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Gradient theories of brain activation: A novel application to studying the parental brain

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Abstract

Purpose of review: Parental brain research primarily employs general-linear-model-based (GLM-based) analyses to assess blood-oxygenation-level-dependent responses to infant auditory and visual cues, reporting common responses in shared cortical and subcortical structures. However, this approach does not reveal intermixed neural substrates related to different sensory modalities. We consider this notion in studying the parental brain.

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Recent findings: Spatial independent component analysis (sICA) has been used to separate mixed source signals from overlapping functional networks. We explore relative differences between GLM-based analysis and sICA as applied to an fMRI dataset acquired from women while they listened to infant cries or viewed infant sad faces.

Summary: There is growing appreciation for the value of moving beyond GLM-based analyses to consider brain functional organization as continuous, distributive, and overlapping gradients of neural substrates related to different sensory modalities. Preliminary findings suggest sICA can be applied to the study of the parental brain.

Keywords

neuroimaging; balanced excitation/inhibition; independent component analysis; parent brain; infant cue; general linear model

Introduction

The Parental Brain

Neural reorganization across the course of pregnancy and the postpartum period may facilitate neurobiological preparedness required for sensitive and adaptive caregiving postpartum (1**). Accumulating research in humans has begun to document the “parental brain,” with a particular focus on mothers’ neural response to infant affective cues (facial expressions and vocalizations) during the first year postpartum. The term “parental brain” has been used to describe the central neural circuits supporting caregiving, which are considered critical for healthy infant development (2,3*,4).

To understand the parental brain, functional magnetic resonance imaging (fMRI) studies have used general-linear-model-based (GLM-based) analyses to assess blood-oxygenation-level-dependent (BOLD) responses to infant auditory (e.g., cry) and visual (e.g., face) emotional cues (2, 3*, 5–7). These studies have found that either cries or faces separately activate auditory or visual sensory cortex, respectively, but these stimuli activate common structures as well, including the association cortex (e.g., frontoparietal cortex) and subcortical structures (e.g., amygdala, striatum, and thalamus) (8–12), consistent with theories that the association cortex and subcortical structures are functionally heterogeneous and emotional cues are multimodal (13–15).

Although fMRI studies have proven valuable in advancing our understanding of the neural circuitry of parenting, meta-analytic research suggests there may be a more limited set of brain regions implicated in maternal responsiveness to infant cues (16*). Concurrently, limited convergence of parental brain circuity could reflect limitations in the employment of GLM-based analyses to probe the parental brain where processing of infant affective cues may not precisely follow traditional neural processing pathways of visual or auditory input. Indeed, while functional specialization is a principle of fMRI modeling, and is a rationale for employing GLM-based analyses to interrogate BOLD time series (17–19), GLM-based findings do not fully reflect the intermixed relationship between neural substrates of the different sensory modalities (20–25).

Gradient Theory of Brain Activation

Gradient theories propose that neural substrates related to a sensory modality are concentrated within a specific region, gradually distribute over extensive regions and overlap with functional gradients related to other modalities (25–30). This theory is supported by multiple findings, including variability in cognitive deficits across different sensory modalities after brain injuries (26–28), balanced systems of neuronal excitation and inhibition (E/I) (31–34**), and functional heterogeneity in the brain (35–39).

BOLD signal changes measured with fMRI may reflect an E/I balance at the local level (40–50). That is, a single fMRI voxel often comprises intermixed neurons with concurrent but opposing changes in activity, which may lead to non-representative or even unobservable BOLD signal changes in GLM-based analyses (40, 44, 51–54). Spatial independent component analysis (sICA) may be used to separate mixed source signals from overlapping functional networks (FNs).

ICA was developed for extracting hidden, unknown source signals from observed signal mixtures (55–59). sICA treats BOLD signal from each voxel as a mixture of different source signals and separates it into spatially independent components (ICs), which represent temporally coherent FNs (55, 58). sICA has demonstrated: 1) FNs often extensively overlap; and, 2) overlapping FNs may show concurrent but opposite task-related modulation (i.e., simultaneous activation and deactivation) (60–66). Given this knowledge, we propose that to more accurately probe the parental brain to account for the potential overlap and interaction of neural circuitry implicated in processing infant auditory and visual cues, it would be valuable to incorporate both GLM-based analysis and sICA to fMRI data.

Preliminary Application of sICA to in Understanding Responses to Infant Cues

Recently, we started to consider whether GLM-based analyses and sICA would yield differential and complementary findings in studying infant cues. In beginning to lay the foundation for studying parental brain function, we explored neural responses to infant cries and sad infant faces in a sample of 35 women. Specifically, we applied GLM-based analyses and sICA to infant cries of low distress and infants faces with sad expressions (Figure 1; see supplemental materials for methodology). GLM-based analyses revealed expected patterns of primary sensory and associative cortex activity in response to infant cry and face stimuli. Relative to unmodeled baseline activity, cry stimuli were associated with increased BOLD response in the temporal cortex, including the primary auditory cortex (A1), while face stimuli were associated with an increased BOLD response in the fusiform gyrus and occipital cortex, including the primary visual cortex (V1). Both cry and face stimuli were associated with increased BOLD signal in the lateral and medial prefrontal cortex (PFC), anterior cingulate (ACC), insula, parietal cortex, striatum, amygdala, and hippocampus.

sICA identified 14 distinct FNs that were significantly engaged in processing negative infant stimuli and were differentially engaged by cry and face stimuli (Table 1). These FNs comprised a mixture of positive and negative signal integration and exhibited a high degree of spatial overlap. FNs generated by sICA overlapped extensively throughout most brain volumes including subcortical structures and the sensory and association cortices. Some

overlapping FNs exhibited double dissociations in responses to cries and faces; i.e., they were oppositely modulated by the two cues. Importantly, bimodal and unimodal FNs integrated signals in sensory cortices with signals in frontal, parietal, and subcortical regions typically associated with salience attribution, suggesting that the coordination of several neural mechanisms may contribute to processing infant stimuli.

Overall, our sICA findings suggest a gradient brain functional organization and that neural substrates related to infant auditory and visual cues overlap and interact throughout the brain. These findings suggest that overlapping clusters with opposite changes in signal may contribute to non-representative or negative findings of BOLD signal changes in higher-order association cortical and subcortical structures in GLM-based analyses. That is, GLM-based analyses may reveal task-related changes in BOLD signal in regions strongly dominated by neural substrates relating to one sensory modality relative to other sensory modalities, especially when stimuli integrate visual and auditory information. This may be one reason why meta-analytic investigation reports implicate limited brain regions in parental brain functioning (16), warranting the application of sICA to these data sets.

Future Applications of sICA to the Parental Brain

Our preliminary observations suggest that there are multiple FNs related to processing of infant auditory and/or visual cues that are extensively distributed and overlapping, including in subcortical and cortical structures. Moving forward, sICA may identify FNs, and data may be modeled to identify how these FNs may be differently engaged by different subject groups (e.g., mothers and fathers versus women and men without children) during experimental tasks that present infant face and cry stimuli. Such an approach will be important theoretically with respect to understanding normative developmental changes in functional brain organization during the perinatal period. To date, evidence suggests structural brain changes in the maternal brain from pre-pregnancy to postpartum, and across the postpartum period (1**, 67, 68). However, we know very little regarding functional brain changes (especially within FNs) across this critical period of maternal and child development. Importantly, the application of sICA may yield more consistent findings than GLM-based approaches, where there is limited convergence in studies of maternal responsiveness to infant cues (16). Such an approach may also provide greater sensitivity in the examination of associations between parental brain functioning and caregiving behaviors.

In addition to being of theoretical interest, the application of sICA to the study of parental psychopathology may also be of value. Multiple studies have begun to explore whether neural responses to infant affective cues are affected by clinical disorders and symptoms, primarily in mothers. For instance, decreased BOLD responses to infant face and cry stimuli have been observed in mothers currently using substances as compared to non-substance-using mothers across prefrontal and limbic regions (69). Relatively decreased sensitivity has been observed across multiple brain regions, including the ventral striatum and ventromedial prefrontal cortex, to own-infant, as compared to unknown infant, smiling faces in mothers in treatment for substance-use disorders (70). The impact of maternal depression on processing infant (and non-infant) affective cues has also been examined (71–73). Consequently, the

application of sICA to clinical populations of mothers and fathers could provide insight both into the pathophysiology of maternal psychopathology, as well as mechanistic insight into aberrant caregiving, which has sometimes been associated with these clinical disorders. Of note, individuals with addictions have been shown using sICA to differentially engage FNs in fMRI tasks involving the processing of rewards/losses, decision-making, and cognitive control (74–76), and such examinations into the function of the parental brain in individuals with and without addiction is needed. Furthermore, interactions between FNs may be modeled in future studies, as has been done in graph theoretical studies of addictions (77).

Conclusions

Increasing interest has focused on the parental brain to understand the neural basis of caregiving. While theoretically interesting, there is hope that neurobiological insights will facilitate new clinical directions for supporting parents with psychopathology to optimize their own, as well as their children's, well-being. To date, the vast majority of parental brain studies have examined BOLD responses to infant affective stimuli with GLM-based analyses; however, we have considered the potential for overlapping neural substrates for different sensory modalities. In particular, we discuss the utility of sICA to separate mixed source signals from overlapping functional networks and sICA's application to an fMRI dataset acquired from women while they listened to infant cries or viewed infant sad faces. Importantly, sICA identified a broader range of brain regions involved in the processing of infant cries and faces and yielded intriguing findings relating to how women may process these cues at a brain-based level. We propose that future studies of the parental brain, in clinical and non-clinical samples, will benefit from a gradient theory approach to further understand the prioritization of neural responses elicited by infant affective stimuli.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Compliance with Ethics Guidelines

Conflict of Interest

Marc Potenza reports support from the Connectict Department of Mental Health and Addiction Services, the Connecticut Council on Problem Gambling, the Connecticut Mental Health Center and the National Center for Responsible Gaming. Patrick Worhunsky reports grants from NIDA during the conduct of the study. Sarah Yip reports grants from NIDA during the conduct of the study. Helena Rutherford, Jiansong Xu, Rubin Zhang, Kristen Morie, Vince Calhoun, Sohye Kim, Lane Strathearn and Linda Mayes declare no conflicts of interest relevant to this manuscript.

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•• Of major importance

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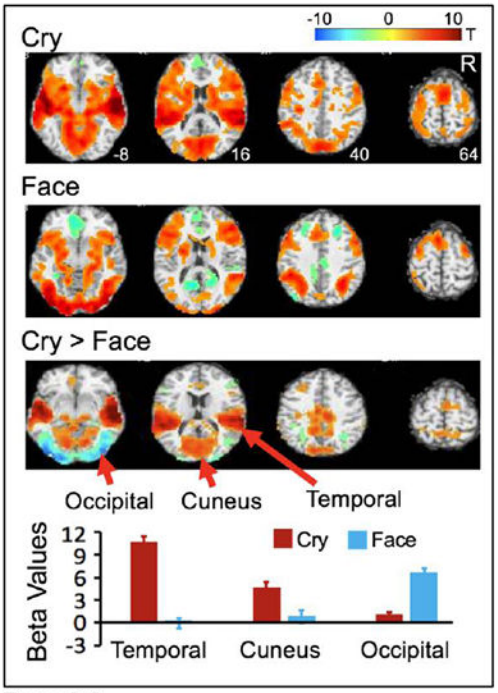
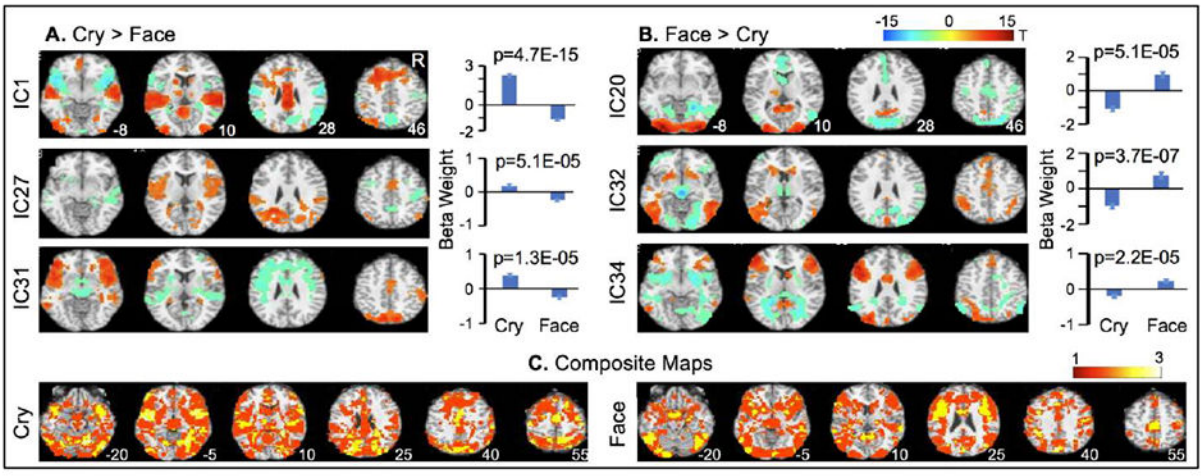


Panel A.



Panel B.

Fig. 1.

A Cry- and face-related changes in BOLD signal as revealed by GLM-based analyses. The colors on the T1 templates in MNI space show significant increases (red/orange) or decreases (blue/green) in BOLD signal for cry and face stimuli relative to baseline, and for cry relative to face stimuli (cry > face). The color bar indicates the t values. Only voxels surviving p<.01 and cluster p<.05, FWE-corrected for multiple comparisons of voxel-wise whole-brain analysis, are shown. The bar graph demonstrates mean beta values in three regions of interests (ROIs) for cry and face stimuli. The error bars represent standard errors

(SE) of the means. The numbers presented next to each brain image in the top row indicate the Z coordinates in MNI space; R=right hemisphere. **Fig. 1B.** Bimodal FNs oppositely engaged by cry and face trials. (A & B) The colors on the T1 templates in MNI space show spatial distributions of positive (red/orange) and negative (blue/green) clusters in each labeled IC. The color bar at the top of the figure indicates the t values. Only voxels surviving $p<0.001$, FDR-corrected for multiple comparisons of voxel-wise whole-brain analysis are shown. The bar graph demonstrates mean beta weights at cry and face trials. The p value on each bar graph is corrected for multiple comparisons using FDR and indicates significant difference of mean beta-weights for the two stimuli types. The error bars represent SEs. The number at the right bottom of each brain image in the top row indicates the Z coordinate in MNI space; R=right hemisphere. (C) Composite maps of all significant clusters in the six ICs. The cry panel presents all clusters showing significant positive cry-related engagement and negative face-related engagement. The face panel presents all clusters showing significant positive face-related engagement and negative cry-related engagement. The color bar indicates the number of overlapping ICs.

Table 1.

Regional composition of functional networks showing differential Cry vs. Face engagement

	Positive Clusters	Negative Clusters
Bimodal FNs		
IC1	Lingual G., Fusiform G., MOG[a], SPL[b], PCC[c], STG[d], ACC[e], SFG[f], Medial PFC[g]	Insula, IFG[h], TPJ[i], Precuneus
IC27	MTG[j], Insula, Medial PFC, OFC[k], Cuneus	Precentral G[l], MTG
IC31	IFG, Insula, SPL[m], MTG, Medial PFC	IPL[n], Fusiform G.
IC20	MOG, IOG[o], Cuneus, Lingual G., Precuneus, PCC, Fusiform G.	ITG[p], MTG, Parahippocampal G., Precuneus, ACC, Medial PFC
IC32	MTG, STG, Cuneus, Paracentral G, IPL, Caudate, Medial PFC	Midbrain, Thalamus, Precuneus, PCC, MFG[q], STG, Lingual G., Fusiform G.
IC34	IFG, MFG. SOG[r], ITG, Paracentral G, Caudate	MOG, IPL, Insula, Putamen, STG
Unimodal, Cry-related FNs		
IC2	Precentral G, Precuneus	FEF[s], PCC, Medial PFC
IC9	Paracentral G, IFG, Insula, Fusiform G, Caudate	Putamen, SFG, Precentral G., Postcentral G.
IC13	TPJ, MFG, Midbrain, Caudate, MTG	Middle Cingulate, Medial PFC
IC15	Striatum, Midbrain, IFG	ACC, Medial PFC
IC16	Cuneus, IFG, IOG, SFG, Precentral G, MFG	Cuneus, Medial PFC, Insula
IC7	Fusiform G., Lingual G., ACC, TPJ, Postcentral G., STG, Parahippocampal G., Insula	IOG, Cuneus, SFG
Unimodal, Face-related FNs		
IC17	MFG, IFG, Precentral G., Precuneus, SPL, MOG, Fusiform G., Lingual G.	Fusiform G., Cuneus
IC25	Paracentral G, Lingual G, MOG, IPL, MFG	SPL, Precuneus, Insula, IFG

Abbreviations:

[a]MOG: Middle occipital gyrus;

[b]SPL: Superior parietal lobule;

[c]PCC: Posterior cingulate;

[d]STG: Superior temporal gyrus;

[e]ACC: Anterior cingulate;

[f]MSFG: Medial superior frontal gyrus;

[g]PFC: Prefrontal cortex;

[h] IFG: Inferior frontal gyrus;

[i] TPJ: Temperoparietal junction;

[j] MTG: Middle Temporal Gyrus;

[k] OFC: Orbitofrontal cortex;

[l] G: Gyrus;

[m] SPL: Superior parietal lobule;

[n] IPL: Inferior parietal lobule;

[o] IOG: Inferior occipital gyrus;

[p] ITG: Inferior Temporal Gyrus;

[q] MFG: Middle frontal gyrus;

[r] SOG: Superior Occipital Gyrus;

[s] FEF: Frontal eye field.