Biological Psychiatry: CNNI

Archival Report

Chronic Early Stress Impairs Default Mode Network Connectivity in Preadolescents and Their Mothers

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ABSTRACT

BACKGROUND: Early life stress (ELS) bears long-term negative consequences throughout life. Yet ELS effect is mostly unknown, and no study has followed children to test its impact on the default mode network (DMN) in relation to maternal behavior across childhood. Focusing on brain oscillations, we utilized a unique cohort of war-exposed preadolescent children (11–13 years of age) and their mothers followed from early childhood to examine the effects of ELS combined with observed parenting on DMN connectivity and power in mother and child.

METHODS: Participants included 161 mothers and children (children: 39 exposed/36 control subjects; mothers: 44 exposed/42 control subjects) who underwent magnetoencephalography scanning during rest.

RESULTS: Stress exposure reduced DMN connectivity in mother and child; however, in mothers, the impaired connectivity occurred in the alpha band, whereas among children it occurred in the theta band, a biomarker of the developing brain. Maternal anxiety, depression, and posttraumatic symptoms in early childhood predicted lower maternal DMN connectivity. Among children, the experience of intrusive, anxious, and uncontained parenting across the first decade and greater cortisol production in late childhood predicted reduced DMN connectivity in preadolescence. Impairments to theta DMN connectivity increased in children with posttraumatic stress disorder.

CONCLUSIONS: Findings indicate that ELS disrupts the synchronous coordination of distinct brain areas into coherent functioning of the DMN network, a core network implicated in self-relevant processes. Results suggest that one pathway for the lifelong effects of ELS on psychopathology and physical illness relate to impaired coherence of the DMN and its role in maintaining quiescence, alternating internal and external attention, and supporting the sense of self.

Keywords: Cortisol, Default mode network, Early life stress, Magnetoencephalography, MEG, Mother-child interactions, Neural oscillations

https://doi.org/10.1016/j.bpsc.2018.09.009

Early life stress (ELS), chronic stress that begins early and persists across the initial period of brain maturation, bears long-term negative consequences throughout life. Individuals exposed to ELS are more susceptible to psychiatric disorders, social maladjustment, dysfunctional stress response, and impairments in brain structure and function (1,2). Yet, despite the fact that ELS is the most prevalent adversity, impacting millions of children worldwide, research on its long-term effects has some methodological limitations that leave open several key issues. First, studies on ELS typically rely on adults' retrospective accounts of their childhood experiences, and very few studies followed children prospectively from infancy. Second, ELS interacts with early caregiving patterns that augment or buffer its toxic effects; still, no study utilized repeated observations of caregiving over time to examine the combined effects of early stress and parenting on later brain function. Finally, ELS is a heterogeneous construct, including individuals experiencing a wide range of adversities, thereby limiting specificity of its detrimental elements. Here, we utilized a unique cohort of war-exposed preadolescents and their mothers followed from early childhood to test the effects of a distinct ELS condition combined with observed parenting on default mode network (DMN) connectivity in mother and child.

The DMN is a network of cortical areas that becomes more active during rest and deactivates when the brain is engaged in task-related activity (3). It comprises several regions, including the left angular gyrus (LAG) and right angular gyrus (RAG), posterior cingulate cortex (PCC)/precuneus, ventromedial prefrontal cortex (vMPFC), dorsomedial PFC (dMPFC), right medial PFC, and left inferior temporal gyrus (LITG) (4). The DMN plays a critical role in self-referential mental activity, intrinsic focus, integration of internal and external attention, and recollection of past experiences; thus, it is a core system that colors both the sense of self and experience of the external world (3,5). DMN functioning is sensitive to multiple psychiatric conditions, including stress-related disorders (6–10). Furthermore, research on the relations of DMN and stress may shed light on the effects of chronic stress on the

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brain (11–13). Core symptoms implicated in stress-related disorders define disruptions to functions supported by the DMN, such as modulation of hypervigilance (11), alterations of intrinsic and extrinsic attention (12,13), self-referential mental activity (14–16), and recollection of past experiences (17).

Few studies have investigated the relationships of DMN and stress. Compared with control subjects, trauma-exposed veterans showed lower connectivity among DMN nodes including the precuneus, medial PFC, and right superior parietal lobule, regardless of posttraumatic stress disorder (PTSD) status (18). Women with childhood-abuse PTSD displayed reduced connectivity in the PCC/precuneus (6), and both 16-year-old adolescents and young adults growing in poverty exhibited lower DMN connectivity (19,20). While it was suggested that ELS interferes with the development of the DMN (21), no study has examined the effects of ELS on DMN functioning in children.

In adults, the strongest activity in DMN during rest is observed in the alpha band (8–12 Hz), the dominant rhythm of the awake brain (22,23). Yet evidence suggests that spontaneous brain rhythms change throughout life, and alpha activity develops with age, reaching its peak in adulthood (24). In childhood, the more pronounced rhythm is observed in the theta band (4–7 Hz), and research indicates a gradual shift from theta to alpha as children develop (25,26). In a sample of 6-to-16-year-olds (n = 324), a linear trend was found, with low frequencies (<7.5 Hz) decreasing with age and higher frequencies increasing across the same period. While we are unaware of any study that has examined the effects of stress on DMN oscillatory rhythms in adults or children, higher resting-state alpha power has been associated with increased anxiety (27–30). Similarly, anxious individuals exhibited greater theta power, and theta activity in midcingulate cortex correlated with pervasive stress in anxious individuals.

The current study utilized a unique cohort of mothers and children living in Sderot, a small Israeli town on the Gaza border that has been subjected to continuous war-related trauma for nearly two decades, affording a unique "natural experiment" in which all participants in the sample experience the same stress, and individual and contextual factors differentiate among participants. Sderot has been the target of continuous rocket attacks since 2001, with six periods of exacerbations, during which the town was under attack by dozens of daily missiles for several days to several weeks. During attacks, citizens hear a siren warning, leaving them 7 to 15 seconds to reach shelters before an explosion. Even during relatively calm periods, a security threat looms on a daily basis, with occasional missiles launched every few days or weeks.

Patterns of mother–child interaction and cortisol levels were assessed in early and late childhood, and DMN connectivity was measured at rest in preadolescence (11–13 years of age) with magnetoencephalography (MEG). MEG uniquely combines high temporal resolution with adequate corticospatial localization that can describe oscillatory mechanisms implicated in DMN connectivity in children and adults exposed to a specific chronic stress condition. We hypothesized that stress-exposed mothers and children would show lower DMN connectivity in the typical oscillatory band of their age, that is, alpha for mothers and theta for children (hypothesis 1). We also expected that patterns of maternal care across the first decade would impact DMN connectivity. We focused on the mother's intrusive style—the mother's negative, anxious, dyssynchronous, and dysregulating behavior that has shown to predict attachment insecurity, stress reactivity, and psychopathology in children (31–33)—and we expected anxious-intrusive mothering to predict greater disruptions to DMN connectivity (hypothesis 2). Additionally, mothers' emotional symptoms, including anxiety, depression, and PTSD, were expected to interfere with maternal DMN connectivity (hypothesis 3), and greater child cortisol production, indexing greater ELS-derived allostatic load, would predict impaired child DMN connectivity (hypothesis 4).

METHODS AND MATERIALS

Participants

Participants included 232 mother–child pairs in two groups who were observed four times. Details of the first three assessments appear elsewhere (34).

T1: Early Childhood. In early childhood (time 1 [T1]), the initial sample (n = 232) included 47.6% boys and 47.1% firstborns (mean age 2.76 ± 0.91 years). The war-exposed group included 148 families living in the same neighborhoods in Sderot, Israel, located 10 km from the Gaza border. The control group included 84 nonexposed families from comparable towns in the Tel-Aviv area matched to the exposed group by age, gender, birth order, parental age and education, maternal employment, and marital status and subsequently screened for trauma. At T2 (middle childhood), children underwent psychiatric diagnosis; however, we do not use these data here.

T3: Late Childhood. At late childhood (mean age 9.3 ± 1.41 years), 177 families were revisited: 101 war-exposed and 76 control families. Attrition was mainly related to inability to locate families or families moving out of Sderot.

T4: Preadolescence. A total of 161 participants (75 children [43 girls] and 86 mothers), containing 39 war-exposed children and 44 war-exposed mothers, participated in MEG scanning at preadolescence (children's mean age 11.81 ± 1.24 years), including 66 mother–child dyads (33 war-exposed families). Table 1 presents demographic/background information.

Of 111 children initially recruited at T4, 36 did not yield MEG data: 18 were MEG incompatible (mostly owing to metal implants), 6 refused MEG scan, and 12 did not complete the experiment. Of 108 mothers initially recruited at T4, 22 did not yield MEG data: 12 were MEG incompatible (owing to metal implants), 4 refused MEG scan, 5 did not complete the experiment, and 1 had noisy data due to eye movements.

The study was approved by local institutional review board, and written informed consent was obtained from parents after receiving a complete description of the study.

Procedure and Measures

T1: Early Childhood. During the 3.5-hour home visit, a 10-minute mother–child interaction with age-appropriate toys was filmed. Mothers completed the State-Trait Anxiety Inventory (34), Beck Depression Inventory (35), and Posttraumatic Stress

Table 1. Demographic Details

	Exposed Group		Control Group			
	n	Mean ± SD	*n*	Mean ± SD	*t* or χ^2 (*df*)	*p*
Children						
Age, years		11.93 ± 1.35		11.59 ± 1.12	1.15 (73)	NS
Rooms in the house		4.26 ± 1.06		4.37 ± 1.28	−0.41 (73)	NS
IQ-P at T3[a]		11.16 ± 2.56		11.34 ± 2.52	−0.29 (73)	NS
IQ-V at T3[a]		11.49 ± 2.64		11.13 ± 2.76	0.56 (73)	NS
Gender, boys/girls	22/17		10/26		4.5 (1)	.034
Birth order (firstborn/not firstborn)	16/23		21/14		2.65 (1)	NS
Mothers						
Age, years		40.14 ± 5.98		40.83 ± 4.53	−0.61 (84)	NS
Rooms in the house		4.19 ± 1.06		4.63 ± 1.39	−1.65 (84)	NS
Education (high school/academic)	13/31		6/36		2.9 (1)	NS
Marital status (married/single[b])	42/2		39/3		0.61 (1)	NS

IQ-P, Wechsler Intelligence Scale for Children–Revised blocks subtest; IQ-V, Wechsler Intelligence Scale for Children–Revised 95 vocabulary subtest; NS, not significant; T3, time 3.

[a]Standardized score.

[b]Single indicates divorced, widowed, or single parent.

Diagnostic Scale (36), and their combined *Z*-score was termed maternal emotional distress.

T3: Late Childhood. During the 3-hour home visit, the Development and Well-Being Assessment was used to diagnose child Axis I disorders. The Development and Well-Being Assessment is a well-validated structured interview generating ICD-10 and DSM-IV psychiatric diagnoses in 5- to 17-year-old children (37) and was administered by clinicians supervised by a child psychiatrist, blinded to other information, with reliability >85% and cases conferred every few weeks.

Mothers and children were observed in two interactive paradigms involving positive and conflict dialogue, each lasting 7 minutes (33). Interactions at T1 and T3 were coded with the well-validated Coding Interactive Behavior Scale (38), and the maternal intrusiveness construct (5-point Likert-type scale with responses ranging from 1 [low] to 5 [high]) was used, comprising the scales of maternal overriding, negative affect, hostility, anxiety, and dysregulation (alpha: T1 = .78, T3 = .71). Coding was conducted by trained coders, with 20% of tapes coded for reliability. Reliability exceeded 90% on all codes (intraclass *r* = .94, range = .90–.99).

Cortisol (CT) was measured three times between 3:00 and 6:00 PM (at baseline, following testing and interaction, and at recovery [15 minutes after termination of procedures]) by the mother's putting a Salivette (Sarstedt, Rommelsdorf, Germany) in the child's mouth for 1 minute. Salivettes were kept cooled and then stored at −20°C until being centrifuged twice at 4°C at 1500*g* for 15 minutes. CT levels were assayed using a commercial enzyme-linked immunosorbent assay kit (Assay Designs, Inc., Ann Arbor, MI). Measurements were performed in duplicate according to the kit's instructions. CT levels were calculated using MATLAB R2012b (The MathWorks, Inc., Natick, MA) according to the relevant standard curves. The intraassay and interassay coefficients were <10.5% and 13.4%, respectively. Consistent with prior research (33), area under the curve was computed to index overall CT production.

T4: Preadolescence. Spontaneous brain activity was measured using MEG while participants rested with open eyes for 2 minutes. Ongoing brain activity was recorded using a whole-head 248-channel magnetometer array (Magnes 3600WH; 4-D Neuroimaging, San Diego, CA) in supine position inside a magnetically shielded room. Data were sampled online at 1017.23 Hz with bandpass of 0.1 to 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 participants' scalp for recording the head position relative to the 248-sensor array. External noise and heartbeat artifacts were removed using a predesigned algorithm (38). Further data processing and analysis were performed using MATLAB and the FieldTrip toolbox (39). Data were segmented into 1000-ms epochs (with 500-ms overlap between neighboring epochs). Trials containing muscle artifacts and signal jumps were excluded from further analysis by visual inspection. Data were then filtered in the 1- to 100-Hz range with 10 seconds' padding (to avoid distortion of the real signal at the ends of trials). To clean eye blinks, eye movements, and leftover heartbeats, spatial component analysis was applied.

DMN seed coordinates were predefined based on prior research (4) in which resting-state MEG data linked with the DMN network defined in functional magnetic resonance imaging studies to detect the equivalent MEG seed coordinates to functional magnetic resonance imaging studies (seed coordinates appear in Supplemental Table S1). Because children's brain anatomy differs from that of adults, we used different brain templates for children and mothers (Montreal Neurological Institute). The templates were modified to fit each participant's digitized head shape using SPM8 (Wellcome Department of Imaging Neuroscience University College London; http://www.fil.ion.ucl.ac.uk). The head shape was manually digitized (FASTRAK digitizer; Polhemus, Colchester, VT), and the participant's brain volume was divided into a regular grid. Grid positions were obtained by linear transformation in a canonical 1-cm grid. This procedure facilitates group analysis

because no spatial interpolation of the volumes of reconstructed activity is required. For each grid position, spatial filters were reconstructed to record activity from location of interest while suppressing other activity.

To calculate DMN connectivity, we extracted time series from the activation seeds by applying a linear-constrained minimum-variance beamformer in two predefined frequency bands: theta (4–7 Hz) for children and alpha (8–12 Hz) for mothers. Next, we computed the phase locking value (PLV) between all seed pairs (21 pairs). The PLV measures the phase difference between two recorded signals to quantify the consistency of the phase difference over time (40). Additionally, for each frequency band, we computed the power in each seed using partial canonical coherence method. This method directly outputs for each location the Fourier coefficients (i.e., phase and amplitude) for each trial, enabling calculation of the average power across trials in each seed.

Statistical Analysis

Differences in DMN connectivity and power were tested using a mixed repeated-measures analysis of variance with frequency band (theta vs. alpha) as the within-subject variable and exposure (exposed vs. control) and family (child vs. mother) as the between-subject variables, on the averaged connectivity/power across seed-pairs/seeds.

To detect specific significant DMN seed-pairs/seeds, a series of *t* tests was conducted in each group between exposed and control. To correct for multiple comparisons across these tests, permutation tests were conducted in each frequency band for connectivity and power in mother and child. In each permutation test, an independent *t* test was repeated 1000 times, group was randomly assigned for each participant, and the number of significant ($p < .05$) seed-pairs/seeds was recorded. This method is a variation of the cluster-based permutation test. A frequency distribution of the number of significant seed-pairs/seeds was served to determine the critical significant seed-pairs/seeds size, which corresponded to the 50th maximal number (5%). In addition, Pearson correlations were computed between mother and child overall DMN connectivity and power within and between theta and alpha bands.

Differences between groups in hormonal, mental health, and behavioral variables were assessed with *t* tests with Bonferroni's correction, and hierarchical linear regressions were computed to predict DMN connectivity in mother and child from variables cross the first decade.

RESULTS

DMN Connectivity and Power

A significant three-way interaction among frequency band, family, and exposure was found for DMN connectivity (PLV) only ($F_{1,156} = 10.33$, $p < .01$). Results for each group appear below.

Children. Group differences were found in the theta band, indicating higher PLV in control (mean 0.6 ± 0.11) compared with exposed (mean 0.54 ± 0.15) subjects ($t_{73} = 1.99$, $p = .05$). Post hoc analysis revealed higher connectivity in the following pairs among control subjects; RAG-PCC, RAG-dMPFC, and RAG-LITG (see Table 1, Figure 1, and Figure 2A for full results).

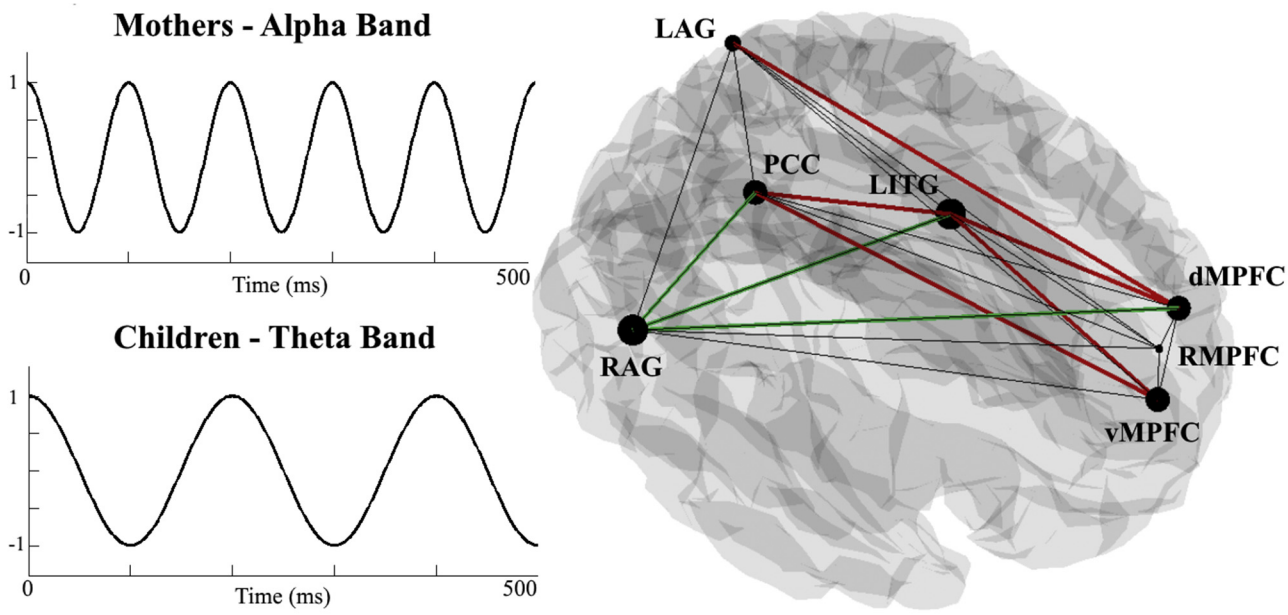

Figure 1. Default mode network connectivity in war-exposed and control children and mothers. Differences in default mode network connectivity between the exposed and control groups. On the left side, an illustration of the two frequencies tested in this study: alpha band for mothers and theta band for children. On the right side, an illustration of all two-seed pairs in the default mode network. Red lines indicate significant pairs in which exposed mothers had lower levels of connectivity than control mothers, while green lines indicate significant pairs in which exposed children had lower levels of connectivity than control children. 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.

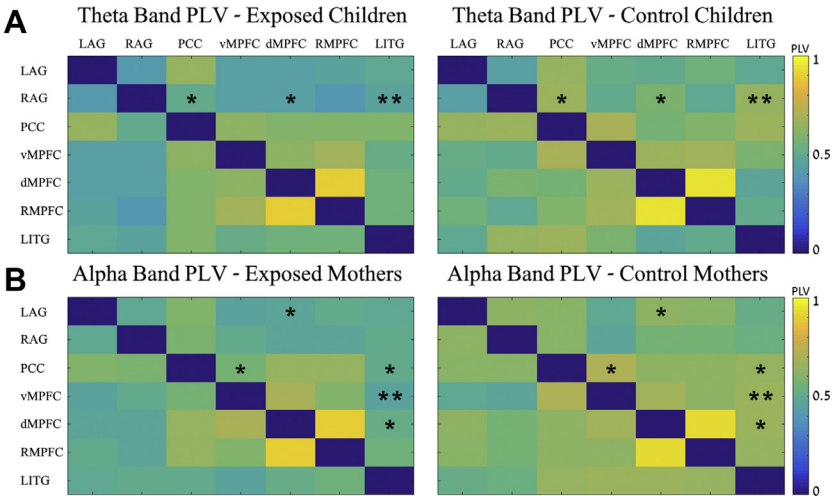

Figure 2. Connectivity values among the various default mode network (DMN) nodes in war-exposed and control children and mothers. **(A)** Phase locking value (PLVs) for exposed and control children in the theta band. *$p < .05$; **$p = .005$. **(B)** PLVs for exposed and control mothers in the alpha band. *$p < .05$; **$p = .005$. 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.

No differences in alpha band emerged between exposed and control children ($t_{73} = -0.17$, $p = .87$).

Mothers. Higher PLV in the alpha band was found for control (mean 0.63 ± 0.17) compared with exposed (mean 0.56 ± 0.17) mothers ($t_{84} = 2$, $p < .05$). Post hoc analysis revealed five significant pairs: LAG-dMPFC, PCC-vMPFC, PCC-LITG, vMPFC-LITG, dMPFC-LITG (see Table 1 and Figure 2B for full results). No differences in theta band emerged between exposed and control mothers ($t_{84} = 1.22$, $p = .23$).

As seen in Table 1, gender distributions differed between groups. To rule out gender as alternative explanation for the reduced theta connectivity, we computed an analysis of variance with gender and exposure as between-subject factors. No gender-by-gender ($F_{1,73} = 0.001$, $p = .98$) or gender-by-exposure ($F_{1,71} < 0.001$, $p = .99$) effects were found. We also computed separate t tests between boys and girls for each group, and no significant differences emerged for exposed ($t_{73} = -0.031$, $p = .98$) or control ($t_{73} = -0.005$, $p = .99$) children.

Correlations Between Mother and Child DMN Connectivity and Power

The correlation between child theta DMN connectivity and mother alpha DMN connectivity was nonsignificant ($r = -.11$, $p = .40$). Correlations emerged between mother alpha DMN power and child DMN power in alpha ($r = .32$, $p = .01$) and theta ($r = .26$, $p < .05$) bands. Child theta DMN power correlated with mother theta DMN power ($r = .42$, $p = .001$).

Behavioral and Hormonal Measures

A series of t tests with Bonferroni's correction ($p < .017$) between the exposed and control groups revealed significant effects for maternal emotional distress at T1 ($t_{84} = -2.69$, $p = .009$), indicating higher combined Z-scores in the State–Trait Anxiety Inventory, Beck Depression Inventory, and Posttraumatic Stress Diagnostic Scale among exposed (mean 0.33 ± 0.97) compared with control (mean −0.15 ± 0.65) mothers. No differences in maternal intrusiveness, measured on a 5-point Likert-type scale ranging from 1 (low), to 5 (high), were found between exposed (mean 2.22 ± 1.17) and control (mean 1.87 ± 0.79) mothers ($t_{84} = -1.62$, $p = .11$), or in child area under the curve CT between exposed (mean 51616.42 ± 69055.57) and control (mean 37695.58 ± 29021.65) children ($t_{50} = -0.99$, $p = .33$).

Predicting DMN Connectivity From Variables Across the First Decade

Two hierarchical multiple regression models were computed, predicting DMN connectivity in mother and child (alpha for mother, theta for child) from behavioral, hormonal, and mental health variables. Intercorrelation matrix appear in Supplemental Table S2, Figure 3A presents the correlation between maternal alpha connectivity and maternal emotional distress at T1, and Figure 3B presents the correlation between child theta connectivity and maternal intrusiveness at T1 and T3. The same three predictors were entered for mother and child, and order of entry considered early to later measurement. In the first step, maternal emotional distress in early childhood was entered. In the second, the mother's intrusive style across the first decade was entered, and in the third, the child's CT levels in late childhood were entered.

Results (Supplemental Table S2) indicate that for children, maternal intrusiveness and higher cortisol each independently predicted diminished DMN connectivity. Among mothers, greater emotional distress, including symptoms of anxiety, depression, and PTSD, and higher child cortisol uniquely predicted lower DMN connectivity.

DMN Connectivity and Child PTSD

The point-biserial correlation between PTSD and theta DMN connectivity in children was found to be significant ($n = 69$, $r = .23$, $p = .05$), indicating that exposed children with PTSD had particularly lower DMN connectivity.

DISCUSSION

Exposure to chronic early stress bears long-term impact on the developing brain. Our results indicate that ELS impairs DMN

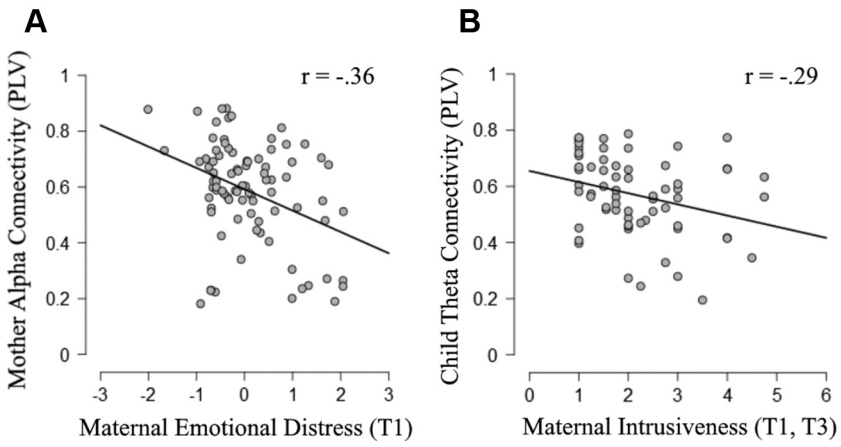

Figure 3. Correlations between default mode network connectivity maternal emotional symptoms and maternal intrusive caregiving. **(A)** Correlation between connectivity in the alpha band among mothers and maternal emotional distress at time 1 (T1). **(B)** Correlation between connectivity in the theta band among children and maternal intrusiveness style at T1 and T3. PLV, phase locking value.

connectivity in both preadolescents and their mothers, suggesting that chronic stress undermines the DMN's ability to function as a coherent network in both sides of the caregiving dyad, child and mother. Utilizing a prospective longitudinal design, following families across the first decade, employing repeated observations of the caregiving context, and focusing on brain oscillations in preadolescence**,** we tested how war-related ELS combines with intrusive, anxiety-provoking caregiving to impair a critical neural circuit implicated in self-reference, internally directed attention, and autobiographical memory.

Prolonged exposure to stress leaves its mark on the DMN, reducing connectivity among its structures. Our findings are the first to show this in children, indicating that by preadolescence, chronic stress impairs DMN connectivity, and pinpointing theta rhythms as the band where such disruptions are found at this age. These findings are important, as the DMN is involved in multiple phenomena known to be impacted by stress, such as hypervigilance and alertness, alterations of intrinsic and extrinsic attention, self-referential mental activity, and recollection of personal experiences. Our results suggest that one pathway for the long-term effects of ELS on the development of anxiety symptoms, PTSD, and behavioral dysregulation may relate to the disruption to DMN functioning caused by chronic stress exposure, particularly the diminished capacity of the DMN to cohere into a functional network and achieve quiescence. The transition to adolescence is a sensitive period for the onset of mood disorders (41), and our findings suggest that ELS may interfere with the development of adequate brain mechanisms to regulate stress, rendering stress-exposed preadolescents susceptible to psychopathology.

While reduced DMN connectivity was found for both mothers and children, it was observed in different oscillatory rhythms: alpha for mothers, theta for children. Whereas alpha is the dominant rhythm in the adult brain at rest, theta oscillations are a biomarker of the developing brain and dominate when brain patterns are established. Furthermore, the disruption was specific to DMN connectivity, and no group differences emerged in alpha (mothers) or theta (children) power. Unlike power, neural oscillations chart the mechanism by which distinct brain regions coordinate their activity. By synchronizing phase from different brain sources, locally distant brain areas connect and function as a coherent network. Such synchronous coordination across distributed brain areas defines a fundamental brain mechanism that underpins every aspect of cognition and behavior (42,43). The high temporal resolution afforded by MEG enabled us to measure DMN connectivity and specify the source of stress-related dysfunction.

Oscillatory rhythms play a distinct role in brain functions. Alpha oscillations mark the dominant rhythm of the awake resting brain and reflect "baseline" mode upon which any mental activity is registered (44). Alpha oscillations strongly correlate with gamma-band activity (45) that indexes neuronal processing (44), and the two integrate top-down and bottom-up processing to perceive incoming stimuli, enable predictive coding, and achieve steady state in the absence of incoming information. Alpha rhythms underpin key functions, including sensory gating, memory, attention, and social functions, and alpha rhythm impairments are observed in affective disorders and PTSD (44). Thus, the diminished DMN alpha-band connectivity in mothers indicates that prolonged stress impacts not only the developing brain, but also the mature brain. It is also possible that disruptions to DMN connectivity in adults occur only in the context of motherhood, when mothers must raise children in the shadow of chronic stress, and our findings need replications in fathers and nonparents.

Among children, impairment to DMN connectivity emerged in the theta band, the rhythm characterizing the developing brain. Theta oscillations are dominant during childhood and link with multiple developmental processes, including top-down control (46) and synaptic plasticity (47). Theta also indexes atypical brain maturation; children with neurological disabilities show more theta and less alpha activity (48) and theta power correlates with poor cognitive performance in adults (26). Thus, in normative development, brain oscillations may shift from theta to alpha as the "default" rhythm, but when development derails, theta may remain dominant for longer periods. This is consistent with the finding that exposed children with PTSD had the lowest DMN theta connectivity and echo the associations found between PTSD and reduced DMN connectivity in adults (6). Possibly, ELS interferes with the developmental shift of theta to alpha, and stress may

specifically target synchronization of brain rhythms across distributed networks rather than activity levels; however, this hypothesis requires replication across multiple ELS conditions.

We focused on the entire DMN matrix to identify DMN regions specifically susceptible to stress in children and adults. In mothers, stress reduced connectivity among the LAG, PCC, LITG, dMPFC, and vMPFC; in children, it impaired connections among the RAG, PCC, LITG, and dMPFC. The PCC and PFC and their connectivity, which were impacted by stress in both mothers and children, have been implicated stress-related psychopathologies, including PTSD, as well as in pain and negative emotional processing (8,48). Interestingly, we found dissociation between mothers and children in the angular gyrus; in children, the RAG was impacted, whereas in mothers it was the LAG. The RAG is critically involved in attention and reasoning processes, social cognition, and emotion regulation (49,50), which are all prone to stress. The LAG and the LITG, disrupted in mothers, are mainly associated with semantic and symbolic processing (51). However, as both the LAG and RAG are more active under psychological stress (52,53), findings pinpoint the nodes showing reduced connectivity under war-related stress in adults and children.

Maternal depression, anxiety, and posttraumatic symptoms during the first years of parenting predicted aberrant DMN connectivity 10 years later. Maternal symptoms in the context of war exposure were found to predict lower maternal sensitivity, higher intrusiveness, and greater posttraumatic symptoms in their children (54), and the current findings highlight their long-term effects on the maternal brain. Patterns of intrusive caregiving are individually stable across the first decade of parenting and predict child maladjustment and greater behavioral problems (55). Here, we show that the continuous experience of intrusive caregiving in the context of ELS, which induces anxiety, leaves children without the mother's sensitive containment of fear, deprives children of the biobehavioral effects of well-adapted caregiving, and interferes with the development of the synchronous coherence of the DMN. Similarly, augmented stress physiology in stress-exposed children develops in children experiencing insensitive early mothering (32), and the current findings demonstrate that increased CT production in late childhood leads to lower DMN connectivity in preadolescence. As such, our findings are the first to show that in the context of ELS, uncontained parenting, greater maternal emotional distress, and augmented physiological stress response function over time disrupt the organization of the DMN into a functional neural network.

Several study limitations should be considered. These include the absence of father data, the small number of children diagnosed with PTSD, and the lack of repeated brain scanning across childhood to determine developmental trajectories. We chose to study neural oscillations using MEG, and future assessments of this cohort should include functional magnetic resonance imaging scanning to better target stress effects on subcortical networks. Two minutes of resting state may not be sufficient to assess stable electroencephalography/MEG signals, and the gold standard requires 4 to 5 minutes, with some studies recording 10 minutes (56). Still, our pilot showed that children had difficulty lying alone in a shielded room with no incoming stimuli for longer than 2 minutes, and a 2-minute assessment is common in resting-state studies of children (57–64). In addition, we considered the DMN a uniform system; however, recent studies describe the DMN as comprising several interrelated subsystems (65–68). This approach was taken due to the novel nature of our study and the spatial constraints of MEG that limit differentiation of DMN subsystems. Furthermore, because MEG source localization is based on inverse estimation, source depth limits its accuracy (69). In the current context, this issue mainly relates to the vMPFC and PCC. Finally, most studies on ELS focused on interpersonal traumas (e.g., emotional, physical, or sexual abuse), while our study focused on war-related trauma. Because the nature of ELS critically impacts later psychopathology (70) and brain maturation (71), our results require replication in other ELS conditions before findings can be generalized.

Despite these limitations, our findings have clear translational implications and point to the long-lasting effects of stress on the developing brain. Our data may suggest that training the brain in task-free paradigms, using, for instance, mindfulness or meditation, may help mothers and children with chronic stress living in zones of war to tune the brain to rest, with the hope that such training may provide the foundation on which resilience can be built.

ACKNOWLEDGMENTS AND DISCLOSURES

Supported by the Simms-Mann Foundation and the NARSAD Independent Investigator Award (to RF).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Aug 8, 2018; accepted Sep 3, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2018.09.009.

REFERENCES

1. Pechtel P, Pizzagalli DA (2011): Effects of early life stress on cognitive and affective function: An integrated review of human literature. Psychopharmacology (Berl) 214:55–70.
2. Heim C, Nemeroff CB (2002): Neurobiology of early life stress: Clinical studies. Semin Clin Neuropsychiatry 7:142–159.
3. Raichle ME (2015): The brain's default mode network. Annu Rev Neurosci 38:433–447.
4. de Pasquale F, Della Penna S, Snyder AZ, Marzetti L, Pizzella V, Romani GL, *et al.* (2012): A cortical core for dynamic integration of functional networks in the resting human brain. Neuron 74:753–764.
5. Whitfield-Gabrieli S, Ford JM (2012): Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 8:49–76.
6. Bluhm RL, Williamson PC, Osuch EA, Frewen PA, Stevens TK, Boksman K, *et al.* (2009): Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. J Psychiatry Neurosci 34:187–194.
7. King AP, Block SR, Sripada RK, Rauch S, Giardino N, Favorite T, *et al.* (2016): Altered default mode network (DMN) resting state functional connectivity following a mindfulness-based exposure therapy for posttraumatic stress disorder (PTSD) in combat veterans of Afghanistan and Iraq. Depress Anxiety 33:289–299.

8. Lanius RA, Bluhm RL, Coupland NJ, Hegadoren KM, Rowe B, Theberge J, *et al.* (2010): Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. Acta Psychiatr Scand 121:33–40.
9. Soares JM, Sampaio A, Marques P, Ferreira LM, Santos NC, Marques F, *et al.* (2013): Plasticity of resting state brain networks in recovery from stress. Front Hum Neurosci 7:919.
10. Soares JM, Sampaio A, Ferreira LM, Santos NC, Marques P, Marques F, *et al.* (2013): Stress impact on resting state brain networks. PLoS One 8:e66500.
11. Arthur A (1987): Stress as a state of anticipatory vigilance. Percept Mot Skills 64:75–85.
12. Bögels SM, Mansell W (2004): Attention processes in the maintenance and treatment of social phobia: Hypervigilance, avoidance and self-focused attention. Clin Psychol Rev 24:827–856.
13. Richards HJ, Benson V, Donnelly N, Hadwin JA (2014): Exploring the function of selective attention and hypervigilance for threat in anxiety. Clin Psychol Rev 34:1–13.
14. Briere J, Elliott DM, Harris K, Cotman A (1995): Trauma symptom inventory: psychometrics and association with childhood and adult victimization in clinical samples. J Interpers Violence 10:387–401.
15. Davis JL, Petretic-Jackson PA, Ting L (2001): Intimacy dysfunction and trauma symptomatology: Long-term correlates of different types of child abuse. J Trauma Stress 14:63–79.
16. Shapiro BL, Schwarz JC (1997): Date rape: Its relationship to trauma symptoms and sexual self-esteem. J Interpers Violence 12:407–419.
17. Kihlstrom J (2006): Trauma and memory revisited. In: Memory and Emotion. Vol 52. London: Blackwell Science; 259–291.
18. DiGangi JA, Tadayyon A, Fitzgerald DA, Rabinak CA, Kennedy A, Klumpp H, *et al.* (2016): Reduced default mode network connectivity following combat trauma. Neurosci Lett 615:37–43.
19. Sripada RK, Swain JE, Evans GW, Welsh RC, Liberzon I (2014): Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. Neuropsychopharmacology 39:2244–2251.
20. Weissman DG, Conger RD, Robins RW, Hastings PD, Guyer AE (2018): Income change alters default mode network connectivity for adolescents in poverty. Dev Cogn Neurosci 30:93–99.
21. Daniels JK, Frewen P, McKinnon MC, Lanius RA (2011): Default mode alterations in posttraumatic stress disorder related to early-life trauma: A developmental perspective. J Psychiatry Neurosci 36:56–59.
22. Hillebrand A, Barnes GR, Bosboom JL, Berendse HW, Stam CJ (2012): Frequency-dependent functional connectivity within resting-state networks: An atlas-based MEG beamformer solution. Neuroimage 59:3909–3921.
23. Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK (2012): Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat Neurosci 15:884–890.
24. Bell MA (1998): The ontogeny of the EEG during infancy and childhood: Implications for cognitive development. In: Garreau B, editor. Neuroimaging in Child Neuropsychiatric Disorders. Berlin: Springer, 97–111.
25. Clarke AR, Barry RJ, McCarthy R, Selikowitz M (2001): Age and sex effects in the EEG: Development of the normal child. Clin Neurophysiol 112:806–814.
26. Klimesch W (1999): EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. Brain Res Rev 29:169–195.
27. Knyazev GG, Slobodskaya HR, Safronova MV, Sorokin OV, Goodman R, Wilson GD (2003): Personality, psychopathology and brain oscillations. Pers Individ Dif 35:1331–1349.
28. Knyazev GG, Savostyanov AN, Levin EA (2004): Alpha oscillations as a correlate of trait anxiety. Int J Psychophysiol 53:147–160.
29. Knyazev GG, Slobodskaya HR, Wilson GD (2002): Psychophysiological correlates of behavioural inhibition and activation. Pers Individ Dif 33:647–660.
30. Knyazev GG, Savostyanov AN, Levin EA (2005): Anxiety and synchrony of alpha oscillations. Int J Psychophysiol 57:175–180.
31. Feldman R (2009): The development of regulatory functions from birth to 5 years: Insights from premature infants. Child Dev 80:544–561.
32. Feldman R, Eidelman AI (2004): Parent-infant synchrony and the social-emotional development of triplets. Dev Psychol 40:1133–1147.
33. Halevi G, Djalovski A, Kanat-Maymon Y, Yirmiya K, Zagoory-Sharon O, Koren L, Feldman R (2017): The social transmission of risk: Maternal stress physiology, synchronous parenting, and well-being mediate the effects of war exposure on child psychopathology. J Abnorm Psychol 126:1087–1103.
34. Halevi G, Djalovski A, Vengrober A, Feldman R (2016): Risk and resilience trajectories in war-exposed children across the first decade of life. J Child Psychol Psychiatry 57:1183–1193.
35. Beck AT (1978): Beck Depression Inventory. San Antonio, TX: The Psychological Corporation/Harcourt Brace Jovanovich.
36. Foa EB (1995): PDS (Posttraumatic Stress Diagnostic Scale): Manual. Oxford: Pearson.
37. Goodman R, Ford T, Richards H, Gatward R, Meltzer H (2000): The Development and Well-Being Assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry 41:645–655.
38. Tal I, Abeles M (2013): Cleaning MEG artifacts using external cues. J Neurosci Methods 217:31–38.
39. Oostenveld R, Fries P, Maris E, Schoffelen J-M (2011): FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011:156869.
40. Lachaux J-P, Rodriguez E, Martinerie J, Varela FJ (1999): Measuring phase synchrony in brains signals. Hum Brain Mapp 8:194–208.
41. Crone EA, Dahl RE (2012): Understanding adolescence as a period of social–affective engagement and goal flexibility. Nat Rev Neurosci 13:636–650.
42. Buzsáki G (2006): Rhythms of the Brain. Oxford, UK: Oxford University Press.
43. Neustadter E, Mathiak K, Turetsky BI (2016): EEG and MEG probes of schizophrenia pathophysiology. In: Abel T, Nickl-Jockschat T, editors. The Neurobiology of Schizophrenia. Amsterdam: Elsevier, 213–236.
44. Crone NE, Sinai A, Korzeniewska A (2006): High-frequency gamma oscillations and human brain mapping with electrocorticography. Prog Brain Res 159:275–295.
45. Jerbi K, Ossandón T, Hamamé CM, Senova S, Dalal SS, Jung J, *et al.* (2009): Task-related gamma-band dynamics from an intracerebral perspective: Review and implications for surface EEG and MEG. Hum Brain Mapp 30:1758–1771.
46. von Stein A, Chiang C, Konig P (2000): Top-down processing mediated by interareal synchronization. Proc Natl Acad Sci U S A 97:14748–14753.
47. Huerta PT, Lisman JE (1993): Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 364:723–725.
48. Vogt BA (2005): Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6:533–544.
49. Seghier ML (2013): The angular gyrus. Neuroscientist 19:43–61.
50. Goldin PR, McRae K, Ramel W, Gross JJ (2008): The neural bases of emotion regulation: Reappraisal and suppression of negative emotion. Biol Psychiatry 63:577–586.
51. Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T (1997): Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 17:353–362.
52. Semple WE, Goyer PF, McCormick R, Compton-Toth B, Morris E, Donovan B, *et al.* (1996): Attention and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. Psychiatry Res Neuroimaging 67:17–28.
53. Wang J, Rao H, Wetmore GS, Furlan PM, Korczykowski M, Dinges DF, Detre JA (2005): Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. Proc Natl Acad Sci U S A 102:17804–17809.
54. Feldman R, Vengrober A (2011): Posttraumatic stress disorder in infants and young children exposed to war-related trauma. J Am Acad Child Adolesc Psychiatry 50:645–658.

55. Feldman R (2010): The relational basis of adolescent adjustment: Trajectories of mother-child interactive behaviors from infancy to adolescence shape adolescents' adaptation. Attach Hum Dev 12: 173–192.
56. Lajiness-O'Neill R, Brennan JR, Moran JE, Richard AE, Flores AM, Swick C, *et al.* (2018): Patterns of altered neural synchrony in the default mode network in autism spectrum disorder revealed with magnetoencephalography (MEG): Relationship to clinical symptomatology. Autism Res 11:434–449.
57. Dimitriadis SI, Laskaris NA, Simos PG, Micheloyannis S, Fletcher JM, Rezaie R, Papanicolaou AC (2013): Altered temporal correlations in resting-state connectivity fluctuations in children with reading difficulties detected via MEG. Neuroimage 83:307–317.
58. Cornew L, Roberts TPL, Blaskey L, Edgar JC (2012): Resting-state oscillatory activity in autism spectrum disorders. J Autism Dev Disord 42:1884–1894.
59. Lansbergen MM, Arns M, Van Dongen-Boomsma M, Spronk D, Buitelaar JK (2010): The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. Prog Neuropsychopharmacol Biol Psychiatry 35:47–52.
60. Boersma M, Smit DJA, De Bie HMA, Van Baal GC, Boomsma DI, de Geus EJ, *et al.* (2010): Network analysis of resting state EEG in the developing young brain: Structure comes with maturation. Hum Brain Mapp 32:413–425.
61. Kozlowska K, Spooner CJ, Palmer DM, Harris A, Korgaonkar MS, Scher S, Williams LM (2018): "Motoring in idle": The default mode and somatomotor networks are overactive in children and adolescents with functional neurological symptoms. Neuroimage Clin 18:730–743.
62. Huang CJ, Huang CW, Hung CL, Tsai YJ, Chang YK, Wu CT, Hung TM (2018): Effects of acute exercise on resting EEG in children with attention-deficit/hyperactivity disorder [published online ahead of print Jun 5]. Child Psychiatry Hum Dev.
63. Milner R, Lewandowska M, Ganc M, Włodarczyk E, Grudzień D, Skarżyński H (2018): Abnormal resting-state quantitative electroencephalogram in children with central auditory processing disorder: A pilot study. Front Neurosci 12:292.
64. Goldstein BL, Shankman SA, Kujawa A, Torpey-Newman DC, Olino TM, Klein DN (2016): Developmental changes in electroencephalographic frontal asymmetry in young children at risk for depression. J Child Psychol Psychiatry 57:1075–1082.
65. Andrews-Hanna JR (2012): The brain's default network and its adaptive role in internal mentation. Neuroscientist 18:251–270.
66. Buckner RL, Andrews-Hanna JR, Schacter DL (2008): The brain's default network. Ann N Y Acad Sci 1124:1–38.
67. Sambataro F, Wolf ND, Pennuto M, Vasic N, Wolf RC (2014): Revisiting default mode network function in major depression: Evidence for disrupted subsystem connectivity. Psychol Med 44:2041–2051.
68. Li W, Mai X, Liu C (2014): The default mode network and social understanding of others: What do brain connectivity studies tell us. Front Hum Neurosci 8:74.
69. Hillebrand A, Barnes GR (2002): A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. Neuroimage 16:638–650.
70. Luthra R, Abramovitz R, Greenberg R, Schoor A, Newcorn J, Schmeidler J, *et al.* (2009): Relationship between type of trauma exposure and posttraumatic stress disorder among urban children and adolescents. J Interpers Violence 24:1919–1927.
71. Perroud N, Paoloni-Giacobino A, Prada P, Olié E, Salzmann A, Nicastro R, *et al.* (2011): Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. Transl Psychiatry 1:e59.