform the development of future interventions. This was a small pilot study involving only seven preterm infants—four of whom had received a patterned feeding experience and three of whom had not. Based on this small sample, we are unable to draw conclusions about the benefit of the intervention on the developing brain. However, the ability to obtain clear images and observe qualitative differences between groups leads to consider a larger study of the intervention's effects on brain and associated development in preterm infants.

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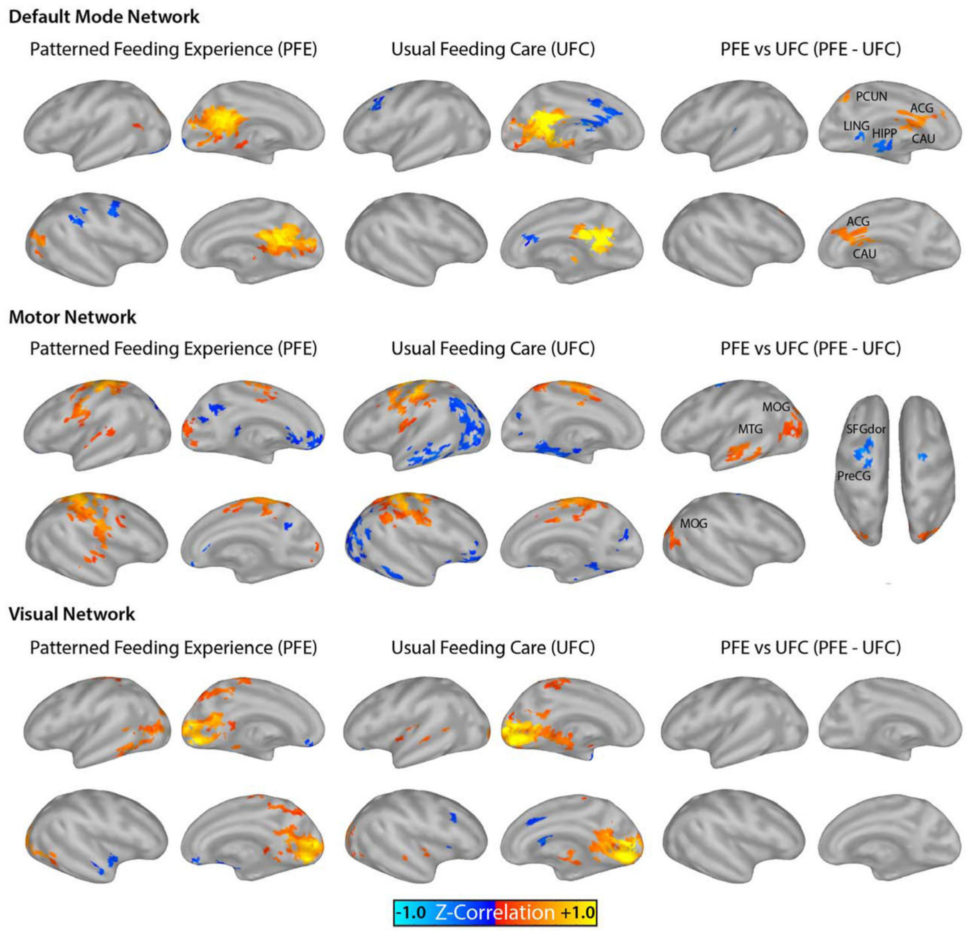

FIGURE 1.

Visualization of functional connectivity in preterm infants with patterned feeding experience (PFE; $n = 4$) intervention or usual feeding care (UFC; $n = 3$). Functional connectivity is depicted on the surface model and pseudocolored based on the Fisher's Z-transformation of the temporal correlation (Z-correlation, see color bar). Within group threshold: voxel-wise $p < .05$. Between-group (PFE vs UFC) threshold: voxel-wise $p < .05$, minimum cluster = 20 face-connected voxels. ACG = anterior cingulate gyrus; CAU = caudate; HIPP = hippocampus; LING = lingual gyrus; MOG = middle occipital gyrus; MTG = middle temporal gyrus; PCUN = precuneus; PreCG = precentral gyrus; SFGdor = superior frontal gyrus dorsal division.

TABLE 1

Definitions of Terms

Term	Definition	
Magnetic resonance imaging (MRI)	•	Technique used in radiology to create pictures of the anatomy and the physiological processes of the body
Functional MRI (fMRI)	•	Specific MRI technique that measures brain activity by detecting changes associated with blood flow. When an area of the brain is in use, blood flow to that region also increases
Functional connectivity MRI (fcMRI)	•	Functional connectivity MRI (fcMRI) can include resting state fMRI and task-based MRI. Functional connectivity is the connectivity between brain regions that share functional properties. Regions do not have to be structurally connected to have functional connectivity
Blood-oxygen-level dependent (BOLD) signal	•	Can be measured using fMRI. Changes in blood flow in the brain that represents brain activity even in the absence of an externally prompted task
Structural connectivity	•	Connectivity of brain regions that are physically attached to each other
Functional connectivity	•	Neural connectivity of brain regions representative of related networks, such as cognition

TABLE 2

Participant Characteristics by Patterned Feeding Experience (Intervention) and Usual Feeding Care (Control) Groups

Characteristic	Statistic	PFE (n = 4)	UFC (n = 3)
Gestational age (weeks)	*M* (*SD*)	31.8 (1.00)	30.1 (1.00)
	Range	30.7–32.8	30.1–32.0
Birth weight (g)	*M* (*SD*)	1864 (302.1)	1537 (619.0)
	Range	1500–2125	894–2129
Sex (male)	*n* (*%*)	4 (100.0)	1 (33.3)
Race (White)[a]	*n* (*%*)	3 (75.0)	2 (66.6)
Morbidity (NMI score)[b]	Mdn	3	3
	Range	2–4	2–3
Discharge age (weeks)	*M* (*SD*)	35.3 (0.27)	34.9 (0.9)
	Range	35.1–35.7	34.1–35.8)

Note. NMI = Neonatal Medical Index.

[a]Other race was African American.

[b]The NMI summarizes infant medical condition using classifications ranging from 1 = *born weighing > 1000 g and without major complications* to 5 = *born weighing < 1000 g and with very serious complications* (Korner et al., 1993).