

Investigating default mode network connectivity disruption in children of mothers with depression

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Background

Exposure to maternal major depressive disorder (MDD) bears long-term negative consequences for children's well-being; to date, no research has examined how exposure at different stages of development differentially affects brain functioning.

Aims

Utilising a unique cohort followed from birth to preadolescence, we examined the effects of early versus later maternal MDD on default mode network (DMN) connectivity.

Method

Maternal depression was assessed at birth and ages 6 months, 9 months, 6 years and 10 years, to form three groups: children of mothers with consistent depression from birth to 6 years of age, which resolved by 10 years of age; children of mothers without depression; and children of mothers who were diagnosed with MDD in late childhood. In preadolescence, we used magnetoencephalography and focused on theta rhythms, which characterise the developing brain.

Results

Maternal MDD was associated with disrupted DMN connectivity in an exposure-specific manner. Early maternal MDD decreased

child connectivity, presenting a profile typical of early trauma or chronic adversity. In contrast, later maternal MDD was linked with tighter connectivity, a pattern characteristic of adult depression. Aberrant DMN connectivity was predicted by intrusive mothering in infancy and lower mother-child reciprocity and child empathy in late childhood, highlighting the role of deficient caregiving and compromised socio-emotional competencies in DMN dysfunction.

Conclusions

The findings pinpoint the distinct effects of early versus later maternal MDD on the DMN, a core network sustaining self-related processes. Results emphasise that research on the influence of early adversity on the developing brain should consider the developmental stage in which the adversity occurred.

Keywords

Depressive disorders; childhood experience; imaging; social functioning; aetiology.

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Maternal major depressive disorder

Maternal major depressive disorder (MDD) is a highly prevalent condition, affecting 12–15% of women in industrial societies and 30% in the developing world. Extant research has demonstrated that exposure to maternal depression carries long-term negative consequences for children's well-being by increasing propensity for psychopathology, disrupting maturation of stress management systems and impairing socio-emotional competencies, executive functions and the capacity for empathy.^{1–6} Less research has focused on the effects of maternal MDD on the developing brain. Although several studies described the effects of maternal postnatal depressive symptoms on the infant brain,^{7–12} prospective longitudinal studies that begin at birth and repeatedly diagnose maternal depression to test its impact on child brain functioning are rare. Specifically, no study, to our knowledge, has examined the effects of maternal MDD experienced at different developmental nodes on neural function. This question taps the broader issue of timing effects and how various adversities, including trauma, abuse, neglect, physical illness and parental psychopathology, affect children's brains when experienced at different stages of brain maturation. In the current study, we focus on default mode network (DMN) connectivity in children exposed to maternal MDD at different points in development, compared with those who were never exposed.

The DMN in psychopathology

The DMN is a core network sustaining the sense of self, autobiographical memory, internal attention and quiescence.^{13–16} The

DMN comprises seven cortical areas (see Fig. 1(b)) that are more active and synchronised when the brain is not engaged in task-positive activity.¹⁶ Connectivity among the DMN structures has been associated with adaptive physiological, cognitive and socio-emotional processes,^{13,14} whereas disruptions to DMN connectivity have been linked with early adversity and psychiatric conditions.¹⁷ Specifically, conditions involving adverse rearing, post-traumatic stress disorder, anxiety disorders and abuse are associated with a reduction in DMN connectivity.^{18–25} Reduced DMN connectivity, in turn, is related to avoidant behaviour, hyperarousal, intrusive memories, and emotional and physical symptoms.^{23,26} Moreover, since the DMN intersects with the social brain network,²⁷ DMN connectivity has been linked with socio-emotional competencies, including empathy,²⁸ trust and reciprocal social behaviour.²⁹

In contrast to the decreased connectivity in conditions involving early trauma, depression is associated with tighter DMN connectivity in adults.^{30–33} Increased connectivity, mainly across the brain's midline structures such as between the medial prefrontal cortex (mPFC) and posterior cingulate cortex/precuneus (PCC), was found to predict the severity of depressive ruminations,^{34–36} and connectivity between the PCC and other brain regions appears to play a role in MDD. Depression increases connectivity between the PCC and mPFC during emotional identification,³⁷ and between the PCC and cingulate cortex during memory tasks.³⁸ When comparing resting state connectivity of patients with MDD and controls, greater connectivity between the PCC and frontal regions emerged in patients with MDD who were not receiving medication.³⁹ Furthermore, a 5-week repetitive transcranial magnetic stimulation directed to the DMN reduced hyperconnectivity in the DMN in 17 patients with MDD, and this reduction was linked with improvement in clinical symptoms.⁴⁰ The authors

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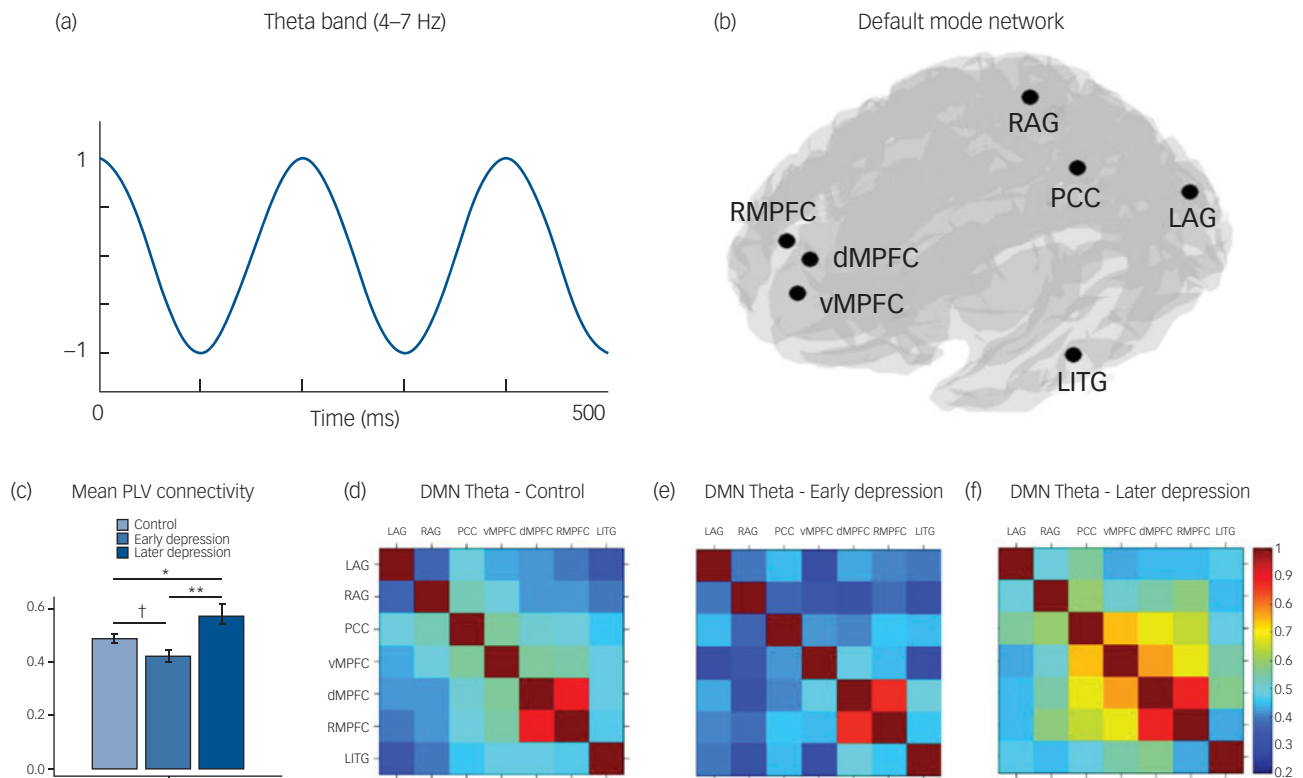


Fig. 1 (a) An illustration of the theta frequency band (4–7 Hz). (b) The locations of the seven seeds of the default mode network (DMN; taken from). Montreal Neurological Institute (MNI) seed coordinates (mm, Left-Posterior-Inferior (LPI)) are as follows: right medial prefrontal cortex (RMPFC; 2, 53, 24); dorsomedial prefrontal cortex (dMPFC; –13, 52, 23); ventromedial prefrontal cortex (vMPFC; –2, 51, 2); right angular gyrus (RAG; 51, –64, 32); left angular gyrus (LAG; –43, –76, 35); posterior cingulate cortex/precuneus (PCC; –3, –54, 31) and left inferior temporal gyrus (LITG; –57, –25, –17). (c) Bar plot of averaged (over all 21 seed-pair connections) theta phase-lock values (PLV). Connectivity values between the different DMN nodes in children exposed to (d) early maternal depression ($n = 13$), (e) later maternal depression ($n = 16$) and (f) healthy controls ($n = 45$). * $P < 0.05$, ** $P < 0.005$, † $P < 0.1$. Error bars represent s.e.

concluded that greater connectivity in the DMN plays a crucial role in MDD, and therefore lowering DMN connectivity can result in clinical improvement.

Although most studies on DMN connectivity target adults, existing studies in children and adolescents point to disruptions in DMN connectivity in various high-risk conditions.^{41–45} Using magnetoencephalography (MEG), it was found that preadolescents exposed to chronic trauma showed decreased DMN connectivity in the theta band,¹⁸ the oscillatory rhythm that characterises the developing brain.^{46,47} DMN connectivity was lowest among children diagnosed with post-traumatic stress disorder, and was longitudinally predicted by maternal intrusive behaviour in infancy. In contrast, a study of 13- to 17-year-olds showed that adolescent depression was associated with increased DMN connectivity;³⁷ however, to our knowledge, no study has examined DMN connectivity in children or adolescents exposed to maternal depression.

Timing effects in exposure to maternal MDD

A ‘sensitive period’, which posits that the brain requires specific environmental inputs at each stage for proper growth,^{48,49} has typically been missing from research on early adversity. Infancy and early childhood mark the most pronounced sensitive periods, when the brain requires attuned maternal caregiving for maturation of core structure and function,^{50,51} and deficient caregiving from mothers with MDD impairs proper brain development.⁵² However, late childhood (before the onset of puberty) involves important brain reorganisation in terms of synaptic pruning,

cortical thinning and white matter restructuring.^{53–55} Brain functions and structural network organisation in late childhood have been linked with dimensions of the mother–child relationship, including reciprocity,⁵⁶ intrusiveness, controlling parenting⁵⁷ and maternal mind-mindedness, autonomy support⁵⁸ and cooperation.⁵⁹ Maternal depression in late childhood is associated with low mother–child reciprocity, which compromises key social abilities, such as empathy and engagement.^{4,60} These disruptions may uniquely affect DMN connectivity at the stage when children leave the family to enter the larger social world.

The current study tested timing effects in the association between exposure to maternal MDD during the first decade of life and disruptions to DMN connectivity in preadolescence. We utilised a unique birth cohort followed for 11 years, which included repeated diagnosis of maternal MDD and extreme-case design in families of otherwise low risk. This enabled us to tease apart children exposed to maternal MDD across early, but not later childhood from those exposed during late childhood, and from those never exposed to maternal MDD or other maternal psychiatric conditions across the first decade – a possibility never before available in research on the long-term effects of maternal MDD. Two hypotheses were formed. First, we expected that exposure to maternal MDD at any point would lead to disruptions in DMN connectivity, and that the effects would depend on timing of exposure. As an open research question, we examined whether exposure to maternal MDD in early, but not later childhood would resemble the profile characterising early trauma and lead to decreased DMN connectivity, whereas later exposure would resemble the tighter connectivity

typical of depression. Second, we expected that the deficient parenting and compromised social abilities associated with maternal depression would predict disruptions to DMN connectivity. Specifically, maternal intrusiveness in infancy was found to predict disrupted DMN connectivity in trauma-exposed youth,¹⁸ and disruptions to the neural basis of empathy in children of mothers with depression.⁶¹ Similarly, lower mother–child reciprocity impairs the neural basis of empathy in young adults,⁶² and low empathy is linked with reduced DMN connectivity in adolescence.^{14,28,44,63} These factors were thus expected to predict disrupted DMN connectivity in children exposed to maternal depression.

Method

Participants

Our 11-year follow-up of a community birth cohort aimed to test the effects of maternal depression on child development and brain maturation, separate from the frequently occurring comorbidity often included in research on maternal depression (e.g. single parenting, poverty, teenage mothering, substance misuse, premature birth); hence, all families were of low risk and mothers and children were healthy. Data collection was conducted in seven waves. At each wave, mothers suffering from a comorbidity were excluded from the study.

Birth

The initial cohort included 1983 consecutive admissions to two university hospitals. Research assistants visited the maternity wards and invited women who were physically healthy, delivered a healthy-term singleton infant, completed at least 12 years of education, were above the poverty line and were cohabitating with the infant's father, to participate in research on maternal postpartum mood. Women completed demographic questionnaires and the Beck Depression Index (BDI)⁶⁴ and State-Trait Anxiety Inventory (STAI)⁶⁵ questionnaires. Of the approached women, 39.8% refused participation, and hospital records showed no differences on demographic variables between participating and declining women.

Six months

Of the 1983 women recruited at birth, we wanted to create cohorts of mothers with consistent depression versus mothers without depression. We thus selected women in the high (BDI scores >11) and low (BDI scores 0–5) ends of the depressive symptoms continuum at birth to complete measures of anxiety and depression by mail at 6 months (900 approached, 680 responded (75.5%); no difference in demographics and mood).

Nine months: questionnaires

From the 680 women who responded at 6 months, we again sent questionnaires to those at the high and low ends of the BDI scores at 9 months (350 approached, 254 responded (72.5%); no differences in demographics and mood).

Nine months: home visit

Of the 254 mothers responding at 9 months, we contacted 210 mothers at the high and low ends of the depressive symptoms continuum who did not report high anxiety (STAI score > 43), and 192 agreed to a home visit (91.4%; no differences in demographics and mood). These mothers were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)⁶⁶ and mother–child interactions were videotaped.

Six years: home visit

Of the 192 families seen at 9 months, we contacted all families we were able to locate at 6 years. We visited 156 families (81.2%), and attrition was mainly related to inability to locate families. At 6 years, mothers were again diagnosed by a clinical psychologist with the SCID-I,⁶⁶ and children diagnosed with the Development and Well-Being Assessment (DAWBA,⁶⁷ see below). This led to two cohorts: 46 mothers who reported high depressive symptoms at birth, 6 and 9 months and were diagnosed with Axis I depression at both 9 months and 6 years, and 103 mothers who reported no elevated symptoms at any time point and had no psychiatric diagnosis.

Ten years: home visit

We visited 125 families (80.1%) of the families visited at 6 years, and attrition was again mainly related to inability to locate families. Maternal and child psychiatric conditions were again diagnosed with the SCID-I and DAWBA, to form three groups: (a) early depression, defined as children exposed to maternal depression across the first 6 years but not at 10 years; (b) later depression, defined as children exposed to maternal depression at late childhood regardless of previous MDD diagnosis; and (c) healthy controls, defined as children whose mothers without an MDD diagnosis or any other psychiatric diagnosis across the first decade.

Eleven years: MEG

We were able to locate and contact 110 families and 90 underwent MEG scanning, excluding children with metal implants (81.8%). Of these, 16 children were in the later depression group, 13 children were in the early depression group, and 45 children were in the healthy control group. MEG data was available for 74 participants (43 boys; mean age 11.0 years, s.d. 1.07). Data were excluded because of muscle artifacts, movement or inability to complete session. Groups did not differ in terms of age ($F(2,73) = 0.54$, $P = 0.592$), gender ($\chi^2(2) = 2.19$, $P = 0.334$), birth order ($\chi^2(2) = 0.41$, $P = 0.816$) and current diagnosis of psychiatric disorders ($\chi^2(2) = 1.19$, $P = 0.551$).

Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the Institutional Review Board of Bar Ilan University, Israel (approval number 2087). Written informed consent was obtained from all participants. Families received a small gift for participation.

MEG data acquisition, analysis and statistics

Spontaneous brain activity was measured by MEG, when participants rested for 2 min with open eyes (to reduce stress among young participants caused by lying still in a shielded room by themselves with no stimuli to engage). Ongoing brain activity was recorded with whole-head 248-channel magnetometer array (4-D Neuroimaging, Magnes 3600WH) in supine position, inside a magnetically shielded room. Data were sampled online at 1017.23 Hz with a bandpass of 0.1–400 Hz. Reference coils located approximately 30 cm above the head, oriented by the x -, y - and z -axes, were used to remove environmental noise. Five coils were attached to the scalp for recording the head position relative to the 248-sensor array. External noise and heartbeat artifacts were removed with a predesigned algorithm.⁶⁸ Further data analysis were performed with MATLAB R2014b for Windows (MathWorks,

Massachusetts, USA; <https://matlab.mathworks.com>) and FieldTrip 2016 toolbox for Windows (Donders Institute, Nijmegen, Netherlands; <https://www.fieldtriptoolbox.org>).⁶⁹ Data were segmented into 1000 ms epochs (with 500 ms overlap). Trials containing muscle artifacts and signal jumps were excluded by visual inspection. Data were then filtered in the 1–100 Hz range, with 5 s of padding. To clean eye blinks, eye movements and leftover heartbeats, spatial component analysis was applied. Finally, visual inspection was conducted and contaminated trials were excluded.

DMN seed coordinates were predefined based on prior MEG functional magnetic resonance imaging research.⁷⁰ Head shape was normalised to fit a child's brain template from the Montreal Neurological Institute, using SPM8 for Windows (Wellcome Department of Imaging Neuroscience, University College London, UK; www.fil.ion.ucl.ac.uk). Brain volumes were divided into a regular 1-cm grid. For each grid position, spatial filters were reconstructed to record activity from location of interest while suppressing other activity.

Consistent with prior research,¹⁸ DMN connectivity was calculated by extracting time series from the activation seeds after applying a linear-constrained minimum-variance beamformer⁷¹ in the theta band (4–7 Hz). Next, we computed the phase-lock value (PLV) between all seed pairs ($\binom{7}{2} = 21$ pairs). PLV measures the phase difference between two recorded signals to quantify phase consistency difference over time.⁷² Differences in averaged PLV connectivity were tested by a one-way ANOVA, with early depression, late depression and healthy control groups as between-participant factors. To detect specific significant DMN seed pairs, a series of *F*-tests were conducted between groups for each of the 21 seed pairs and corrected for multiple comparisons by nonparametric permutation tests.^{18,73} For each permutation, an independent *F*-test was repeated 1000 times, group was randomly assigned for each participant and the number of significant ($P < 0.05$) seed pairs was recorded. A frequency distribution of the number of significant seed pairs was used to determine the critical significant seed-pair size, which corresponded to the 50th maximal number (5%).

Measures across the first decade

Maternal and child psychiatric conditions

Mothers were diagnosed at 9 months, 6 years and 10 years, with the SCID-I.^{36,74} Child psychiatric disorders was diagnosed by a clinical psychologist at 6 and 10 years, using the DAWBA,⁶⁷ a well-validated tool.²⁷ Diagnoses were conducted by four clinical psychologists supervised by child psychiatrist who were blind to all information, with cases conferred every few weeks and reliability above 85%.

Mother intrusiveness at 9 months

We filmed 10 min of mother and child free-play 9 months.⁷⁵ Interactions were coded with the Coding Interactive Behavior (CIB) manual,⁷⁶ a well-validated coding scheme with good psychometric properties.⁷⁷ Two coders, trained to 85% reliability and blind to all other information, coded the interactions, with interrater reliability computed for 20% of interactions exceeding 87% (intraclass $r = 0.91$, range 0.87–0.99). The 'maternal intrusiveness' construct included maternal overriding, forcing, anxiety/hostility, parent-led interactions and inconsistent parenting (Cronbach's alpha 0.90).

Mother–child reciprocity at 10 years

Mothers and their children engaged in positive and negative discussion paradigms.⁶⁰ The reciprocity construct was similarly coded by trained coders using the CIB, with interrater reliability for 20% of

interactions exceeding 89% (intraclass $r = 0.92$, range 0.88–0.99), and included synchrony, mutual adaptation, fluency, recognition of partner's signals, containment, behavioural empathy and giving space (Cronbach's alpha 0.91).

Child empathy at 10 years

Empathy was coded from two observational paradigms, which exposed children to the experimenter's distress, hurting their foot and losing an expensive watch, consistent with prior research.⁷⁸ Each episode was coded (1–5) on several scales,⁷⁹ with reliability >90%. The 'empathy' construct was the average of 'empathic concern' and 'maintaining involvement' scales from the two paradigms.

Statistical analyses

Statistical analyses were conducted with SPSS for Windows (IBM statistics version 26) and Jamovi version 1.6 for Windows (Jamovi project, Sydney, Australia; <http://www.jamovi.org>). Differences between groups were assessed via one-way ANOVAs and *post hoc* pairwise comparisons. The Bonferroni–Holm method⁷⁹ was used for controlling the family-wise error rate. Hierarchical logistic regression assessed added and cumulative contribution of measures across the first decade of life to neurotypical/aberrant DMN connectivity. R^2 was assessed with McFadden's method, and a receiver operating characteristic analysis was performed to graphically represent the connection and trade-off between clinical sensitivity and specificity for every possible cut-off of each test or combination of tests.⁸⁰

Results

DMN connectivity

Significant group effect was found for overall averaged DMN PLV connectivity ($F(2,71) = 6.21$, $P = 0.003$, $\eta^2 = 0.149$). Pairwise comparisons indicated (Fig. 1(c)) higher PLV in the later depression group (mean 0.569, s.d. 0.149) relative to healthy controls (mean 0.483, s.d. 0.111) ($t(59) = 2.54$, $P = 0.026$) and the early depression group (mean 0.418, s.d. 0.086) ($t(27) = 3.46$, $P = 0.003$). Children in the early depression group displayed marginally significant lower PLV than healthy controls ($t(56) = -1.75$, $P = 0.084$). Importantly, within the later depression group, there were no differences between children of mothers with continuous depression since birth ($n = 9$, mean 0.578, s.d. 0.186) and those whose mothers were diagnosed with MDD at 10 years ($n = 7$, mean 0.557, s.d. 0.097) ($t(14) = 0.271$, $P = 0.79$).

Post hoc analyses revealed seven significant seed-pair connections. The permutation analysis indicated that these did not reflect false positives ($P = 0.001$). Of these, four connections indicated significantly higher connectivity for the later depression group relative to the healthy control group, and three indicated significantly lower connectivity for the early depression group relative to the healthy control group (all $P < 0.05$). The PCC-dorsomedial prefrontal cortex (dMPFC), PCC-ventromedial prefrontal cortex (vMPFC), vMPFC and right angular gyrus (RAG)-right medial prefrontal cortex (RMPFC) displayed higher connectivity for the later depression group relative to the healthy control group (Fig. 2(a,c)); the RAG-PCC, RAG-vMPFC and vMPFC-left inferior temporal gyrus (LITG) displayed lower connectivity for the early depression group relative to the healthy control group (Fig. 2(b,d)).

Predicting aberrant DMN connectivity from variables across the first decade

Following the results indicating extreme (low or high) DMN values in children exposed to early or later maternal MDD, the DMN PLV

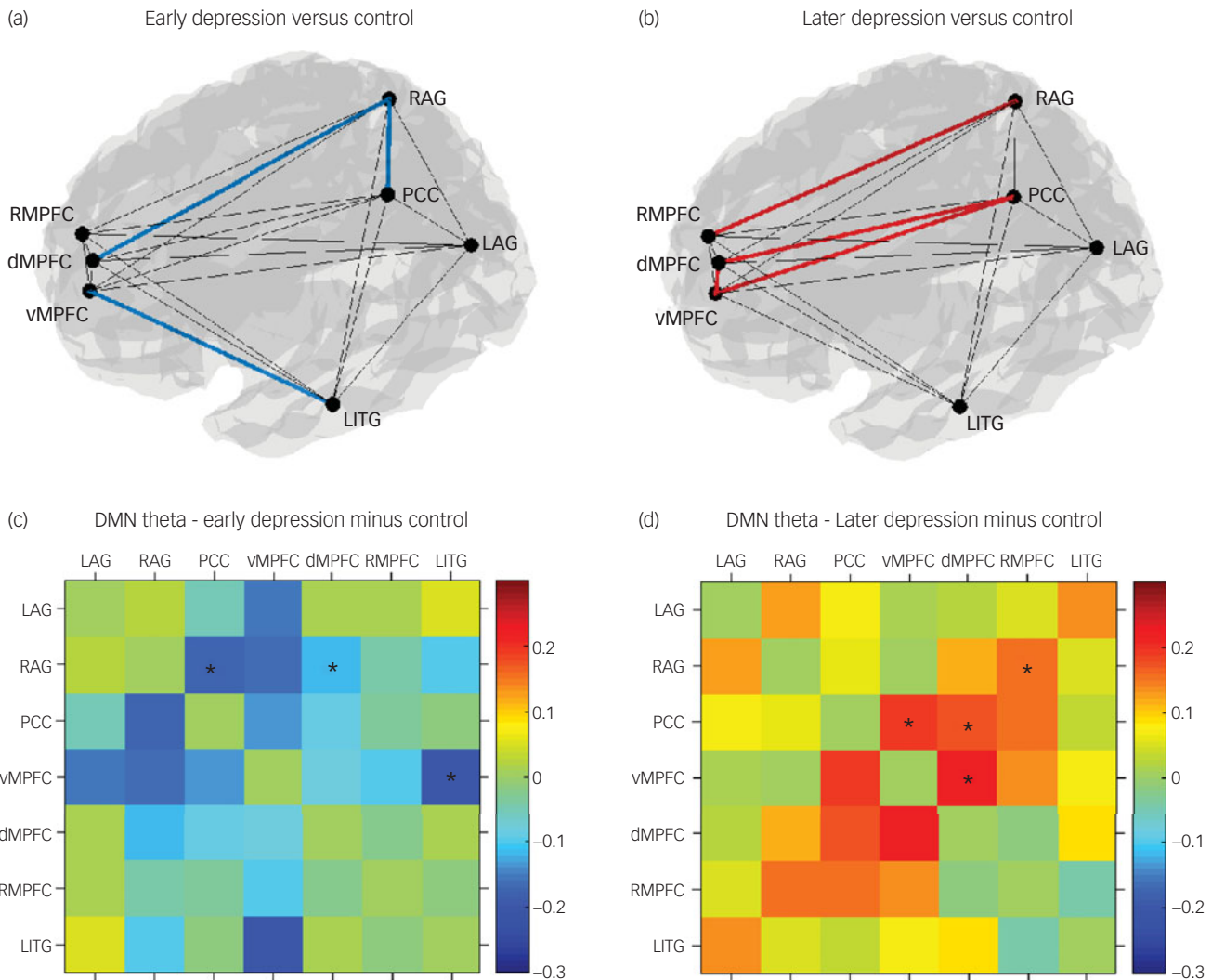


Fig. 2 Default mode network (DMN) phase-lock value (PLV) connectivity differences between children exposed to early maternal depression ($n = 13$) (a and c) and later maternal depression ($n = 16$) (b and d), relative to healthy controls ($n = 45$). (a and b) All possible seed-pair DMN PLV connections, with black lines indicating non-significant connections, blue lines indicating connections weaker than controls and red lines indicating connections stronger than controls. (c and d) Strength of connectivity values between the different DMN nodes. Significant connections are marked by *. dMPFC, dorsomedial prefrontal cortex; LAG, left angular gyrus; LITG, left inferior temporal gyrus; PCC, posterior cingulate cortex/precuneus; RAG, right angular gyrus; RMPFC, right medial prefrontal cortex; vMPFC, ventromedial prefrontal cortex.

connectivity values of all participants were classified either as mid-level connectivity (second and third quartiles), high connectivity (fourth quartile) or low connectivity (first quartile). One-way ANOVAs indicated significant group differences for maternal intrusiveness at 9 months ($F(2,71) = 3.75$, $P = 0.028$, $\eta^2 = 0.095$), and mother-child reciprocity ($F(2,68) = 7.96$, $P < 0.001$, $\eta^2 = 0.19$) and child empathy ($F(2,67) = 5.88$, $P = 0.004$, $\eta^2 = 0.149$) at 10 years. Descriptive statistics showed that the high-connectivity and low-connectivity groups differed from the mid-level connectivity group on all three measures but did not differ from each other. Infants in both high-connectivity and low-connectivity groups experienced more maternal intrusiveness (high connectivity: $\text{mean}_{\text{difference}} = 0.514$, $\text{s.e.}_{\text{difference}} = 0.219$, $t(54) = 2.2$, $P = 0.023$; low connectivity: $\text{mean}_{\text{difference}} = 0.486$, $\text{s.e.}_{\text{difference}} = 0.221$, $t(53) = 2.2$, $P = 0.032$) and less reciprocity (high connectivity: $\text{mean}_{\text{difference}} = -0.378$, $\text{s.e.}_{\text{difference}} = 0.129$, $t(51) = -2.94$, $P = 0.005$; low connectivity: $\text{mean}_{\text{difference}} = -0.427$, $\text{s.e.}_{\text{difference}} = 0.104$, $t(50) = -4.12$, $P < 0.001$), and showed decreased empathy (high connectivity: $\text{mean}_{\text{difference}} = -0.485$, $\text{s.e.}_{\text{difference}} = 0.243$, $t(51) = -2$, $P = 0.051$; low connectivity: $\text{mean}_{\text{difference}} = -0.766$, $\text{s.e.}_{\text{difference}} = 0.247$, $t(50) = -3.1$, $P = 0.003$),

compared with the mid-level connectivity group. Additionally, the high-connectivity and low-connectivity groups did not differ on intrusiveness, reciprocity and empathy (all $P > 0.3$). Thus, high-connectivity and low-connectivity groups were combined into an aberrant connectivity group. Fig. 3(a) presents t -tests indicating significant differences (Holm-Bonferroni corrected) between the aberrant connectivity and control (mid-level connectivity) groups for intrusiveness ($t(72) = 2.75$, $P = 0.007$), reciprocity ($t(69) = -4$, $P < 0.001$) and empathy ($t(68) = -3.44$, $P = 0.003$). Notably, the aberrant and mid-level DMN connectivity (control) groups did not differ on child psychiatric disorders at a 6 or 10 years (overall psychopathology, mood disorders or externalising disorders) (all $P > 0.3$).

To test the effects of caregiving and socio-emotional factors across the first decade on DMN connectivity (aberrant versus mid-level) in preadolescence, a hierarchical logistic regression analysis was conducted. Specifically, we tested the added and cumulative predictive utility, beyond age and gender (step 1), of maternal intrusiveness at 9 months (step 2), and mother-child reciprocity and child empathy at 10 years (step 3; see Table 1), on aberrant

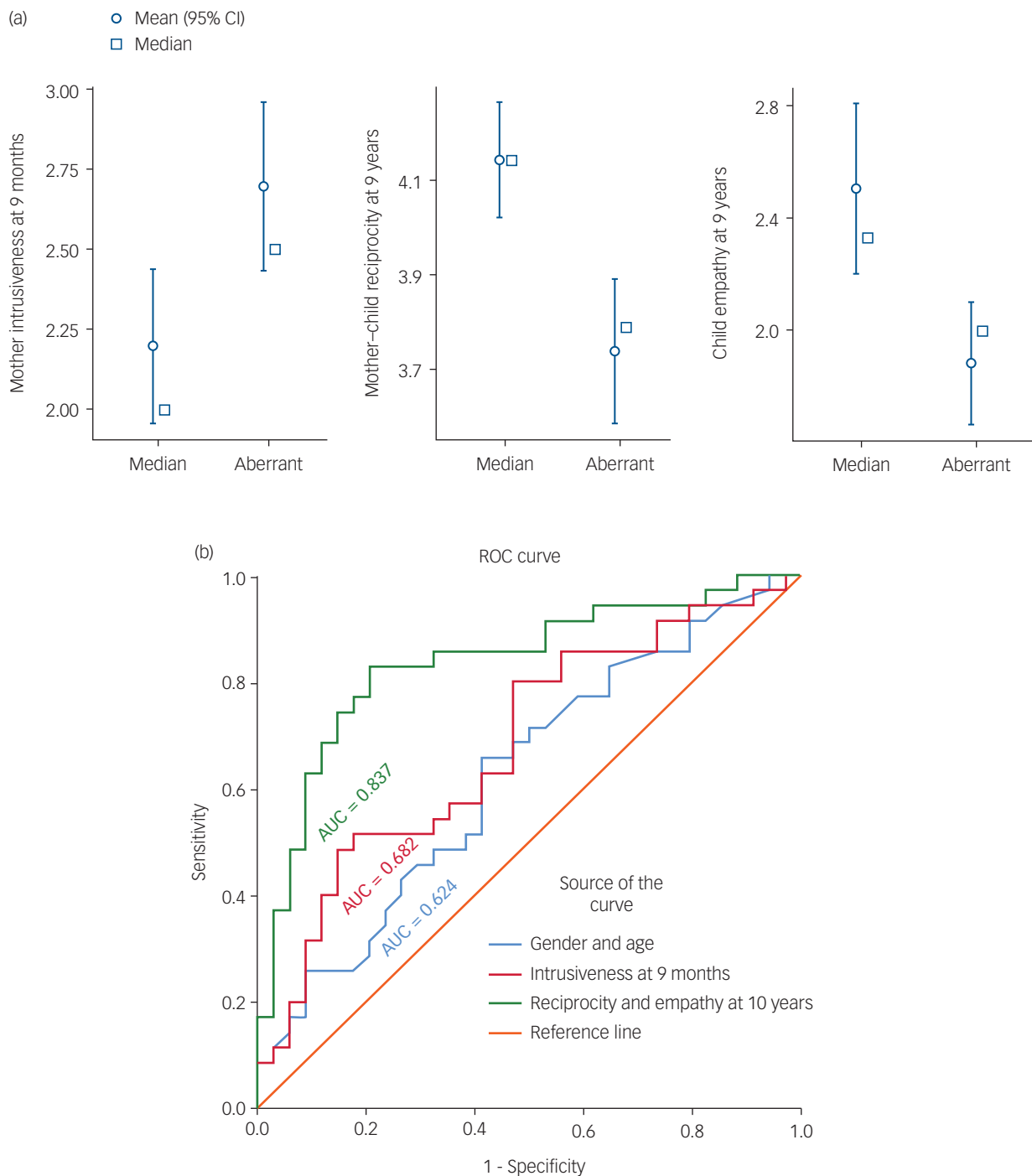


Fig. 3 (a) Means, medians and 95% confidence intervals of mother intrusiveness at 9 months of age, mother-child reciprocity at 10 years of age, and child empathy at 10 years of age, for default mode network (DMN) mid-level connectivity (controls: $n = 37$) and DMN aberrant connectivity ($n = 37$) groups. (b) Receiver operating characteristic (ROC) curves of the gender/age variables (blue) compared with a model also including intrusiveness (red), and a model also including reciprocity and empathy variables (green). Reference line (orange) denotes chance-alone classification level.

Table 1 Hierarchical logistic regression results for step 3 model

Step 3 model		B	s.e.	d.f.	P-value	Exp(B)	95% CI	
							Lower	Upper
9 months	Age	0.473	0.301	1	0.116	1.604	0.890	2.891
	Gender	0.288	0.618	1	0.642	1.333	0.397	4.476
10 years	Maternal intrusiveness	0.307	0.391	1	0.432	1.359	0.632	2.922
	Empathy	-0.942	0.384	1	0.014	0.390	0.184	0.827
	Reciprocity	-2.435	0.875	1	0.005	0.088	0.016	0.487
	Constant	5.358	4.927	1	0.277	212.302		

DMN connectivity at preadolescence. Results indicated that although age/gender (step 1) were not significantly predictive ($\chi^2(2) = 3.4, P = 0.182$), when entering maternal intrusiveness (step 2) ($\chi^2(3) = 8.17, P = 0.043, R_{McFadden}^2 = 0.086$), the model significantly predicted aberrant DMN connectivity, and the further addition of reciprocity and empathy (step 3) ($\chi^2(5) = 27.68, P < 0.0001, R_{McFadden}^2 = 0.29$) contributed meaningfully to prediction. Statistically significant increments in the regression models were observed for step 2 versus step 1 ($\chi^2_{difference}(1) = 4.77, P = 0.029$), and step 3 versus step 2 ($\chi^2_{difference}(2) = 19.51, P < 0.0001$).

Final models were further submitted to receiver operating characteristic analysis. Three curves were plotted (Fig. 3), each corresponding to age and gender (step 1), mother intrusiveness (step 2) and reciprocity and empathy (step 3) factors. The area under the curve (AUC) for the age and gender model was not significant beyond chance-alone reference (AUC = 0.624, s.e. 0.067, $P = 0.076$; 95% CI 0.49–0.75); however, the AUCs for both mother intrusiveness (AUC = 0.682, s.e. 0.064, $P = 0.009$; 95% CI 0.55–0.81) and reciprocity/empathy (AUC = 0.837, s.e. 0.05, $P < 0.000$; 95% CI 0.74–0.93) were significant and indicate an excellent diagnostic accuracy.⁸⁰ The contribution of the final step 3 model (maternal intrusiveness, reciprocity and empathy) beyond the age and gender variables increased the AUC by 21.3%, with marginal overlap (of 1%) of the 95% confidence interval, indicating an important and significant contribution to the distinction of aberrant versus healthy control DMN connectivity.

Discussion

Timing effects, the differential effects of environmental adversities experienced at different stages of brain maturation, has rarely been tested in prospective longitudinal research. By utilising a unique community cohort followed from birth to preadolescence and repeatedly evaluating maternal MDD, we were able to pinpoint, for the first time, the effects of exposure to maternal depression in early life from the effects of late-childhood exposure on the DMN, a core network sustaining multiple self-related functions. We found that DMN connectivity in the theta band, the pronounced rhythm of the developing brain, was impaired in children exposed to maternal MDD in a time-sensitive manner. Exposure in early life reduced DMN connectivity, paralleling the profile of trauma or early adversity, whereas exposure in late childhood led to tighter DMN connectivity, mirroring the findings for adult depression and presenting cross-generational similarity. Aberrant DMN connectivity, whether hyper- or hypo-connectivity, was predicted by age-specific disruptions to caregiving – intrusive mothering in infancy⁸¹ and lower reciprocity in late childhood – presenting deficiencies in the dialogical and empathic dyadic style associated with maternal depression.⁴ Children's capacity for empathy, which is shaped by the experience of reciprocal parenting,⁸² was similarly deficient in children of mothers with depression, and predicted aberrant DMN connectivity, consistent with prior research indicating that breaches in caregiving and disruptions in core socio-emotional competencies impair DMN maturation.^{18,58,83}

The reduced DMN connectivity found for the early depression group is consistent with prior studies showing decreased DMN connectivity in preadolescence in the context of early trauma.¹⁸ In both studies, the decreased connectivity implicated connectivity with RAG.^{18,84} The RAG plays a key role in social cognition and emotion regulation, which are impaired in children of mothers with depression.^{85–87} The reduced connectivity of the RAG with the PCC and dMPFC found in both studies supports the hypothesis that early maternal depression that abates before the child reaches puberty may be registered in the brain as early trauma. Further,

reduced RAG-PCC connectivity was observed in adults who experience early-life trauma.²⁰ The RAG is more active during psychological stress, and is critically involved in attention and mental functions, social cognition and emotion regulation, factors that are impaired in children and adolescents of mothers with depression and in those suffering from early trauma.^{85–89} Hence, reduced RAG connectivity may augment the effects of early maternal depression on social and mental dysfunctions in later life, similar to early trauma.


In contrast, exposure to MDD in later childhood increased DMN connectivity. Specifically, findings show tighter connectivity in the DMN's medial nodes. The DMN midline structures were found to be consistently and conjointly activated during self-related processing,^{15,90–92} and are suggested to underpin the sense of self.^{93,94} The DMN undergoes hierarchical DMN organisation and integration, and at the transition to adolescence, DMN activity and connectivity become similar to that of adults.⁹⁵ Specifically, a gradual increase in functional connectivity between anterior and posterior DMN regions takes place between 7 and 15 years⁹⁶ and between 10 and 13 years,⁹⁷ suggesting that preadolescence is a sensitive period for maturation of the DMN's functional architecture. Our findings suggest that exposure to maternal MDD in late childhood may have distinct effects on DMN functionality that may undermine the development of the sense of self.

Depression is often accompanied by persistent ruminations³⁴ that are self-focused³⁵ and implicate heightened activity and connectivity over the DMN's midline structures.^{15,35,98,99} Our findings show a similar pattern of increased connectivity in medial nodes of the DMN in preadolescents exposed to maternal MDD in late childhood. It is possible that in preadolescence, the child's brain activity presents a profile that resembles that of the mother with MDD. Such a parallel in the depressive profile is consistent with extant research indicating that exposure to maternal depression in early childhood increases rates of child anxiety disorders while exposure to maternal depression by late childhood/adolescence leads to depression.^{79,100,101}

Both maternal caregiving and child socio-emotional outcomes have been linked with DMN activity,^{18,84} and our findings are consistent with this research. Mother-child reciprocity and children's empathic capacities predicted normative versus aberrant DMN connectivity in preadolescence above and beyond exposure to maternal depression. These findings have clinical implications for the ever-increasing population of children exposed to maternal depression. Dyadic interventions aimed at improving the mother's ability to engage in reciprocal dialogue that acknowledges the child's verbal and nonverbal communications and respects multiple perspectives, particularly in late childhood, may have important implications for neural development at the transition to adolescence.

Several limitations should be acknowledged. First, although longer MEG recordings of the resting state are preferable, previous experiments with children^{18,84} have indicated that children are unable to stay still in isolated shielded environments for longer periods. Second, we did not conduct assessments of mothers and children between 6 and 10 years, which could have allowed for a more fine-grained clinical grouping. Third, the small number of children in the late childhood exposure group did not allow further division of this group into those exposed to chronic depression versus those experiencing only late depression, although our comparisons show no differences between these two subgroups on any study variable. Future research is needed to follow up on our findings with larger samples. It is important to note that large community cohorts followed from birth to preadolescence with repeated assessments of both mother and child, are rare at best, and all longitudinal studies of maternal depression involve highly heterogeneous clinical samples. Our unique sample may be important in

pinpointing specific factors across the first decade of life that may uniquely affect DMN consolidation in a time-sensitive manner. Future studies can build on these results and examine differential DMN connectivity patterns following early and later exposure to other adversities, including abuse, mass trauma and other parental psychopathology. The findings that early childhood exposure that later resolves leaves its mark on the brain in the form of early trauma, whereas later childhood exposure leads to adult-like aberrations, may help in the diagnosis and treatment of children of mothers with depression. Furthermore, implementing a ‘sensitive period’ in careful longitudinal brain research, and applying the findings toward intervention efforts, may assist in the development of more targeted, efficient interventions for children exposed to various forms of trauma and adversity at different stages of development.

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Data availability

The data that support the findings of this study are available from the corresponding author, R.F., upon reasonable request.

Author contributions

M.Z.-W. and Y.D.-Z. contributed to data analysis, interpretation of data and drafting the manuscript, and approved the manuscript for publication. M.P. contributed to the conception of the study and data acquisition, and approved the manuscript for publication. A.G. contributed to the conception of the study and approved the manuscript for publication. R.F. oversaw the longitudinal studies, conceptualisation the study, contributed to data analysis, interpretation of data and writing the manuscript, and approved the manuscript for publication.

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Declaration of interest

None.

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