RESEARCH ARTICLE

WILEY | ADAA ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA

Hub distribution of the brain functional networks of newborns prenatally exposed to maternal depression and SSRI antidepressants

Naama Rotem-Kohavi[1] | Lynne J. Williams[9] | Angela M. Muller[3] | Hervé Abdi[4] | Naznin Virji-Babul[3] | Bruce H. Bjornson[5,6,9] | Ursula Brain[6] | Janet F. Werker[7] | Ruth E. Grunau[2,6] | Steven P. Miller[8] | Tim F. Oberlander[2,6,10]

[1]Graduate Program in Neuroscience, School of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[2]BC Children's Hospital Research Institute, Vancouver, Canada

[3]Department of Physical Therapy, University of British Columbia, Vancouver, Canada

[4]School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, Texas

[5]Brain Mapping, Neuroinformatics and Neurotechnology Laboratory, Division of Neurology, British Columbia Children's Hospital, Vancouver, Canada

[6]Department of Pediatrics, University of British Columbia, Vancouver, Canada

[7]Department of Psychology, University of British Columbia, Vancouver, Canada

[8]Division of Neurology, Department of Pediatrics, The Hospital for Sick Children and the University of Toronto, Toronto, Canada

[9]BC Children Hospital MRI Research Facility, Vancouver, BC, Canada

[10]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

Correspondence
Tim F. Oberlander, BC Children's Hospital Research Institute, F605 4480 Oak Street, Vancouver, BC V6H 3V4, Canada.
Email: toberlander@bcchr.ca

Abstract

Background: Prenatal maternal depression (PMD) and selective serotonin reuptake inhibitor (SSRI) antidepressants are associated with increased developmental risk in infants. Reports suggest that PMD is associated with hyperconnectivity of the insula and the amygdala, while SSRI exposure is associated with hyperconnectivity of the auditory network in the infant brain. However, associations between functional brain organization and PMD and/or SSRI exposure are not well understood.

Methods: We examined the relation between PMD or SSRI exposure and neonatal brain functional organization. Infants of control ($n = 17$), depressed SSRI-treated ($n = 20$) and depressed-only (HAM-D ≥ 8) ($n = 16$) women, underwent resting-state functional magnetic resonance imaging at postnatal Day 6. At 6 months, temperament was assessed using Infant Behavioral Questionnaire (IBQ). We applied GTA and partial least square regression (PLSR) to the resting-state time series to assess group differences in modularity, and connector and provincial hubs.

Results: Modularity was similar across all groups. The depressed-only group showed higher connector hub values in the left anterior cingulate, insula, and caudate as well as higher provincial hub values in the amygdala compared to the control group. The SSRI group showed higher provincial hub values in Heschl's gyrus relative to the depressed-only group. PLSR showed that newborns' hub values predicted 10% of the variability in infant temperament at 6 months, suggesting different developmental patterns between groups.

Conclusions: Prenatal exposures to maternal depression and SSRIs have differential impacts on neonatal functional brain organization. Hub values at 6 days predict variance in temperament between infant groups at 6 months of age.

KEYWORDS
depression, fMRI, infant, prenatal exposure, SSRIs

1 | INTRODUCTION

Depression during pregnancy affects between 14% and 23% of women, shaping offspring's development (Gentile, 2015; Stein et al.,

2014). Importantly, both depressed mood and selective serotonin reuptake inhibitor (SSRI) antidepressants used as treatment (Vigod et al., 2016) are associated with socioemotional, behavioral, and cognitive developmental risks across infancy and childhood

(Brummelte, Mc Glanaghy, Bonnin, & Oberlander, 2017; Hanley, Brain, & Oberlander, 2015; Rotem-Kohavi & Oberlander, 2017; Talge, Neal, & Glover, 2007). Distinguishing effects of these two key gestational exposures is challenging, but critical for understanding the differential mechanistic pathways of each and for helping clinicians and mothers decide the best treatment option.

Recent studies using magnetic resonance (MR) imaging have now begun to shed light on early developmental alterations related to prenatal exposure to maternal mood. Rifkin-Graboi et al., (2013) reported that prenatal depression is associated with reduced microstructure, but not with the volume of the right amygdala in newborn infants. Qiu et al. (2015) reported hyperconnectivity of the amygdala with the left temporal cortex, insula, anterior cingulate with ventromedial frontal cortices with higher levels of pregnancy-related maternal depressive symptoms. Altered functional connectivity of the amygdala was also reported by Posner et al. (2016).

Associations between prenatal SSRI exposure and brain function and structure during early infancy are also emerging (Jha et al., 2016; Lugo-Candelas et al., 2018; Podrebarac et al., 2017). Lugo-Candelas et al. (2018) reported that infants exposed to SSRIs in utero had concomitant increases in amygdala and insula volume correlated with increases in white-matter connectivity relative to infants of untreated depressed mothers and control infants (Lugo-Candelas et al., 2018). Jha et al. (2016) reported widespread microstructure reduction in prenatally SSRI-exposed compared to control infants, while Videman et al. (2016), using electroencephalography, demonstrated alterations of connectivity patterns associated with prenatal exposure to SSRIs. In addition, we have reported that prenatal SSRI exposure is associated with hyperconnectivity in the putative auditory network relative to control infants and to infants of nonpharmacologically treated depressed mothers (Rotem-Kohavi et al., 2018). Together, these findings suggest that prenatal depression and prenatal SSRI exposure are associated with microstructural and functional alterations mostly in the insula, anterior cingulate, and the amygdala. However, to date a network perspective has not been used to study the impact of prenatal depression and SSRI exposure.

Graph theory analysis (GTA) views the brain as a network, where nodes are brain regions and edges are the pathways (structural or functional) connecting them (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). The relationship between nodes and edges offers insight into the topological properties of functional organization and efficiency of brain networks (Sporns, Chialvo, Kaiser, & Hilgetag, 2004), with optimal communication in "small-world" networks, comprising both local segregation and global integration (Watts & Strogatz, 1998). GTA applied to resting-state functional magnetic resonance imaging (rs-fMRI) has been used to characterize the functional topography of the human brain from the fetal period through to adulthood (Bathelt, O'Reilly, Clayden, Cross, & De Haan, 2013; De Asis-Cruz, Bouyssi-Kobar, Evangelou, Vezina, & Limperopoulos, 2015; Gao et al., 2015; Thomason et al., 2017; van den Heuvel et al., 2018).

Wen et al. (2018) have shown that during the first year of life the modular organization of the brain functional network is progressively increasing and subdividing into an increasing number of functional modules together with stabilizing intramodular connection and clustering and intermodular connections. Patterns of gradual increase in intermodular connectivity have also been demonstrated in fetuses with increasing gestational age (Thomason et al., 2014).

Using GTA, studies have reported the existence of highly connected brain regions, called "hubs", in both adults (Bullmore & Sporns, 2009), infants (Gao et al., 2015), and fetuses (van den Heuvel et al., 2018). Hub nodes have a greater impact on information traffic within the network and are critical in facilitating efficient neuronal communication (Bullmore & Sporns, 2012). It is hypothesized that hubs underlie complex cognitive processes through their high connectedness and ability to integrate information (Bullmore & Sporns, 2009; Fransson, Åden, Blennow, & Lagercrantz, 2010). However, hub regions are more vulnerable to pathology (Bullmore & Sporns, 2012). For example, the insula, anterior and posterior cingulate and dorsolateral prefrontal cortex—all hub regions—are considered "at-risk" in depressed adults, suggesting that hubs are more susceptible than regions with lower impact on information flow (reviewed in Gong & He., 2015).

While evidence on the effects of in-utero influences on brain function (A. Qiu et al., 2015; Rifkin-Graboi et al., 2013; Salzwedel et al., 2015) and behavior (Hanley et al., 2015; Oberlander et al., 2007; Weikum, Mayes, Grunau, Brain, & Oberlander, 2013) have been well demonstrated, studies using measures of brain function to predict behavioral outcomes are limited. Recently, Yoshida et al. (2017) showed that in adults positive correlations between the default mode network and superior frontal gyrus were predictive of depressive symptoms. Moreover, Rifkin-Graboi et al. (2015) in a prospective, birth cohort study found that lower levels of microstructure of the right insula, middle occipital, and temporal regions of newborn infants may predict externalizing behaviors at 1 year, but findings were not significant after correction for multiple comparisons.

In the present study, we applied GTA to characterize organization of the resting-state networks (RSNs) in the neonatal brain, to the data previously reported by Rotem-Kohavi et al (Rotem-Kohavi et al. (2018). Our first aim was to describe network alterations associated with prenatal exposure to maternal depression and/or SSRI exposure compared with control infants. Given previous functional connectivity findings (Posner et al., 2016; A. Qiu et al., 2015), we expected the impact of prenatal maternal depression would differ from SSRI exposure, however, based on the specificity of our previous results showing a localized effect (Rotem-Kohavi et al., 2018), we did not expect significant differences at the global level. We hypothesized that prenatal depression would associate with increased hub values of key stress-related regions such as the amygdala, insula, and anterior cingulate compared to controls. However, prenatal SSRI exposure would be associated only with higher hub values of regions related to auditory function (Rotem-Kohavi et al., 2018). Second, we aimed to test whether hub measures defined by GTA at 6 days, predicted mothers' rating of infant temperament at 6 months of age. Due to the critical role hubs play in cognitive function (Bullmore & Sporns, 2012), we expected that prenatal exposures would shape

associations between newborns' hub values and infants' behavior at 6 months. As no other studies have examined links between GTA measures with infant temperament in this context, we chose a nonbiased approach for analysis.

2 | METHOD

2.1 | Participants

With informed maternal consent and approval from the University of British Columbia Clinical Research Ethics Board and the BC Women's Hospital Research Review Committee, women were recruited at their second trimester of pregnancy, from family physician clinics, Reproductive Mental Health Clinic, and Midwifery Services from Vancouver, Canada. Healthy pregnant women, depressed pregnant women with no pharmacological treatment, and depressed pregnant women treated with SSRIs were recruited. Upon enrolment, the Mini-Neuropsychiatric Interview (Lecrubier et al., 1997) was used to determine depression diagnoses. If the participant met the criteria for a unipolar depressive mood disorder per *DSM-5* clinical criteria and was previously diagnosed by a qualified physician, the participant was included in the depressed-only group; mothers who did not meet these criteria were included in the control group. The SSRI group comprised women who had been diagnosed with a unipolar mood disorder, were treated with SSRIs for a minimum of 75 days during the third trimester of pregnancy based on their clinical need. Women treated with SSRIs (fluoxetine, paroxetine, sertraline, citalopram, and citalopram), and also with selective-norepinephrine reuptake inhibitors (desvenlafaxine, duloxetine, and venlafaxine) were included. For reasons of simplicity, we will not differentiate between these two pharmacological treatments. Only healthy, term pregnancies with one fetus were included in the study. Mothers with substance abuse, bipolar disorder, and those with significant medical, obstetrical, or fetal conditions were excluded from the study.

2.2 | Maternal mood symptoms

We assessed prenatal maternal mood at 26 and 36 weeks gestation using the Hamilton Rating Scales for Depression (HAM-D; Hamilton, 1960). HAM-D depressive symptom scores served to create three groups (Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013): infants with maternal HAM-D below 8 (control), infants of depressed mother with HAM-D ≥8 with no SSRI exposure (depressed-only), and infants exposed to in-utero SSRIs (SSRI). To assess an additional distinct dimension of pregnancy-related maternal emotional experience, we also used the Pregnancy Experiences Scale (PES; DiPietro, Ghera, Costigan, & Hawkins, 2004). PES assesses pregnancy-related maternal uplifts and stressors to evaluate how women experience their pregnancy and was included in the GTA as a covariate.

2.3 | Infant temperament at 6 months

At 6 months of age, mothers reported on their infant's ability to regulate stress using the Infant Behavior Questionnaire

(IBQ; Rothbart, 1981) which is a widely used caregiver-report questionnaire consisting of 94 questions tapping on specific infant behaviors. These questions produce six scales assessing temperament dimensions of: activity level (level of gross motor activity) smiling & laughing (as indicators of arousal under safe conditions) distress latency (defined as acceptance or rejection of new objects or persons), distress limitation (persistence and goal orientation), soothability (adaptability, how easily the baby is able to sooth), duration of orientation (measure both attention span and distractibility). Indicators of internal consistency for the IBQ have ranged from 0.67 to 0.84 (Rothbart, 1981). Parent-report temperament measures are recognized for their ability to provide data on infant behavior across settings (Gartstein, Bridgett, & Low, 2012), with IBQ items constructed to minimize "global judgments" of infant behaviors that may introduce bias (Gartstein & Rothbart, 2003; Rothbart, 1981)

2.4 | MR image acquisition

All scans were performed at the BC Children's Hospital MRI Research Facility in Vancouver, BC, Canada. Infants were fed, swaddled, and positioned in an MR-compatible neonatal incubator (Advanced Imaging Research, Inc, dba SREE Medical Systems, Cleveland, OH) cushioned with pillows. Ear protectors and ear muffs were used to reduce noise from the MRI. Physiologic measures of heart rate and oxygen saturation were monitored by a registered pediatric nurse during the study. Infants underwent structural, microstructural, resting-state functional and metabolic imaging at 40.9 weeks (postmenstrual age). We recruited 95 women to the study, 11 woman/infant dyads did not complete the imaging component of the study and were excluded (see Supporting Information S1), 84 infants underwent MR scanning during natural sleep (n = 31 control, n = 24 depressed-only, and n = 29 SSRI) without sedation using methods described previously (Rotem-Kohavi et al., 2018).

The rs-fMRI scan was acquired: oblique axial echo-planar imaging, TR = 3,000 ms, TE = 18.4 ms, flip angle = 90°, 39 interleaved slices, 2 mm isotropic, no gap (Rotem-Kohavi et al., 2018). The T1 structural images were acquired using a three-dimensional fast-spoiled gradient echo scan (TE = 2.95 ms, TR = 7.7 ms), with a voxel size of $1 \times 1 \times 1\,mm^3$ and reconstructed to 0.4 mm and were used to align the functional images.

2.5 | Image preprocessing

We preprocessed rs-fMRI as described in (Rotem-Kohavi et al., 2018). In short, fMRIB Software Library (FSL) was used for preprocessing (www.fmrib.ox.ac.uk/fsl). FEAT (FMRI Expert Analysis Tool) v6.0, was used to remove nonbrain structures with brain extraction tools (Smith, 2002), correct for slice timing, spatial smoothing (3 mm FWHM [full width at half maximum]), intensity normalization, and high-pass temporal filtering (σ = 50 s). FSL Melodic (Beckmann & Smith, 2004) and AFNI 3dDespike (Cox, 1996) were used for motion correction. FLIRT was used to register functional images to standard space
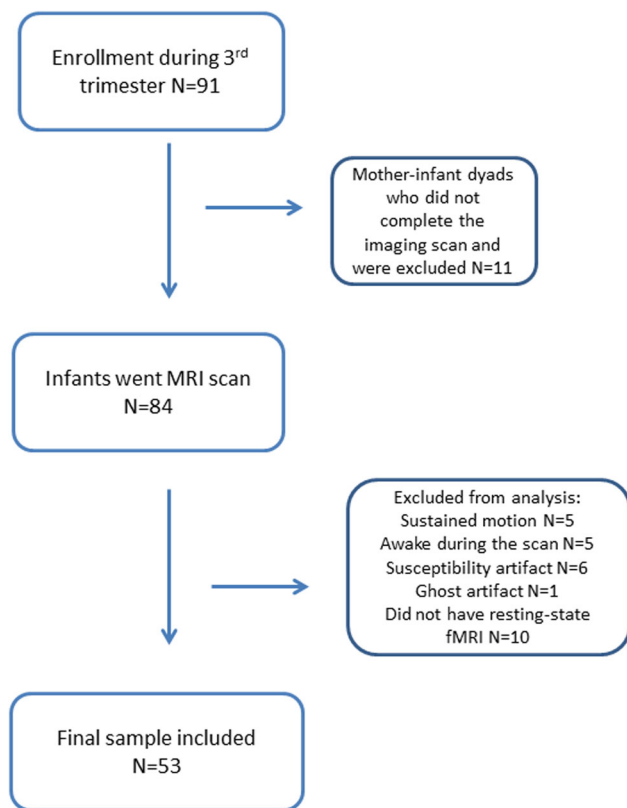
FIGURE 1 Study flowchart. An overview of the inclusion and exclusion of mother/infant dyads in the study

(T1-weighted MR image of 40 weeks gestation neonatal template (Jenkinson & Smith, 2001; Serag et al., 2012). Data from 53 infants were included in the final analysis. For an overview of the inclusion and exclusion of mother/infant dyads, see the flowchart illustrated in Figure 1. Functional images from 21 infants were excluded due to motion (sustained motion $n = 3$, and infant woke up during the scan $n = 5$), susceptibility ($n = 6$), and ghost ($n = 1$) artefacts, and errors in data acquisition ($n = 6$). 10 additional infants did not go through the resting-state functional imaging and were excluded from the study ($n = 5$ SSRI-exposed infants, $n = 3$ depressed-only). Excluded infants were similar in all demographic measures to infants included in the final analysis ($p > 0.07$; Table S5). To evaluate motion parameters in our data we followed recent guidelines for the analysis of neonatal rs-fMRI (Mongerson et al., 2017). We used two motion parameters using MCFLIRT (Jenkinson et al., 2002); absolute displacement (AD) which compares the transformation matrix at timepoint N with a reference timepoint, and relative displacement (RD) which compares two subsequent timepoints. For most subjects ($n = 48$), only minimal motion was exist throughout the scan with a maximum values of AD of less than 1 mm with a mean absolute displacement of 0.282 ± 0.20 mm, and relative displacement of 0.092 ± 0.05 mm. Additional five subjects ($n = 3$ SSRI-exposed, $n = 1$ depressed-only) had one or two brief episodes of large (ranged from 1 to 2.94 mm). However, following denoising with MCFLIRT (Jenkinson et al., 2002) and AFNI 3dDespike (Cox, 1996) AD for these five infants ranged between 0.02 and 0.06. Overall, all 53 subjects AD ranged between

0.05 mm to 2.94 mm (mean = 0.433 ± 0.55) and relative displacement (RD) ranged from 0.03 to 0.69 (mean = 0.11 ± 0.1). No significant group differences were detected ($p > 0.1$, using one-way analysis of variance [ANOVA]). Following denoising, AD values were reduced and ranged between 0.001 and 0.15 (mean = 0.032 ± 0.025) and RD ranged from 0.001 to 0.04 (mean = 0.019 ± 0.01), with no group differences ($p > 0.7$ using one-way ANOVA).

Following preprocessing, we defined 90 cortical and subcortical regions according to the Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002) algorithm of the Edinburgh Neonatal Atlas ENA33 segmentation tool (Cabez et al., 2016). According to Cabez et al., the ENA33 tool was transformed from an adult atlas, so it is consistent with adult label protocols, and the size of each brain region in the atlas corresponds to its actual size in the neonatal brain. In addition, Region of interest (ROIs) in the left and right hemisphere were symmetric. The 90 regions were then individually mapped onto the residual fMRI time series coregistered to a 40 weeks gestation neonatal template (Serag et al., 2012). To generate the individual subject graphs, data were extracted from all of the voxels within the 90 regions to create a time by voxel matrix. For each graph, voxels within each of the 90 regions were averaged to create a correlation matrix between each of the 90 regions or nodes. This yielded a 90×90 undirected weighted correlation matrix which was then normalized using Fisher's z-transformation in Matlab (MathWorks Inc., Natick, MA).

2.6 | Graph metrics

We used the brain connectivity toolbox (Rubinov & Sporns, 2010) for the computation of graph metrics. Our focus was on better understanding the global network organization of the newborns' brains as well as the role of single nodes in this network. To this end, we chose the GTA parameters "Modularity" which evaluates how well the brain is divided into submodules, and to which submodule each region belongs to (Girvan & Newman, 2002). We also measured the "Global cluster coefficient" which informs us on the degree to which different nodes tends to connect to their neighboring nodes, and how well the neighbors tend to connect to each other on the global level (Achard & Bullmore, 2007). At the nodal level, we were interested to quantify the importance of each single node for the communication between the modules ("Participation coefficient" or connector hub), as well as its role in the communication within its own module/subnetwork ("Within-module degree z-score" or pro-vincial hub; Fan et al., 2011; Guimera & Amaral, 2005). Higher connector or provincial hub values indicate a node's "hubbiness" and ability to play a greater role in the intermodule/intramodule communication. Additional graph measures examined are described in Supporting Information data.

2.7 | Statistical analysis

To examine group difference in global GTA measures, we used the general linear model (GLM), with sex, infant age at the MRI, and PES

scores as covariates in the model. To determine whether a node could be considered a hub region, we examined the difference in the group average of positive and negative weights to delineate quartiles in our data. Only nodes at the 75th percentile and above were considered as hub regions and were included in a multivariate GLM model (Chan, Alhazmi, Park, Savalia, & Wig, 2017). For GLM analyses, Bonferroni-Holm methods (Abdi, 2010a) were used to correct for multiple comparisons.

2.8 | Behavioral measures prediction at 6 months of age

Projection to latent structures regression (PLSR) was performed using the methods outlined in Abdi (2010b). PLSR is a latent variable approach to modeling the covariance structure between predictor (X) and predicted (Y) variables, whereby the latent variables of X best explain the variance in Y. PLSR can be used in cases where there is multicollinearity in X—a case when standard multivariate regression will fail. In the current case, the provincial and connector hub values were included as the predictors with group treatment contrasts added. The predictor set was then used to predict mothers' ratings of their infant's behavior at 6 months of age using the IBQ (Gartstein & Rothbart, 2003).

3 | RESULTS

3.1 | Participant characteristics

Maternal and neonatal characteristics are summarized in Table 1. Mothers treated with SSRIs and mothers belonging to the depressed-only group had significantly higher PES hassle intensity scores compared to control mothers. At age 6 months, infant IBQ measures were available for 48 infants (summarized in Table 2). No group differences were observed ($p > 0.085$).

3.2 | Graph measures

The mean connectivity matrices for each group are shown in Figure 2 (left) and revealed no anticorrelations, but showed qualitative differences between the control group and the SSRI and depressed-only groups. We found no significant group differences in global clustering coefficiency measures ($p > 0.5$, univariate GLM). Using the Louvain algorithm (Blondel, Guillaume, Lambiotte, & Lefebvre, 2008), we identified three modules in each of the groups (see Figure 2, right). Module 1 comprised mostly primary, frontal regions, and the insula. Module 2 comprised mostly limbic, occipital, and parietal regions. Module 3 comprised basal ganglia, auditory, and temporal regions. No significant differences were found in modularity

TABLE 1 Demographics

Participants characteristics	Control (n = 17)	Depressed-only (n = 16)	SSRI (n = 20)	p value
Maternal characteristics				
Maternal age, mean ± SD (years)*	32.92 ± 2.79	33.79 ± 2.02	36.75 ± 4.55	0.003
SSRI duration, mean ± SD (days)	–	–	258.9 ± 33.8	–
SSRI dose at 36 weeks gestation (mg)	–	–	41.31 ± 50.8	–
Maternal education, mean ± SD (years)	18.71 ± 3.01	17.56 ± 3.34	17.2 ± 2.7	0.305
Smoking per pregnancy, mean ± SD (no. of cigarettes)	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.24	0.447
Alcohol per pregnancy, mean ± SD (no. of single drinks)	0.59 ± 2.45	0.44 ± 1.31	1.35 ± 4.53	0.65
Prenatal HAM-D 3rd trimester Average, mean ± SD*	4.911 ± 1.82	10.687 ± 3.17	11.12 ± 4.47	–
Prenatal PES HASS frequency 3rd trimester Average, mean ± SD	6.76 ± 2.27	8.21 ± 1.85	7.8 ± 1.76	0.098
Prenatal PES Uplift frequency 3rd trimester Average, mean ± SD	9.29 ± 0.86	9.5 ± 0.68	8.8 ± 1.18	0.085
Prenatal PES Uplift intensity 3rd trimester Average, mean ± SD	2.16 ± 0.47	2.15 ± 0.35	2.14 ± 0.39	0.982
Prenatal PES HASS intensity 3rd trimester Average, mean ± SD*	1.37 ± 0.33	1.61 ± 0.32	1.84 ± 0.38	0.001
Neonatal characteristics				
Type of delivery (vaginal/C-section)	14/3	12/4	10/10	0.087
Birth GA, mean ± SD (weeks)	39.9 ± 1.81	39.84 ± 1.60	38.97 ± 1.53	0.165
Age at the MRI (hr)	199.85 ± 161.01	292.58 + 217.94	262.53 + 199.23	0.378
Sex male/female	12/5	10/6	8/12	0.154
Birth weight, mean ± SD (kg)	3.48 ± 0.36	3.55 ± 0.45	3.29 ± 0.59	0.272
Birth length, mean ± SD (cm)*	51.89 ± 1.46	52.09 ± 2.28	49.62 ± 2.41	0.001
Head circumference, mean ± SD (cm)	34.78 ± 1.77	34.79 ± 1.62	34.42 ± 1.44	0.706
Apgar score 1 min, mean ± SD*	8.18 ± 1.5	8.19 ± 1.94	6.6 ± 2.37	0.027
Apgar score 5 min, mean ± SD	9.00 ± 0.0	8.81 ± 0.91	8.25 ± 1.37	0.061

Abbreviations: GA: gestetional age; HAM-D: Hamilton Rating Scales for Depression; HASS: hassles; MRI: magnetic resonance imaging; PES: Pregnancy Experiences Scale; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor.
*Significant level using one-way analysis of variance $p < 0.05$.

TABLE 2 Infant Behavior Questionnaire (IBQ) measures at 6 months of age

IBQ measures at 6 months	Control n = 17)	SSRI (n = 17)	Depressed-only (n = 14)	p value
Activity level	4.04 ± 0.771	4.00 ± 0.748	4.38 ± 0.665	0.307
Smiling & laughing	4.56 ± 0.624	5.01 ± 0.663	5.03 ± 0.703	0.085
Distress latency	2.47 ± 0.66	2.29 ± 0.48	2.55 ± 0.67	0.469
Distress limitation	3.23 ± 0.731	3.70 ± 0.77	3.52 ± 0.665	0.176
Soothability	5.21 ± 0.71	5.21 ± 0.744	5.27 ± 0.674	0.967
Duration of orientation	3.86 ± 0.706	4.11 ± 1.10	3.56 ± 0.898	0.254

Note. All measures are showing mean values ± standard deviation.
Abbreviation: SSRI: selective serotonin reuptake inhibitor.
p Values are corrected for multiple comparisons (Bonferroni).

levels between groups ($p > 0.80$, univariate general linear model). However, subtle, qualitative differences were observed in the community structure of infants from the depressed-only group compared to control and SSRI groups. While module 3 in the depressed-only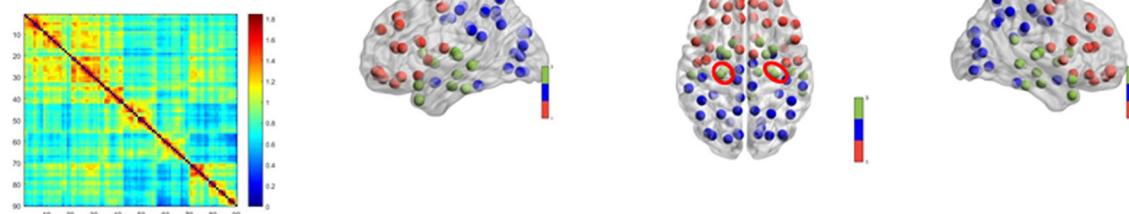 group included the hippocampus and parahippocampal regions, those regions were included in module 2 in the control and SSRI groups.

To evaluate the ability of a node to serve as a hub within the network, two measures were considered: the participation coefficient, which evaluates the ability of a node to serve as a connector (intermodular) hub;
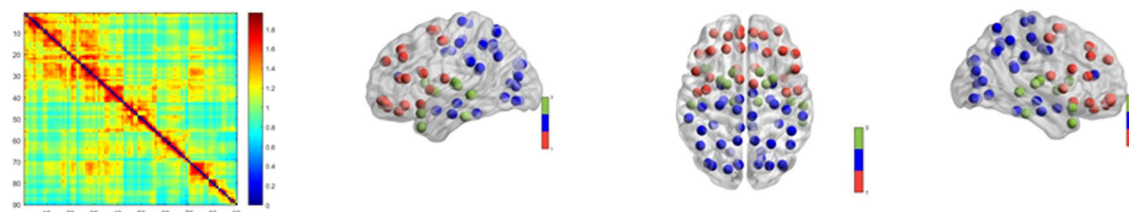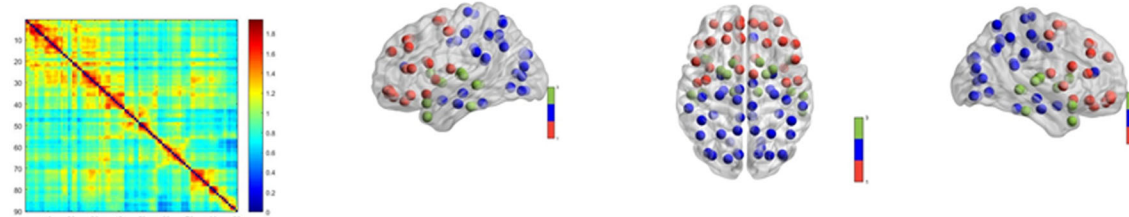

FIGURE 2 Left: The averaged unthresholded correlation matrix shows subtle differences between groups. In these correlation matrices, the blue color represents lower correlations, and red color represents higher correlations between 90 subcortical and cortical regions (Cabez et al., 2016). Brain connectivity toolbox was used to create the matrices (Rubinov & Sporns, 2010). Right: Using the Louvain algorithm, we identified three modules in each group. Submodules within the network, averaged for control (upper), depressed-only (middle), SSRI (lower) groups. Green, blue and red represent the different submodules within the network. Modularity level did not differ between groups ($p > 0.800$, general linear model). Subtle differences (red circles) were observed in the community structure of the depressed-only compared to control and SSRI groups. SSRI: selective serotonin reuptake inhibitor

and within-module degree, which evaluates the ability of a node to serve as a provincial (intramodular) hub. Connector hubs included the Heschel's gyrus bilaterally, the rectus, insula, anterior cingulate, superior temporal caudate, putamen, pallidum, right thalamus, and right operculum (Table S1). Provincial hubs included the left Heschel's gyrus, bilateral olfactory, caudate, putamen and pallidum, right angular gyrus, right fusiform gyrus, left rectus, bilateral posterior cingulate, left superior occipital gyrus, right cuneus, right and middle anterior cingulate gyri, bilateral amygdala, and left superior and middle orbital gyri (Table S2).

For connector hub values, a multivariate GLM analysis corrected for sex, age at the MRI and PES scores revealed a significant group effect in the left insula, $F(5, 47) = 3.826$, $p = 0.029$, $\eta_p^2 = 0.140$); left anterior cingulate, $F(5,47) = 5.874$, $p = 0.005$, $\eta_p^2 = 0.200$; left caudate, $F(5,47) = 5.207$, $p = 0.009$, $\eta_p^2 = 0.181$, adjusted p values. Pairwise comparisons showed group differences in the left caudate, anterior cingulate, and insula, stemming from significantly higher values in infants of the depressed group compared to the control group, whereas differences between the SSRI and control or the depressed group were not significant (see Figure 3 and Table S3a,b).

For provincial hubs, a multivariate GLM analysis corrected for sex, age at the MRI and PES scores revealed a significant group effect in the right medial frontal orbital $F(5,47) = 3.494$, $p = 0.038$, $\eta_p^2 = 0.129$, left amygdala $F(5,47) = 3.192$, $p = 0.050$, $\eta_p^2 = 0.120$, and left Heschel's gyrus $F(5,47) = 5.345$, $p = 0.008$, $\eta_p^2 = 0.185$, (Bonferroni-corrected). Pairwise comparisons showed that differences in the left amygdala stemmed from higher provincial hub levels in infants of the depressed group compared to the control group, whereas for left Heschel's gyrus and the right medial frontal orbital gyrus, infants in the SSRI group had significantly higher levels compared to the depressed group (see Figure 4 and Table S4a,b).

3.3 | PLSR

PLS regression was applied to the 90 provincial and 90 connector hub values. This analysis revealed that hub values representing the

75th percentile of provincial and connector hubs best predicted mothers' ratings of their infants' temperament at 6 months of age. Thus, with the goal of reducing the number of variables in the prediction model, only 44 regions of interest (22 provincial hubs and 22 connector hubs) were used as predictors in subsequent analyses (see Tables S1 and S2).

To determine the number of factors to take into account, we used the ratio of the residual sums of squares and predicted residual sum of squares (Abdi, 2010b). Factors with values above a threshold of 0.0975 were considered for further interpretation (Abdi, 2010b), resulting in a prediction model based on a single factor. This single factor model predicted 11% of the variance in mothers' ratings using all subscale behavioral measures (activity level, smiling and laughter, distress latency, distress of limitation, soothing and duration of orientation; see Table 2). Provincial hubs, including the left superior temporal gyrus and Heschl's gyrus bilaterally, best predicted orientation ratings, whereas lower connector hub levels in the right fusiform and right mid-cingulate regions best predicted ratings of smiling behavior, activity levels and distress to limitations subscales in a way that is more closely related to the SSRI and depressed-only groups compared to the control group (see Figure 5.). Together, these findings suggest that early local connections of provincial hubs in the auditory regions, associated with prenatal exposure to depressed mood and SSRI, predict later orienting behavior, whereas more long-range connections of connector hubs of visual and frontal regions are associated with subsequent smiling and reaching behavior.

4 | DISCUSSION

This study examined the impact of prenatal exposure to maternal depression and SSRI antidepressants on the characteristics of newborn's functional networks. We found that each exposure is associated with different characteristics of the RSN topology extracted using a graph computational approach, applied on rs-fMRI
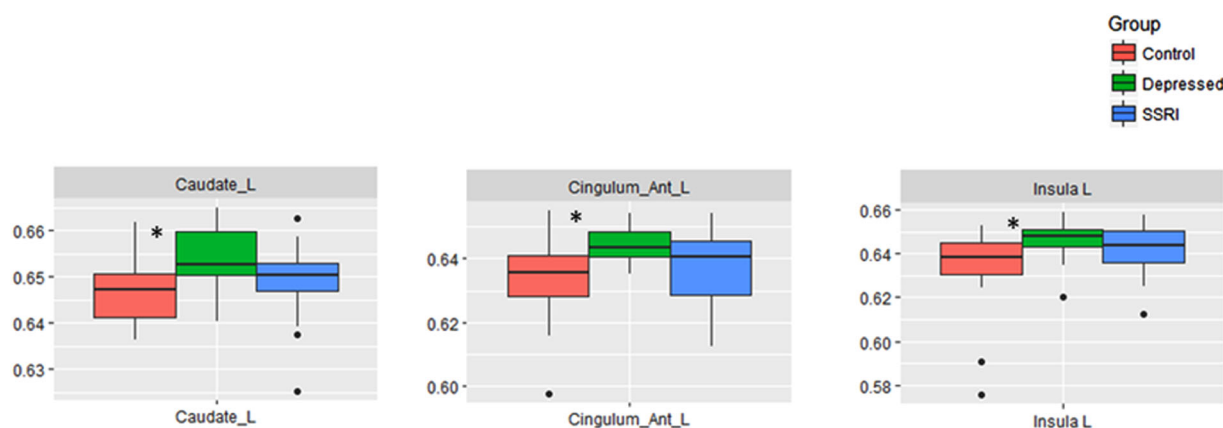

FIGURE 3 Boxplot showing differences between groups for connector hubs. A multivariate GLM analysis corrected for sex, age at the MRI, and PES revealed group differences between depressed-only and control groups, Bonferroni-corrected for multiple comparisons (also see Table S3). GLM: general linear model; MRI: magnetic resonance imaging; PES: Pregnancy Experiences Scale; SSRI: selective serotonin reuptake inhibitor
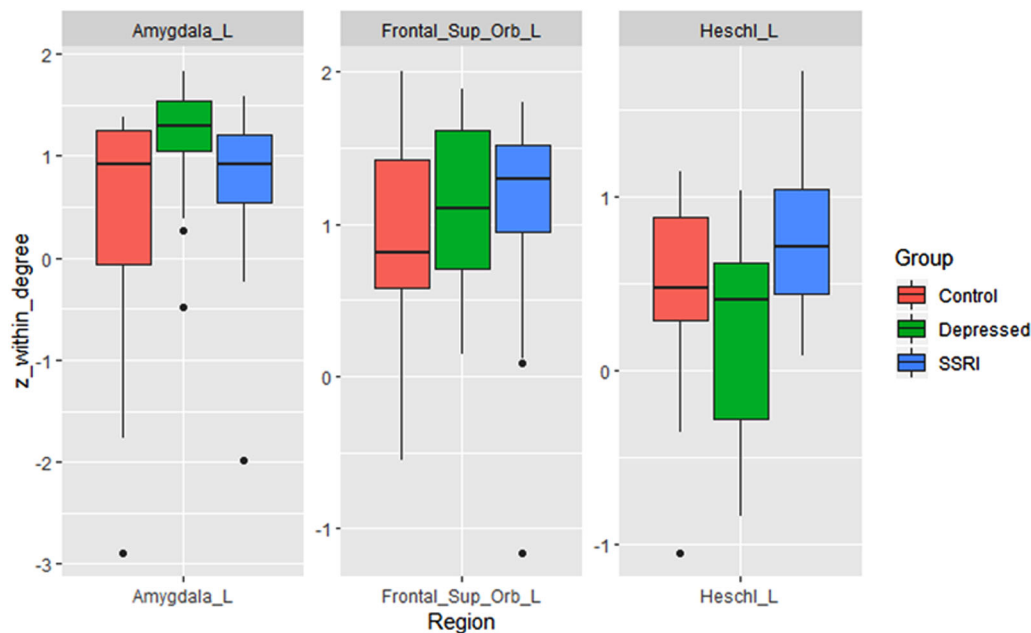
FIGURE 4 Boxplot showing differences between groups for provincial hubs. A multivariate GLM analysis corrected for sex, age at the MRI, and PES revealed group differences between the depressed-only and control groups for the amygdala, and between SSRI and depressed-only for the right frontal orbital and left Heschl gyrus corrected for multiple comparisons, Bonferroni (also see Table S4a,b). GLM: general linear model; MRI: magnetic resonance imaging; PES: Pregnancy Experiences Scale; SSRI: selective serotonin reuptake inhibitor
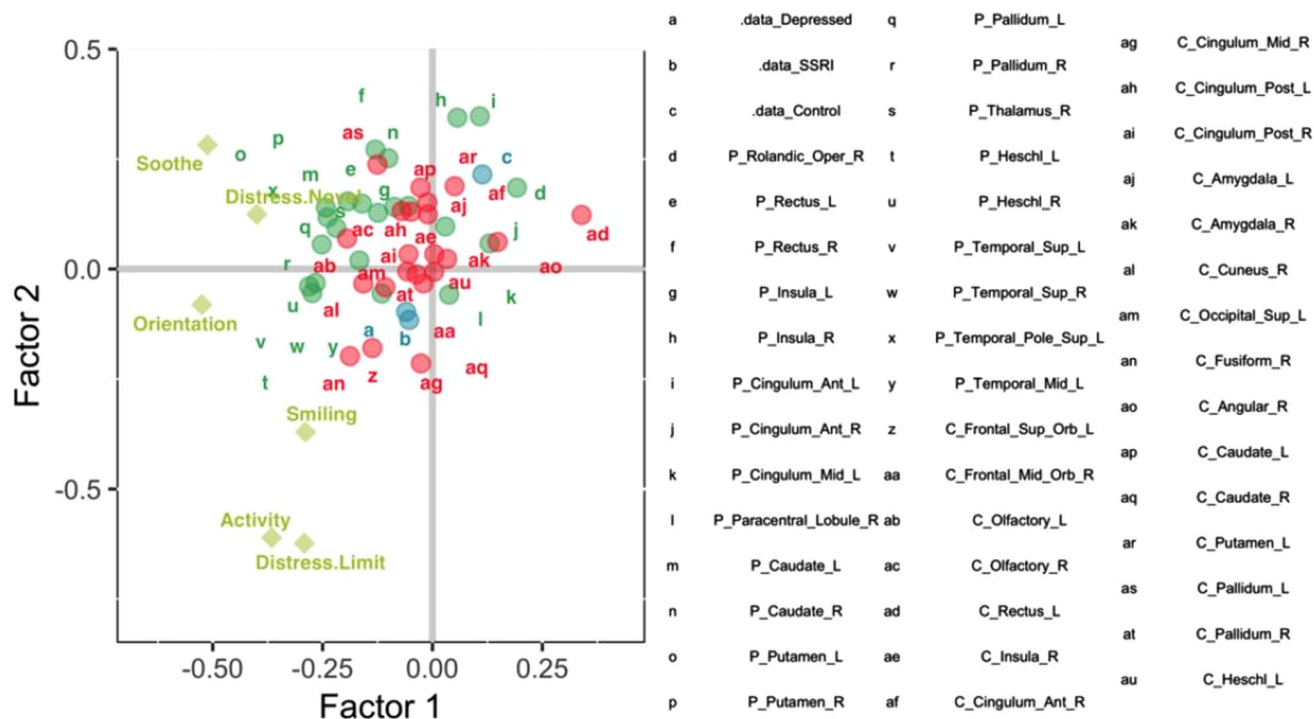

FIGURE 5 PLSR results—Y (predicted) in the space of W (X variables). Dark green circles represent provincial hubs, and red circles represent connector hubs. Blue circles of a, b, and c represent depressed, SSRI, and control groups, respectively, letters i-y represents provincial hubs (prefix p_), and letters z-au represents connector hub (prefix c_). This model predicted 11% of the variance in mothers' ratings on the IBQ (in light green: activity level, smiling and laughter, distress latency, distress of limitation, soothing, and duration of orientation, see Table 2). IBQ: Infant Behavior Questionnaire; SSRI: selective serotonin reuptake inhibitor

data of infants at 6 days of age. Differences between groups were not evident at the global level; both global clustering coefficient and the overall division of the functional network into submodules were similar between groups. In particular, the general network community structure, reflected by modularity and clustering coefficient, was not associated with prenatal maternal exposure to either depression or SSRIs, suggesting no global differences between the groups. Similarly, in adults, major depression did not correlate with clustering coefficient (Zhang et al., 2011), but in contrast to our results, major depression did correlate with increased network modularity compared to healthy controls (Ye et al., 2015). Also, symptom severity (reported using HAM-D) was positively correlated with modularity (Ye et al., 2015). As modularity has been shown to gradually increase in the first year of life (Wen et al., 2018), it might be that alterations in global modularity do not exist in the neonatal brain but might develop over time. Also, mothers in our cohort showed only mild-depressive symptoms (see Table 1). Thus, it could be that symptoms severity was not adequate to alter global network modularity.

When the regional characteristics—which provide information at the nodal level—were examined, a different picture appeared. At first, we identified both connector hubs, which are thought to play an important role in integrating information from one module to other modules in the network (Rubinov & Sporns, 2010) and provincial hubs, hypothesized to serve as a relay station for information flow, exerting their influence mostly within their own submodule. Our data showed that the identified connector and provincial hubs largely overlap with regions previously described as hubs in the neonatal and fetal brain (de Asis-Cruz et al., 2015; Gao et al., 2011; van den Heuvel et al., 2018) and also in the adult brain (Gong & He, 2015; He et al., 2009).

Importantly, our analysis revealed increased connector hub values in the left caudate, insula, and anterior cingulate in infants in the depressed-only group, relative to the control group whereas the SSRI group did not differ from the other groups. In addition, exposure to maternal depression was also associated with higher provincial hub values in the amygdala. Independently, prenatal SSRI exposure had an impact. Provincial hub values were significantly higher in Heschl's gyrus and the right medial frontal orbital gyrus, compared to the depressed group. Together, these findings appear to reflect a regional specific differential susceptibility to maternal depression and SSRI exposure. Similarities between control and SSRI groups in connector hubs suggest that antidepressants may have a "corrective" effect on early brain development that occurs with exposure to prenatal maternal depressed mood. Whereas, differences in provincial hub connectedness between SSRI-exposed and depressed nonexposed infants may reflect a direct impact of SSRI exposure.

Using PLSR on a subset of infants, we have shown that hub values of connector and provincial hubs extracted from rs-fMRI at 6 days of age accounted for more than 10% of the variance in temperament between infant groups at 6 months of age. Importantly, the regions that best predicted temperament subscales are critical to early orientation and face recognition, namely,

decreased connector "hubbiness" in the right fusiform and right mid-cingulate regions predicted smiling behavior at 6 months, while auditory region connectedness levels were the best predictors of orienting behavior, in a pattern which is more closely associated with the SSRI and depressed-only groups than the control group. These findings support the importance of early brain connectivity in creating foundations for later cognitive and social-cognitive functions (Bullmore & Sporns, 2012), and highlights possible differing developmental trajectories between SSRI-exposed and depressed-only, and nonexposed infants (Hanley, Brain, & Oberlander, 2013; Weikum et al., 2013). Nonetheless, the small predictive value of hub regions in relation to subsequent behavior suggests that additional biological factors and ongoing environmental influences also play a role in shaping infants' social-emotional development.

Our findings are consistent with reports from studies using animal models (Bonnin, Zhang, Blakely, & Levitt, 2012; Simpson et al., 2011). Prenatal stress is shown to be associated with increased numbers of neurons in the anterior cingulate, which were labeled with c-Fos (a marker for neuronal activation), suggesting a link between prenatal stress and hyperconnectivity of the anterior cingulate (Rosene et al., 2004). In addition, larger numbers of amygdalar glial cells and neurons have been reported in prenatally stressed adult rats (Salm et al., 2004). In animal models of prenatal exposure to SSRIs, alterations of the premature 5HT circuitry were correlated with the aberrant connectivity of the raphe and callosal, alterations in processing patterns of sensory and auditory information, and in the development of myelin (Bonnin et al., 2012; Simpson et al., 2011). However, the relationship between the alterations in 5HT circuitry in animal models and the neurodevelopmental consequences in humans are still not clear. Importantly, our findings are consistent with the adult literature related to depression (Connolly et al., 2013; Meng et al., 2014; Ramasubbu et al., 2014) showing altered connectivity architecture of the anterior cingulate cortex (ACC), amygdala, insula, and basal ganglia, which are all stress regulatory brain regions. Thus, the intrauterine environment associated with depressed but nonpharmacologically treated mothers may shape the development of the neural circuits in a way that might increase their vulnerability for future depression.

Our findings also reflect previously reported associations between elevated prenatal maternal depressive symptoms and greater connectivity of the left amygdala with the ACC and left insula in 6-month-old infants of mothers with depression during pregnancy (A. Qiu et al., 2015). Our results suggest that these brain regions are hyperconnected and such connectedness may indicate increased efficiency in supporting neuronal communications in the resting-state network of infants of depressed mothers. Further, resting-state hyperconnectivity might be linked to a disproportionally heightened response of the amygdala and insula to negative valance expressions such as fearful, angry, or sad faces which have been demonstrated (Surguladze et al., 2005). Importantly, such negative biases processing emotions and information are critical to the etiology and maintenance of depression (Beck, Rush, Shaw, & Gary, 1979) and our findings showing similar

patterns of hyperconnectivity may shed light on the fetal origins of these psychological disturbances (A. Qiu et al., 2015; Rifkin-Graboi et al., 2013). Further, our findings also reflect an impact of fetal exposure to maternal depression on functional brain development (Belsky & Pluess, 2009) in ways that may increase risk for subsequent psychopathology (A. Qiu et al., 2015).

Our results also point to a SSRI fetal programming effect that might help elucidate the developmental impact of SSRI exposure. Using a data driven analytical approach, we found higher hub values in Heschl's gyrus among SSRI group compared to the depressed-only group, consistent with our previous report of hyperconnectivity in the auditory network with prenatal SSRI exposure (Rotem-Kohavi et al., 2018). These findings suggest a more efficient flow of information in local regions connected to Heschl's gyrus in SSRI-exposed infants and support the accelerated auditory language perception development observed in SSRI-exposed infants, which was already evident at 36 weeks gestation (Weikum et al., 2012). Although a causal relationship cannot be determined, the hyperconnectivity within the auditory network, together with higher hub values in Heschl's gyrus with SSRI exposure, reveals a functional connectivity change that could potentially reflect accelerated onset of speech perception observed in fetuses and infants exposed to SSRIs. Though, it is not clear yet whether this language perception shift is beneficial or detrimental to subsequent language development.

The hub values differences we found are lateralized, and were demonstrated only for the left hemisphere. Previous reports have reported lateralized differences in neonatal functional connectivity following prenatal exposures. Left lateralization of language networks has been reported in newborn infants (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002), suggesting higher susceptibility within left lateralized auditory regions. However, though Qiu et al. (2015) reported increased vulnerability of the left side, others have reported alterations on the right side (Posner et al. 2016). Further investigations are needed to understand the nature of these inconsistencies.

Importantly, mothers treated with SSRI could have inherently different characteristics compared to mothers with depression not pharmacologically treated. Although we used two different control groups for the SSRI-treated group (depressed-only, non-SSRI-treated, and non-depressed) we could not rule out the effect of residual confounding, such as variations in depressive symptoms, and genetic variations related to mood disturbances which also confer developmental risks for the child. Our study provides a glimpse into functional topology of early brain development, but it is limited by measurements at only one timepoint. Additional studies using longitudinal designs are needed to determine whether these in-utero exposures have long term associations with developmental variations in functional topology.

5 | CONCLUSION

Our findings support the hypothesis that the environment inside the womb has a critical role in preparing the fetus for life following birth

(Barker, 2000). We report differences in the functional network topology for the different exposures, which implies that different in-utero conditions might set a path to different developmental trajectories that may increase or reduce developmental risk.

At present it remains unclear how—at a neural level—the impact of SSRIs in the context of maternal depression during gestation differs from the impact of depression alone. Both prenatal factors lead to similar behavioral disturbances presumably reflecting altered central serotonin signaling. SSRIs readily cross the placenta (Rampono et al., 2009) and the blood–brain barrier, and have been shown both in animal models (Rampono et al., 2009) and in human studies (Davidson et al., 2009; Hilli et al., 2009; Laine, Heikkinen, Ekblad, & Kero, 2003) to alter 5HT signaling in the fetus. It has been hypothesized that acute in-utero SSRI exposure leads to higher serotonin levels in the fetal brain, and in the long term leads, via negative feedback, to constrained development of serotonin circuitry, reduced serotonergic tone and lower effective levels of serotonin in the brain during development (Oberlander, Gingrich, & Ansorge, 2009). Moreover, given 5HT's role as a trophic factor regulating various aspects of fundamental developmental processes such as cell growth, differentiation, migration, myelination, synaptogenesis, and pruning (Gaspar, Cases, & Maroteaux, 2003), it is conceivable that changes in the levels of 5HT as a result from exposure to SSRI in those critical periods of brain development before birth might influence developmental pathways differently from the in-utero exposure to depression. Differences in behavioral outcomes between depressed-only and SSRI-exposed infants and children have been reported (Skurtveit, Selmer, Roth, Hernandez-Diaz, & Handal, 2014; Weikum et al., 2013, 2012), however, the neural correlates reflecting these outcomes and clinical implications still need to be determined.

Further, using PLSR, our findings provide support for associations between region-specific hubs in the newborn brain and subsequent differences in developmental pathways for specific infant behaviors in the context of prenatal exposure to maternal depression and SSRI antidepressants. Whether these paths lead to particular long term developmental outcomes warrants additional investigation.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA ACCESSIBILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Naama Rotem-Kohavi http://orcid.org/0000-0002-4235-4320
Lynne J. Williams http://orcid.org/0000-0001-6790-1362
Tim F. Oberlander http://orcid.org/0000-0003-4781-6579

REFERENCES

Abdi, H. (2010a). Holm's Sequential Bonferroni Procedure. In N. Salkind (Ed.), *Encyclopedia of Research Design*. Thousand Oaks, CA: Sage.

Abdi, H. (2010b). Partial least squares regression and projection on latent structure regression (PLS Regression). *Wiley Interdisciplinary Reviews: Computational Statistics*, 2(1), 97–106. https://doi.org/10.1002/wics.51

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLOS Computational Biology*, 3(2), 174–183. https://doi.org/10.1371/journal.pcbi.0030017

de Asis-Cruz, J., Bouyssi-Kobar, M., Evangelou, I., Vezina, G., & Limperopoulos, C. (2015). Functional properties of resting state networks in healthy full-term newborns. *Scientific Reports*, 5, 17755. https://doi.org/10.1038/srep17755

Barker, D. J. (2000). In utero programming of cardiovascular disease. *Theriogenology*, 53(2), 555–574. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10735050

Bathelt, J., O'Reilly, H., Clayden, J. D., Cross, J. H., & De Haan, M. (2013). Functional brain network organisation of children between 2 and 5years derived from reconstructed activity of cortical sources of high-density EEG recordings. *NeuroImage*, 82, 595–604. https://doi.org/10.1016/j.neuroimage.2013.06.003

Beck, A. T., Rush, J. A., Shaw, B. F., & Gary, E. (1979). *Cognitive therapy of depression*. New York, NY: Guilford Press.

Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on Medical Imaging*, 23(2), 137–152. https://doi.org/10.1109/TMI.2003.822821

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, 135(6), 885–908. https://doi.org/10.1037/a0017376

Blondel, V. D., Guillaume, J.-L., Lambiotte, R., & Lefebvre, E. (2008). Fast unfolding of communities in large networks. *Journal of Statistical Mechanics: Theory and Experiment*, 2008(10), P10008. https://doi.org/10.1088/1742-5468/2008/10/P10008

Bonnin, A., Zhang, L., Blakely, R. D., & Levitt, P. (2012). The SSRI citalopram affects fetal thalamic axon responsiveness to netrin-1 in vitro independently of SERT antagonism. *Neuropsychopharmacology*, 37(8), 1879–1884. https://doi.org/10.1038/npp.2012.35

Brummelte, S., Mc Glanaghy, E., Bonnin, A., & Oberlander, T. F. F. (2017). Developmental changes in serotonin signaling: Implications for early brain function, behavior and adaptation. *Neuroscience*, 342, 212–231. https://doi.org/10.1016/j.neuroscience.2016.02.037

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, 10(3), 186–198. https://doi.org/10.1038/nrn2575

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, 13(5), 336–349. https://doi.org/10.1038/nrn3214

Cabez, M. B., Serag, A., Wilkinson, A. G., Anblagan, D., Telford, J., Pataky, R., ... Boardman, J. P. (2016). Parcellation of the healthy neonatal brain into 107 regions using atlas propagation through intermediate time points in childhood. *Frontiers in Neuroscience*, 10(May), 1–13. https://doi.org/10.3389/fnins.2016.00220

Chan, M. Y., Alhazmi, F. H., Park, D. C., Savalia, N. K., & Wig, G. S. (2017). Resting-state network topology differentiates task signals across the adult life span. *The Journal of neuroscience*, 37(10), 2734–2745. https://doi.org/10.1523/JNEUROSCI.2406-16.2017

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., ... Yang, T. T. (2013). Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biological Psychiatry*, 74(12), 898–907. https://doi.org/10.1016/j.biopsych.2013.05.036

Cox, A. D. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, 29, 162–173.

Davidson, S., Prokonov, D., Taler, M., Maayan, R., Harell, D., Gil-ad, I., ... Medical, R. (2009). Effect of exposure to selective serotonin reuptake inhibitors in utero on fetal growth: Potential role for the IGF-I and HPA axes. *Pediatric Research*, 65(2), 236–241.

Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional Neuroimaging of Speech Perception in Infants. *Science*, 298(5600), 2013–2015. https://doi.org/10.1126/science.1077066

DiPietro, J. A, Ghera, M. M., Costigan, K., & Hawkins, M. (2004). Measuring the ups and downs of pregnancy stress. *Journal of Psychosomatic Obstetrics and Gynaecology*, 25(December), 189–201. https://doi.org/10.1080/01674820400017830

Fan, Y., Shi, F., Smith, J. K., Lin, W., Gilmore, J. H., & Shen, D. (2011). Brain anatomical networks in early human brain development. *NeuroImage*, 54(3), 1862–1871. https://doi.org/10.1016/j.neuroimage.2010.07.025

Fransson, P., Åden, U., Blennow, M., & Lagercrantz, H. (2010). The functional architecture of the infant brain as revealed by resting-state fMRI. *Cerebral Cortex*, 21(1), 145–154. https://doi.org/10.1093/cercor/bhq071

Gao, W., Alcauter, S., Smith, J. K., Gilmore, J. H., Lin, W., Smith, K., ... Lin, W. (2015). Development of human brain cortical network architecture during infancy. *Brain Structure & Function*, 8(12), 1699–1712. https://doi.org/10.1016/j.rasd.2014.08.015.Social

Gao, W., Gilmore, J. H., Giovanello, K. S., Smith, J. K., Shen, D., Zhu, H., & Lin, W. (2011). Temporal and spatial evolution of brain network topology during the first two years of life. *PLOS One*, 6(9), e25278. https://doi.org/10.1371/journal.pone.0025278

Gartstein, M. A, & Rothbart, M. K. (2003). Studying infant temperament via the Revised Infant Behavior Questionnaire. *Infant Behavior and Development*, 26(1), 64–86. https://doi.org/10.1016/S0163-6383(02)00169-8

Gartstein, M. A, Bridgett, D. J., & Low, C. M. (2012). Asking questions about temperament: Self- and other-report measures across the lifespan, *Handbook of Temperament*. The Guilford Press.

Gaspar, P., Cases, O., & Maroteaux, L. (2003). The developmental role of serotonin: News from mouse molecular genetics. *Nature Reviews Neuroscience*, 4(12), 1002–1012. https://doi.org/10.1038/nrn1256

Gentile, S. (2015). Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience*, *342*(2015), 154–166. https://doi.org/10.1016/j.neuroscience.2015.09.001

Girvan, M., & Newman, M. E. J. (2002). Community structure in social and biological networks. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(12), 7821–7826. https://doi.org/10.1073/pnas.122653799

Gong, Q., & He, Y. (2015). Review depression, neuroimaging and connectomics: A selective overview. *Biological Psychiatry*, *77*, 223–235. https://doi.org/10.1016/j.biopsych.2014.08.009

Guimera, R., & Amaral, L. (2005). Functional catography of complex metabolic networks. *Nature*, *433*, 895–900.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, *23*(1), 56–62. https://doi.org/10.1136/jnnp.23.1.56

Hanley, G. E., Brain, U., & Oberlander, T. F. (2013). Infant developmental outcomes following prenatal exposure to antidepressants, and maternal depressed mood and positive affect. *Early Human Development*, *89*(8), 519–524. https://doi.org/10.1016/j.earlhumdev.2012.12.012

Hanley, G. E., Brain, U., & Oberlander, T. F. (2015). Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behavior. *Pediatric Research*, *78*(2), 174–180. https://doi.org/10.1038/pr.2015.77

He, Y., Wang, J., Wang, L., Chen, Z. J., Yan, C., Yang, H., … Evans, A. C. (2009). Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PLOS One*, *4*(4), e5226. https://doi.org/10.1371/journal.pone.0005226

van den Heuvel, M. I., Turk, E., Manning, J. H., Hect, J., Hernandez-Andrade, E., Hassan, S. S., … Thomason, M. E. (2018). Hubs in the human fetal brain network. *Developmental Cognitive Neuroscience*, *30*, 108–115. https://doi.org/10.1016/j.dcn.2018.02.001

Hilli, J., Heikkinen, T., Rontu, R., Lehtimäki, T., Kishida, I., Aklillu, E., … Laine, K. (2009). MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. *European Neuropsychopharmacology*, *19*(5), 363–370. https://doi.org/10.1016/j.euroneuro.2009.01.006

Jenkinson, M., Bannister, P., Brady, M., Smith, S., Peter, Bannister, B., … Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825–841.

Jenkinson, M., & Smith, S. M. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156.

Jha, S. C., Meltzer-Brody, S., Steiner, R. J., Cornea, E., Woolson, S., Ahn, M., … Knickmeyer, R. C. (2016). Antenatal depression, treatment with selective serotonin reuptake inhibitors, and neonatal brain structure: A propensity-matched cohort study. *Psychiatry Research—Neuroimaging*, *253*, 43–53. https://doi.org/10.1016/j.pscychresns.2016.05.004

Laine, K., Heikkinen, T., Ekblad, U., & Kero, P. (2003). Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Archives of General Psychiatry*, *60*(7), 720–726. https://doi.org/10.1001/archpsyc.60.7.720

Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., … Dunbar, G. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224–231. https://doi.org/10.1016/S0924-9338(97)83296-8

Lugo-Candelas, C., Cha, J., Hong, S., Bastidas, V., Weissman, M., Fifer, W. P., … Posner, J. (2018). Associations between brain structure and connectivity in infants and exposure to selective serotonin reuptake inhibitors during pregnancy. *JAMA Pediatrics*, *172*, 525. https://doi.org/10.1001/jamapediatrics.2017.5227

Meng, C., Brandl, F., Tahmasian, M., Shao, J., Manoliu, A., Scherr, M., … Sorg, C. (2014). Aberrant topology of striatum's connectivity is associated with the number of episodes in depression. *Brain*, *137*(2), 598–609. https://doi.org/10.1093/brain/awt290

Mongerson, Chandler, R. L., Jennings Russell, W., Borsook, D., Becerra, L., & Dusica, Bajic (2017). Resting-state functional connectivity in the infant brain: Methods, pitfalls, and potentiality. *Frontiers in Pediatrics*, *5*(1), 159. https://doi.org/10.3389/fped.2017.00159

Oberlander, T. F., Gingrich, J. a, & Ansorge, M. S. (2009). Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: Molecular to clinical evidence. *Clinical Pharmacology and Therapeutics*, *86*(6), 672–677. https://doi.org/10.1038/clpt.2009.201

Oberlander, T. F., Reebye, P., Misri, S., Papsdorf, M., Kim, J., & Grunau, R. E. (2007). Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. *Archives of Pediatrics & Adolescent Medicine*, *161*(1), 22–29. https://doi.org/10.1001/archpedi.161.1.22

Podrebarac, S. K., Duerden, E. G., Chau, V., Grunau, R. E., Synnes, A., Oberlander, T. F., & Miller, S. P. (2017). Antenatal exposure to antidepressants is associated with altered brain development in very preterm-born neonates. *Neuroscience*, *342*, 252–262. https://doi.org/10.1016/j.neuroscience.2016.11.025

Posner, J., Cha, J., Roy, A. K., Peterson, B. S., Bansal, R., Gustafsson, H. C., … Monk, C. (2016). Alterations in amygdala–prefrontal circuits in infants exposed to prenatal maternal depression. *Translational Psychiatry*, *6*(11), e935. https://doi.org/10.1038/tp.2016.146

Qiu, A., Anh, T. T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B. F. P., … Meaney, M. J. (2015). Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Translational Psychiatry*, *5*(2), e508. https://doi.org/10.1038/tp.2015.3

Ramasubbu, R., Konduru, N., Cortese, F., Bray, S., Gaxiola-Valdez, I., & Goodyear, B. (2014). Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. *Frontiers in Psychiatry*, *5*, 17. https://doi.org/10.3389/fpsyt.2014.00017

Rampono, J., Simmer, K., Ilett, K., Hackett, L., Doherty, D., Elliot, R., … Forman, T. (2009). Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*, *42*(3), 95–100.

Rifkin-Graboi, A., Bai, J., Chen, H., Hameed, W. B. R., Sim, L. W., Tint, M. T., … Qiu, A. (2013). Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. *Biological Psychiatry*, *74*(11), 837–844. https://doi.org/10.1016/j.biopsych.2013.06.019

Rifkin-Graboi, A., Meaney, M. J., Chen, H., Bai, J., Hameed, W. B. R., Tint, M. T., … Qiu, A. (2015). Antenatal maternal anxiety predicts variations in neural structures implicated in anxiety disorders in newborns. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(4), 313–321. e2. https://doi.org/10.1016/j.jaac.2015.01.013

Rosene, D. L., Lister, J. P., Schwagerl, A. L., Tonkiss, J., McCormick, C. M., & Galler, J. R. (2004). Prenatal protein malnutrition in rats alters the c-Fos response of neurons in the anterior cingulate and medial prefrontal region to behavioral stress. *Nutritional Neuroscience*, *7*(5–6), 281–289. https://doi.org/10.1080/10284150400015573

Rotem-Kohavi, N., & Oberlander, T. F. (2017). Variations in neurodevelopmental outcomes in children with prenatal SSRI antidepressant exposure. *Birth Defects Research*, *109*(12), 909–923. https://doi.org/10.1002/bdr2.1076

Rotem-Kohavi, N., Williams, L. J., Virji-Babul, N., Bjornson, B. H., Brain, U., Werker, J. F., … Oberlander, T. F. (2018). Alterations in resting state networks following in utero SSRI exposure in the neonatal brain. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*, 39–49. https://doi.org/10.1016/j.bpsc.2018.08.004

Rothbart, M. K. (1981). Measurement of temperament in infancy. *Child Development*, *52*(2), 569–578. https://doi.org/10.1111/j.1467-8624.1981.tb03082.x

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Salm, A. K., Pavelko, M., Krouse, E. M., Webster, W., Kraszpulski, M., & Birkle, D. L. (2004). Lateral amygdaloid nucleus expansion in adult rats is associated with exposure to prenatal stress. *Developmental Brain Research*, *148*(2), 159–167. Retrieved from. https://www.sciencedirect.com/science/article/pii/S0165380603003468

Salzwedel, A. P., Grewen, K. M., Vachet, C., Gerig, G., Lin, W., & Gao, W. (2015). Prenatal drug exposure affects neonatal brain functional connectivity. *Journal of Neuroscience*, *35*(14), 5860–5869. https://doi.org/10.1523/JNEUROSCI.4333-14.2015

Serag, A., Aljabar, P., Ball, G., Counsell, S. S. J., Boardman, J. J. P., Rutherford, M. A. M., ... Rueckert, D. (2012). Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression. *NeuroImage*, *59*(3), 2255–2265. https://doi.org/10.1016/j.neuroimage.2011.09.062

Simpson, K. L., Weaver, K. J., de Villers-Sidani, E., Lu, J. Y.-F., Cai, Z., Pang, Y., ... Lin, R. C. S. (2011). Perinatal antidepressant exposure alters cortical network function in rodents. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(45), 18465–18470. https://doi.org/10.1073/pnas.1109353108

Skurtveit, S., Selmer, R., Roth, C., Hernandez-Diaz, S., & Handal, M. (2014). Prenatal exposure to antidepressants and language competence at age three: Results from a large population-based pregnancy cohort in Norway. *BJOG: An International Journal of Obstetrics and Gynaecology*, *121*(13), 1621–1631. https://doi.org/10.1111/1471-0528.12821

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1016/B978-0-12-375082-2.10001-1

Sporns, O., Chialvo, D. R., Kaiser, M., & Hilgetag, C. C. (2004). Organization, development and function of complex brain networks. *Trends in Cognitive Sciences*, *8*(9), 418–425. https://doi.org/10.1016/j.tics.2004.07.008

Stein, A., Pearson, R. M., Goodman, S. H., Rapa, E., Rahman, A., McCallum, M., ... Pariante, C. M. (2014). Effects of perinatal mental disorders on the fetus and child. *The Lancet*, *384*(9956), 1800–1819. https://doi.org/10.1016/S0140-6736(14)61277-0

Surguladze, S., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., ... Phillips, M. L. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry*, *57*(3), 201–209. https://doi.org/10.1016/j.biopsych.2004.10.028

Talge, N. M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *48*(3–4), 245–261. https://doi.org/10.1111/j.1469-7610.2006.01714.x

Thomason, M. E., Brown, J. A., Dassanayake, M. T., Shastri, R., Marusak, H. A., Hernandez-Andrade, E., ... Romero, R. (2014). Intrinsic functional brain architecture derived from graph theoretical analysis in the human fetus. *PLOS One*, *9*(5), e94423. https://doi.org/10.1371/journal.pone.0094423

Thomason, M. E., Scheinost, D., Manning, J. H., Grove, L. E., Hect, J., Marshall, N., ... Romero, R. (2017). Weak functional connectivity in the human fetal brain prior to preterm birth. *Scientific Reports*, *7*(39286), 1–10. https://doi.org/10.1038/srep39286

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, *15*(1), 273–289. https://doi.org/10.1006/nimg.2001.0978

Videman, M., Tokariev, A., Saikkonen, H., Stjerna, S., Heiskala, H., Mantere, O., & Vanhatalo, S. (2016). Newborn brain function is affected by fetal exposure to maternal serotonin reuptake inhibitors. *Cerebral Cortex*, 3208–3216. https://doi.org/10.1093/cercor/bhw153

Vigod, S., Hussain-Shamsy, N., Grigoriadis, S., Howard, L. M., Metcalfe, K., Oberlander, T. F., ... Dennis, C.-L. (2016). A patient decision aid for antidepressant use in pregnancy: Study protocol for a randomized controlled trial. *Trials*, *17*(1), 110. https://doi.org/10.1186/s13063-016-1233-4

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of "small-world" networks. *Nature*, *393*(6684), 440–442. https://doi.org/10.1038/30918

Weikum, W. M., Mayes, L. C., Grunau, R. E., Brain, U., & Oberlander, T. F. (2013). The impact of prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and maternal mood on mother-infant interactions at 3 months of age. *Infant Behavior & Development*, *36*(4), 485–493. https://doi.org/10.1016/j.infbeh.2013.04.001

Weikum, W. M., Oberlander, T. F., Hensch, T. K., & Werker, J. F. (2012). Prenatal exposure to antidepressants and depressed maternal mood alter trajectory of infant speech perception. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(Suppl 2), 17221–17227. https://doi.org/10.1073/pnas.1121263109

Wen, X., Zhang, H., Li, G., Liu, M., Yin, W., Lin, W., ... Shen, D. (2018). First-year development of modules and hubs in infant brain functional networks. *NeuroImage*, *185*. Neuroimage. https://doi.org/10.1016/j.neuroimage.2018.10.019

Ye, M., Yang, T., Qing, P., Lei, X., Qiu, J., & Liu, G. (2015). Changes of functional brain networks in major depressive disorder: A graph theoretical analysis of resting-state fMRI. *PLOS One*, *10*(9), e0133775. https://doi.org/10.1371/journal.pone.0133775

Yoshida, K., Shimizu, Y., Yoshimoto, J., Takamura, M., Okada, G., Okamoto, Y., ... Doya, K. (2017). Prediction of clinical depression scores and detection of changes in whole-brain using resting-state functional MRI data with partial least squares regression. *PLOS One*, *12*(7), e0179638. https://doi.org/10.1371/journal.pone.0179638

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., & Gong, Q. (2011). Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biological Psychiatry*, *70*(4), 334–342. https://doi.org/10.1016/j.biopsych.2011.05.018

Zimmerman, M., Martinez, J. H., Young, D., Chelminski, I., & Dalrymple, K. (2013). Severity classification on the Hamilton Depression Rating Scale. *Journal of Affective Disorders*, *150*(2), 384–388. https://doi.org/10.1016/j.jad.2013.04.028

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.