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Neonatal Brain Response to Deviant Auditory Stimuli and Relation to Maternal Trait Anxiety

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Abstract

Objective: Excessive response to deviant stimuli during infancy and early childhood represents an early risk marker for anxiety disorders. However, research has yet to delineate the specific brain regions underlying the neonatal response to deviant stimuli near birth and the relation to risk for anxiety disorders.

Methods: The authors used task-based functional magnetic resonance imaging (fMRI) to measure response to deviant auditory stimuli in N=45 sleeping neonates (mean age 27.8 days, 60% female, 64% African American). In 41 of the infants, neural response to deviant stimuli was examined in relation to maternal trait anxiety on the State-Trait Anxiety Inventory (STAI-T), a familial risk factor for offspring anxiety.

Results: Neonates manifest a robust and widespread neural response to deviant stimuli that resembles patterns found previously in adults. Higher maternal trait anxiety relates to higher responses within multiple brain regions including bilateral anterior insula, ventrolateral prefrontal cortex, and multiple areas within anterior cingulate cortex. These areas overlap with brain regions previously linked to anxiety disorders and other psychiatric illnesses in adults.

Conclusion: The neural architecture sensitive to deviant stimuli robustly functions in newborns. Excessive responsiveness of some circuitry components at birth may signal risk for anxiety and other psychiatric disorders.

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INTRODUCTION

Anxiety disorders are common impairing conditions (1) that can endure following treatments in up to 50% of affected individuals (2). Evidence suggests that the altered neurodevelopmental trajectory associated with anxiety may start as early as birth (3–5) and include an early appearing excessive responsivity to unexpected or 'deviant' stimuli. However, little is known about the specific neural systems underlying this excessive responsivity. The current study uses task-based functional magnetic resonance imaging (fMRI) to delineate the neonatal response to deviant stimuli and its relationship to maternal trait anxiety, a risk factor for problematic anxiety in offspring (6, 7). An altered neonatal response to unexpected stimuli could signal increased risk for later anxiety, and the associated brain systems may provide targets for preventative interventions.

Prior research relates anxiety in children and adults to increased behavioral and physiological responses to environmental change (8). Similar hyper-responsivity manifests in infants at risk for anxiety disorders (3). Infants born to mothers with an anxiety disorder face a five-fold increased risk for anxiety disorders (9). This increased risk exists along a continuum, as normative variation in maternal trait anxiety is associated with variation in offspring trait anxiety (6), which in turn relates to later risk for an anxiety disorders (7). In non-clinical samples, higher antenatal maternal anxiety is associated with increased electroencephalographic (EEG) evoked responses to deviant sounds in offspring near birth (10) and at age 9 months (11). Such increased EEG evoked responses are also associated with early childhood temperaments that predict risk for adult anxiety disorders (3). Behavioral inhibition, an early appearing temperament that includes increased reactivity to novel or deviant stimuli, is a potent risk factor for anxiety disorders (3). Despite this behavioral and physiological evidence, the relevant brain regions remain unknown in infants.

The brain response to deviant stimuli and its relationship to anxiety are better understood in older children and adults than infants. In adults, deviant stimuli engage numerous brain regions, including the bilateral anterior insula (AI), the dorsal anterior cingulate (dACC), the inferior frontal junction (IFJ), and the ventrolateral prefrontal cortex (vlPFC) (12). These regions derive from multiple different 'functional brain networks' that connect regions into distinct maps, such as the salience (SN) (13), cingulo-opercular (CON) (14), dorsal attention (DAN), and ventral attention (VAN) networks (15). Although the functional brain network architecture of the neonatal brain is incompletely understood, evidence indicates that network connectivity is reduced in neonates, suggesting that networks are in a more immature form (16, 17). Anxiety disorders in older children and adults have been robustly associated with increased activity in regions within the SN, CON, and VAN in response to salient stimuli as well as salient task conditions such as making an error (18). Beyond this increased salience response, recent meta-analyses indicate that anxiety and other psychiatric disorders are additionally associated with activity alterations in the AI, dACC, vlPFC, subgenual anterior cingulate (sgACC), and pregenual anterior cingulate (pgACC) during a range of cognitive (19) and emotional (20) tasks.

Examining brain function in neonates may illuminate risk markers that could be obscured in older samples due to compensatory adaptations. Prior research suggests that some of

the neural correlates of pediatric anxiety disorders represent adaptive changes, such as increased prefrontal regulatory processes (21). Measuring brain activity differences during infancy may uncover 'core' deficits that occur before these secondary changes. Uncovering these early risk profiles is important given anxiety prevalence (22) and clinical impact (23). Moreover, children with anxiety disorders face elevated risks in adulthood for many other disorders, including depression (24), substance use disorders (25), eating disorders (26), and bipolar disorder (27). Therefore, uncovering early risk profiles could inform attempts to identify mechanism-based targets that reduce the burden from many mental disorders.

To address these issues, we use fMRI to measure brain activity evoked by deviant auditory stimuli in n=45 sleeping neonates. Following a commonly used strategy, we assess the 'oddball' response by playing loud white noise bursts at irregular intervals in the context of a repeating sequence of background sounds (12); in this case the ongoing fMRI scanner sounds provide the background. Prior work has established the feasibility and utility of measuring fMRI responses to sounds in neonates (28–30). In addition, we relate variation in the evoked response to normative variation in maternal trait anxiety in a subset of 41 neonates. We relate neonatal activity to maternal *trait* anxiety, thereby modelling risk associated with mothers' stable tendencies to experience anxiety in various situations (31), a known familial risk factor (6). We focus on familial risk as it might be transmitted by genetic or environmental effects, through *in utero* exposure to mothers' biological stress response (32). In *post hoc* analyses, we additionally control for confounding influences from maternal depression, reported stress, and state anxiety.

METHODS

Sample

This study was approved by the Human Studies Committees at Washington University and informed consent was obtained from a parent of all participants. We recruited participants from a separate study at Washington University: the Early Life Adversity, Biological Embedding, and Risk for Developmental Precursors of Mental Disorders (eLABE) study. Participants in eLABE were themselves recruited during the 2nd or 3rd trimester of pregnancy, and eLABE collected a battery of maternal assessments as well as structural MRI in neonates (average age 21.4 days, range 3 to 40 days). Note that participants recruited for the current study comprised a normative sample and were not enriched for psychiatric symptoms. Parents of infants born full term (36 weeks gestational age or older) were asked to participate in the current study, which involved a subsequent task-based fMRI visit. This session occurred on average 6.8 days (range 0 to 18) following the structural scan. Additional recruitment details, comparison of participants in the current study relative to all of eLABE, and inclusion/exclusion criteria are in the Supplemental Methods.

Maternal and Family Assessments

We utilized questionnaires from eLABE pertaining to psychiatric symptoms and demographic data. The primary measure of maternal anxiety was the trait scale from the State-Trait Anxiety Inventory (STAI), which provides a stable metric of enduring trait-like anxiety (31). The STAI was completed by n=41 women, including 34 who completed the

measure within a 5-week period following birth and 7 who completed the measure within an 8-week period following the child's first birthday. Results did not change substantively when restricting to mothers who had completed the STAI near birth (Supplemental Figure 10). Two women who completed the STAI near birth had missing items on the state subscale only, resulting in n=41 women with trait scores (STAI-T) and n=39 women with state scores (STAI-S). Additional assessments of psychiatric and demographic variables are detailed in the Supplemental Methods.

Imaging Data Acquisition and Pre-processing

Imaging was performed without sedating medications using a Siemens 3T Prisma scanner and 64-channel head coil. Details of procedures, fMRI parameters, and pre-processing are in the Supplemental Methods. We acquired between one and eleven fMRI blood-oxygen level dependent (BOLD) scans, depending on how the infant tolerated the scan. All BOLD scans were collected on the same day. The scans were 5.7 minutes in length for the first 37 infants and 6.7 minutes in length for the next 8 infants.

During each BOLD run, we played white noise auditory stimuli lasting 400 ms at irregular intervals, using E-prime (Psychology Software Tools, Sharpsburg, PA) and played via the external speaker on the Prisma. Infants wore MiniMuff ear protection to attenuate sounds to safe levels. Each run began with 56 seconds of background scanner noise (no white noise pulses). Next, a total of 24 oddball auditory stimuli were presented at random intervals every 9 to 14 seconds; the first oddball was always presented at exactly 56 seconds after scanner onset. In the first 47 infants, scanning ended after the last oddball; in the last 8, an additional 56 seconds of background scanner noise was played. Estimates were not substantively affected by the addition of this time (Supplemental Figure 14). The background scanner noise from the BOLD sequence was regular and did not vary throughout the scan. The task paradigm is illustrated in Supplemental Figure 1.

We censored frames with framewise displacement (FD) greater than 0.9 mm (in Talairach atlas space) to reduce motion artifact. This FD cutoff has been empirically demonstrated to be optimal for task-based fMRI (33); we repeated the primary analyses using an FD cut-off of 0.2 mm and obtained similar results (Supplemental Figure 11). Task runs with fewer than 150 remaining frames after censoring were excluded from analysis, resulting in a total of 2 runs eliminated from a single subject. We obtained a median of 33 minutes of data in each participant (see Supplemental Figure 1), including a median of 31 minutes (SD 14 minutes) after censoring.

Statistical Analyses

Pre-processed BOLD data were analyzed with a general linear model (GLM) as implemented using in-house software (www.nil.wustl.edu/labs/fidl/). Details of modeling are presented in the Supplemental Materials. Importantly, the auditory response was modeled by using separate finite impulse response (FIR) regressors (34) for each of the 40 BOLD frames following white noise onset (40 frames × 0.8 seconds TR yielding = 32 seconds modeled).

We computed a whole-brain repeated measures ANOVA with timepoint (1–40 frames after stimulus onset) as a within-subject factor using all subjects (n=45). The main effect of

timepoint in this analysis indicates voxels with significant activity changes in response to the stimulus. Next, we computed a repeated measures ANOVA in the subset of participants with maternal trait anxiety data (n=41). Factors were timepoint (1–40 frames after the stimulus onset), maternal trait anxiety on the STAI, and timepoint × maternal anxiety interaction. Maternal anxiety was treated as a continuous variable, though 2 participants with high maternal anxiety scores were winsorized (see Supplemental Methods). Supplemental Figure 2 provides a histogram of maternal trait anxiety scores. We performed additional supplemental statistical analyses relating neonatal brain activity to maternal trait anxiety based on median split (Supplemental Figures 7 and 8) as well as maternal state anxiety (Supplemental Figure 9).

Data were spatially smoothed using a 6mm FWHM Gaussian kernel. All results were multiple comparisons corrected to achieve a whole-brain cluster-wise error rate of $p<0.01$. Details on multiple comparisons correction, derivation of regions-of-interest (ROIs) and timecourses from statistical maps, network characterization, assessments of movement during scans, control for confounding variables, and tests to determine how the neural responses varied over the course of each run are provided in the Supplemental Methods.

RESULTS

Sample demographics are in Table 1 and zero-order relations among variables are in Supplemental Table 2. Maternal trait anxiety overall was in the normative range (mean STAI-T score 31.2, SD 7.5, range 20–53) and unrelated to socioeconomic status, infant sex, or gestational age. Based on a score of 40 or higher on the STAI-S (35), 10.3% had clinically significant anxiety. As expected, maternal trait anxiety was significantly related to maternal state anxiety as measured with the STAI-S ($r=0.71$, $p<0.001$), stress as measured with the Perceived Stress Scale ($r=0.60$, $p<0.001$), and depression as measured with the Edinburgh Postnatal Depression Scale ($r=0.50$, $p=0.001$). Head movement overall was low (mean FD after censoring 0.12mm, SD 0.13mm) and was no more likely to occur at the onset of the sound relative to other times in the scan ($F(39, 1716)=1.12$, $p=0.28$).

Neonatal Brain Response to Deviant Auditory Stimuli

As depicted in Figure 1, the deviant auditory stimuli elicited activity across a large portion of the neonatal brain. Specific regions included those that respond to auditory stimuli, including the thalamus, putamen, and auditory cortex. In addition, activity increased in regions of cortex that respond to deviant stimuli in adults, including the bilateral dACC, AI, and several discrete regions along the precentral gyrus; as well as in the right superior temporal sulcus extending posteriorly into the temporal-parietal junction (complete list of regions in Supplemental Table 3). Somewhat unexpectedly, the left motor cortex also demonstrated robust activity increases. All activity changes were highly statistically significant, and the shape of the fMRI response across these regions resembled fMRI responses to stimuli in older samples (see Figure 1). Of the 177 regions demonstrating significant activity changes, 176 remained significant when controlling for residual head motion (see Supplemental Table 3). In most brain regions, neural activity changes were highest in magnitude for stimuli that were presented early in each fMRI run, intermediate

for stimuli presented in the middle of each run, and lowest for auditory stimuli that were presented late in each run (see Supplemental Figure 3).

To examine similarity with adults, we overlaid the neonatal brain response with results from a published meta-analysis of the response to deviant stimuli in adults (see Supplemental Figure 4). Nearly all brain regions demonstrating a response to deviant stimuli in adults also responded to deviant stimuli in the neonates. To probe how the neonatal brain functional architecture relates to the adult architecture, we registered adult network definitions (36) to the neonatal brain (see Supplemental Figure 5). While infant brain organization may vary from adults, we used adult network definitions because the organization of the neonatal brain is less well understood. For each adult-defined cortical network, we quantified the percentage of cortical surface area within that network that responded to the deviant stimuli in neonates (see Figure 2). The adult-defined SN, CON, and VAN were among the networks with the highest percentage of surface area responsive to the stimuli in neonates.

Relation of Neural Response to Maternal Trait Anxiety

The activity in many different neonatal brain regions in response to deviant stimuli varied as a function of maternal trait anxiety (Figure 3). Infants born to mothers with higher trait anxiety had higher activity in response to the deviant stimuli in the bilateral AI, dACC, subgenual anterior cingulate, and vlPFC (Figure 4). In addition, in many regions in the occipital and posterior parietal cortex, activity following deviant stimuli was lower in neonates born to mothers with higher trait anxiety (Figure 4). Of the 86 regions in which activity varied with maternal anxiety, 82 remained significant in post-hoc sensitivity analyses that separately controlled for residual head motion, amount of retained data, state anxiety, depression, and stress (see Supplemental Table 4).

We next characterized the adult network definitions of these neonatal brain regions in which activity varied with maternal trait anxiety (Supplemental Figure 6 and Supplemental Table 4). Brain regions with higher activity for neonates born to mothers with higher trait anxiety typically fell within the CON, SN, VAN and anterior default mode network (DMN). There were however some exceptions to this general pattern of results, with some CON, SN, VAN, and DMN regions demonstrating lower activity for infants born to mothers with higher anxiety (see Supplemental Table 4). Brain regions with lower activity for neonates born to mothers with higher trait anxiety tended to fall in the visual network and posterior portions of the DAN and DMN.

DISCUSSION

This study reveals that the neonatal brain exhibits a robust response to deviant auditory stimuli. The specific regions that respond are similar to prior work in adults and include the dACC, AI, the precentral gyrus, the right superior temporal sulcus, and the right temporal-parietal junction; in adults, these regions comprise primarily the SN, CON, and VAN. In a subset of regions, including portions of the vlPFC, AI, dACC, and sgACC, activity following deviant stimuli is higher in neonates born to mothers with higher relative to lower trait anxiety. In other regions, including nearby portions of the AI, precuneus, and visual cortex, activity following deviant stimuli is lower in neonates born to mothers with higher relative

to lower trait anxiety. Relations to maternal trait anxiety remain significant when controlling for maternal state anxiety, depression, and reported stress.

The current results are consistent with other research on early childhood risk. This research suggests that neural stimulus-response properties near birth signal risk for cascades generating later-life anxiety and other psychiatric illnesses (3–5). Infants in the current study born to mothers with higher trait anxiety had increased neural responses in a subset of the brain regions that respond to deviant stimuli. Previous work suggests that early increased neural responsivity to novel stimuli continues through childhood and interacts with other altered processes, such as increased attention to threat or errors, to increase risk for an anxiety disorder later in life (37). Of note, early childhood anxiety disorders are associated with additional psychiatric disorders later in life (25–27), which also have been linked to altered neural responses to deviant stimuli (38–40). Thus, the current data may inform the developmental neurobiology of other mental illnesses. Somewhat unexpectedly, infants born to mothers with higher trait anxiety additionally had lower activity in a separate set of brain regions; the functional significance of this lower activity is an important topic for future work.

Taken in the context of prior work, results from the current study may inform the development of biomarkers for use in early risk stratification and as specific neural targets for preventative efforts. Maternal anxiety in the current study largely varied across the normal range on the trait-anxiety scale. Prior work indicates that such normative variation in maternal anxiety is associated with risk for psychiatric and neurocognitive outcomes in offspring during childhood (41). This familial risk likely reflects impact from both genes and environmental factors, possibly transmitted though *in utero* exposure to maternal physiology. Results from the current study suggest that some of the increased familial risk for higher trait anxiety in neonates may manifest as alterations in basic stimulus-response properties. While similar altered stimulus-response associations have been previously reported using EEG, the current study may clarify the specific brain regions and systems underlying risk. Regionally specific brain activity as measured with fMRI may inform specific targets that are more easily identified longitudinally across development relative to less regionally specific EEG-based measures. Such findings inform basic research in other species attempting to localize neural processes associated with risk.

The current study found that neonatal neural activity varies as a function of maternal trait anxiety in the same brain regions that have been linked to expression of anxiety in adults. A meta-analysis of 283 experiments that totaled over 10,000 participants identified a series of brain regions that robustly show differential brain activity in cognitive tasks between controls and participants with major psychiatric illnesses, including anxiety disorders, depression, schizophrenia, and substance use disorders (19). Regions identified by this meta-analysis included the bilateral anterior cingulate and insular cortices and right vlPFC. A more recent meta-analysis using the same approach but examining emotional rather than cognitive tasks additionally identified the subgenual and pregenual medial prefrontal cortices (20). In the current study, we discovered that these same regions have higher activity in response to simple deviant sounds in sleeping newborn infants born to mothers with higher trait anxiety. This observation suggests that either prior reported results in children and

adults pertain to alterations in basic stimulus-response properties rather than higher-level processes; or that variation in simple stimulus-response mechanisms at birth serves as the developmental foundation for disruption in higher order processes later in life.

Delineating the neural architecture that responds to deviant auditory stimuli in neonates may also illuminate the fundamental neural building blocks of later more complex processes relevant to risk for psychopathology. Prior work indicates that variation in lower order brain processes in the first year of life is associated with variation in more complex cognitive brain processes later in childhood (42). Brain regions that robustly responded to deviant stimuli in the current study, such as the AI and dACC, are involved in more complex operations in adults such as executive function and error monitoring (14). Future longitudinal studies could evaluate whether variation in the response to deviant stimuli at birth predicts variation in other functions performed by these regions later in life, such as executive function.

The current study should be considered in light of its limitations. The sample size was modest (N=45), though this was mitigated in part by a high amount of data per subject (~30 minutes after frame censoring), which may provide for more reliable estimates of responses from each individual (43). The sample included mothers primarily with non-clinical levels of anxiety; future studies can test whether these results extend to clinical samples. Maternal trait anxiety in the current study was highly correlated with other maternal symptoms including depression and perceived stress. Although results remained significant when controlling for these factors, future work is required to disambiguate the impact of these various maternal symptoms on neonatal brain activity. Results in the current study pertained to familial risk as assessed through maternal trait anxiety; future work is required to dissociate the impact of genetic versus environment risk, such as exposure to circulating maternal stress hormones. We were unable to determine sleep stage in our participants, which may affect BOLD activity (44). Finally, future longitudinal studies are required to clarify the relation between the infant oddball response near birth and relations to observed temperament during infancy and clinical symptoms in later childhood.

In summary, the current study reveals that the neonatal brain has a robust and specific response to deviant sounds and that the magnitude of neural activity in many brain regions is related to maternal trait anxiety. Furthermore, the specific brain regions that respond robustly to deviant stimuli, and the regional responses that vary with maternal trait anxiety, are the same regions implicated in the response to deviant stimuli and the pathophysiology of anxiety disorders in adults. These findings have significant implications for the developmental neurobiology of complex human behaviors and the origins of psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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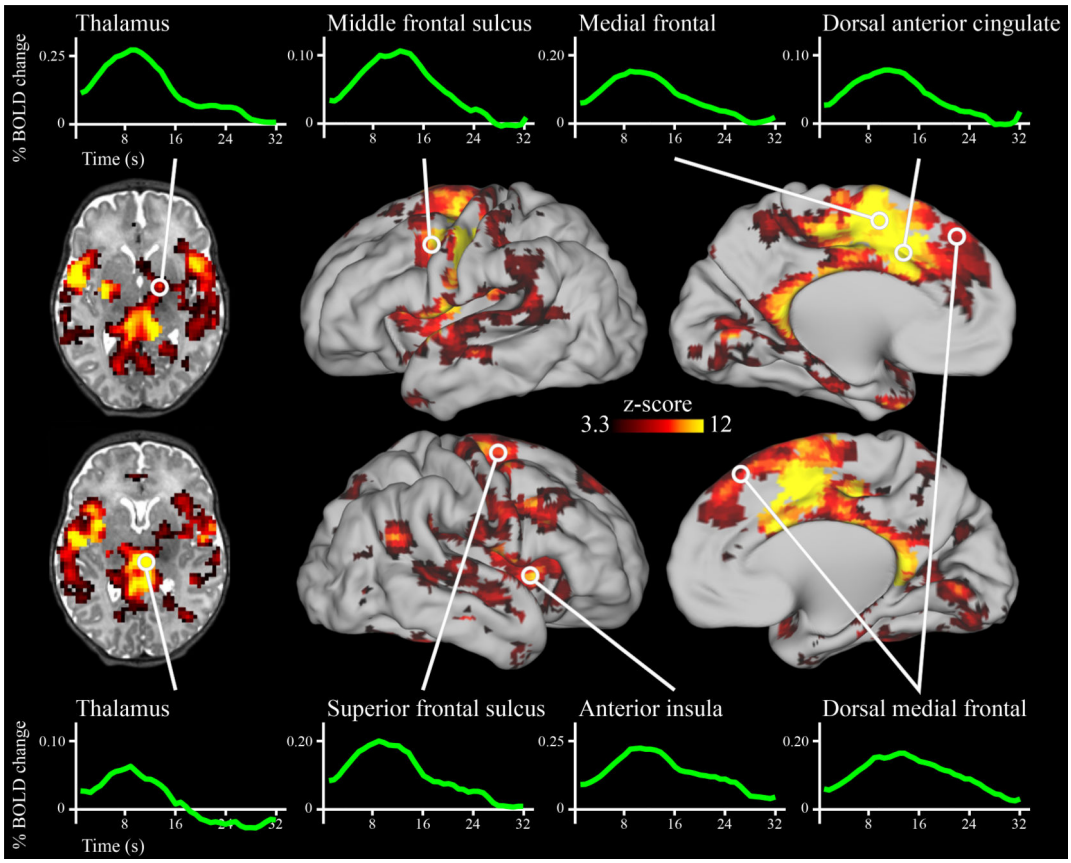

Figure 1.

Brain regions with significant activity modulations in neonates following the onset of deviant sounds. Results are whole-brain multiple comparisons corrected at $p<0.01$, with each significant cluster comprised of a volume of at least $756mm^3$ in which each voxel is significant at $p<0.001$ (45, 46). A full list of regions is provided in Supplemental Table 3.

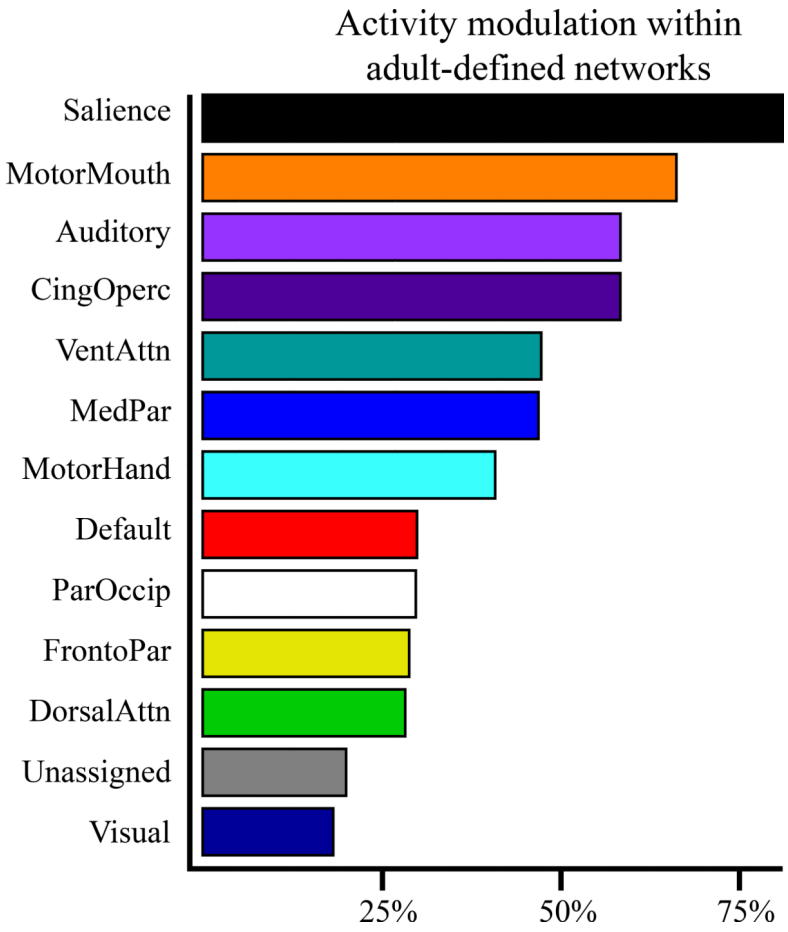

Figure 2.

Proportion of adult-defined networks with significant activity modulations in neonates following the onset of the deviant sounds. Bar length indicates the percentage of cortical surface area for each network in which $z>3.3$ ($p<0.001$), the threshold used for multiple comparisons correction in the whole-brain analyses. MotorMouth: mouth representation within motor network; CingOperc: cingulo-opercular; VentAttn: ventral attention; MedPar: medial parietal; MotorHand: hand representation within motor network; Default: default mode; ParOccip: parietal occipital; FrontoPar: fronto-parietal; DorsalAttn: dorsal attention.

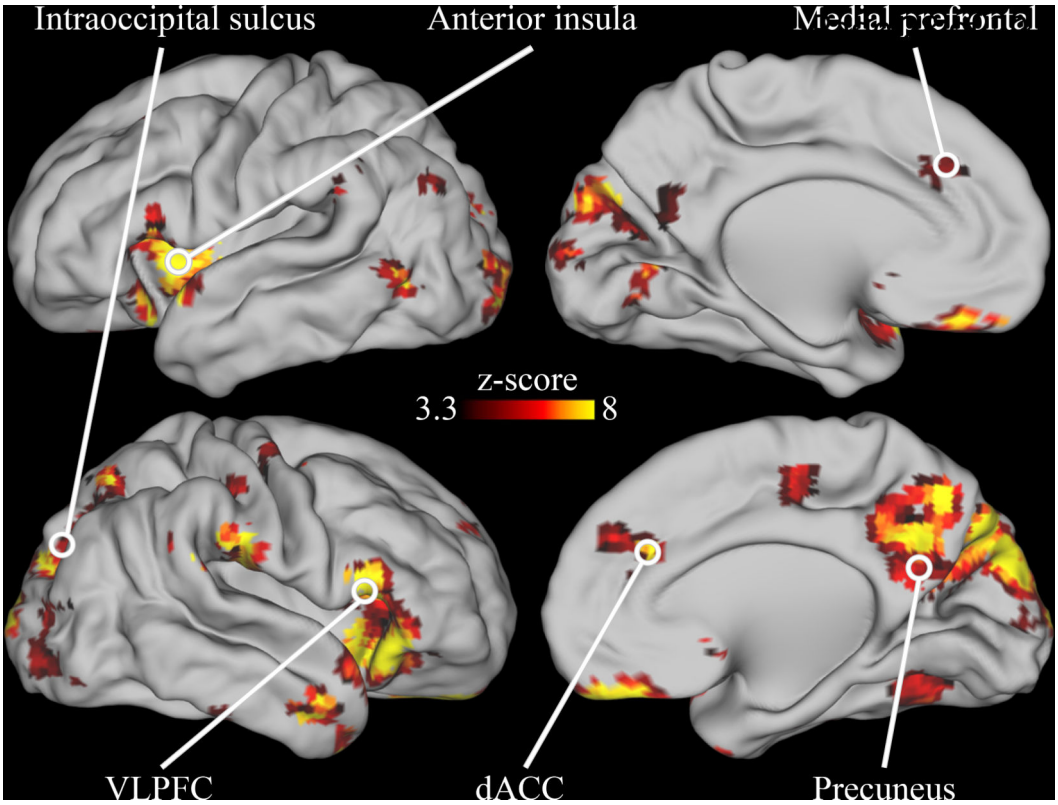

Figure 3.

Brain areas in which neonatal neural activity following the onset of deviant sounds varied depending on maternal trait anxiety. Results are whole-brain multiple comparisons corrected at $p<0.01$, with each significant cluster comprised of a volume of at least $756mm^3$ in which each voxel is significant at $p<0.001$. A complete list of regions is provided in Supplemental Table 4.

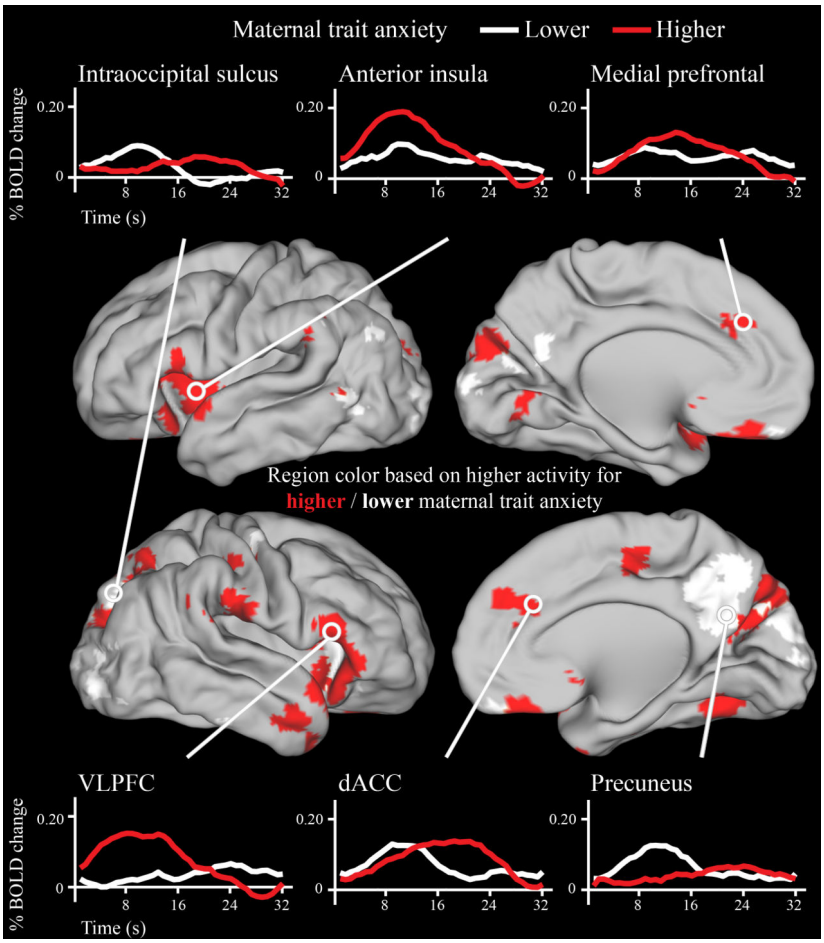

Figure 4.

Timecourses for a subset of brain regions in which neonatal neural activity following onset of deviant sounds varied as a function of maternal trait anxiety. Note that the brain regions depicted here are identical to the brain regions in Figure 3, which is a statistical map of the same data. Trait anxiety was treated as a continuous measure in the statistical analyses, and a median split was used to generate the timecourses above solely for display purposes. Areas of cortex in red had higher peak activity in neonates born to mothers with higher trait anxiety, while areas of cortex in white had higher peak activity in neonates born to mothers with lower trait anxiety.

Table 1.

Sample Demographics

Neonatal Characteristics (n=45)	**n**	**Mean**	**SD**
Sex			
Male	18		
Female	27		
Gestational Age at Birth in Weeks		38.2	1.0
Age at Scan in Days		27.9	9.8
Birthweight in Grams		3115	488
Area Deprivation Index		72.0	22.5
Child's Race			
African American	29		
White	16		
Ethnicity			
Non-Hispanic	45		
Maternal Characteristics	**n**	**Mean**	**SD**
Psychotropic Medicine			
Sertraline	2		
Dextroamphetamine	1		
Dextroamphetamine & Topiramate	1		
STAI Trait Anxiety		31.2	7.5
STAI State Anxiety		28.5	7.6
Edinburgh Postnatal Depression Scale		4.0	3.1
Perceived Stress Scale		12.8	5.7