Exposure to maternal depression has long been known to negatively affect children’s social and emotional development, including increased social withdrawal, compromised peer relationships, poor emotion regulation, and decreased empathy. When the onset of maternal depression occurs during the child’s first months of life and the disorder is of a chronic course, the risk for maladaptive outcome significantly increases. However, although maternal depression is a common psychiatric disorder affecting 15% to 18% of parturient women in industrial societies and up to 30% in developing countries, no study to date has tested its long-term effects on children’s social brain.

Children of mothers with depression show disruptions in the development of empathic response to the distress of others. Preschool-age children of mothers with depression have been found to exhibit less concern for the distress of their mother and an experimenter and less helping behavior to infant crying. A study on guilt found that school-age children of mothers with depression responded with aborted and unresolved narratives to others’ distress compared with controls’ expression of responsibility and reparation, suggesting that the immature mechanisms for processing others’ distress could relate to the encounter with distress in oneself. This indicates that the reported deficits in empathic behavior in children of mothers with depression do not stem from their inability to correctly assess interpersonal situations but from disruptions to emotion regulation mechanisms and difficulties in modulating the high arousal associated with observing others’ distress. Such deficits can block the child’s engagement in overwhelming situations, leading to premature withdrawal or over-excitability that can impede vicarious empathy. However, because not all children reared by mothers with depression show similar social and emotional difficulties, understanding the pathways leading from exposure to maternal depression in early life to the neural and behavioral underpinnings of social adjustment and empathy is critical for early detection and for the construction of individually tailored interventions.

One pathway repeatedly shown to mediate the effects of maternal depression on child outcome is the mother–child relationship, highlighting the importance of early caregiving in shaping children’s neural and behavioral development.

Objective: Exposure to maternal depression across the first years of life markedly increases children’s susceptibility to psychopathology, yet no study has tested its effects on the maturation of children’s social brain.

Method: Using a birth cohort of mothers with no contextual risk (N = 1,983), families were followed at 7 time points from birth to 11 years and repeatedly assessed for maternal depression across the first 6 years to form 2 cohorts: mothers continuously depressed from birth to 6 years and controls without depression. At 11 years of age, children’s (n = 72; depressed, n = 27; nondepressed, n = 45) brain response to others’ pain was measured by magnetoencephalography.

Results: Preadolescents displayed a unique oscillatory pattern with higher alpha power to pain versus no pain expressing as alpha rebound, not alpha suppression, at a late time window (1,100–1,300 ms post-stimulus) in the supplementary motor area. This suggests that top-down processing in areas of the pain matrix can underpin the maturation of vicarious empathy. Children of mothers with depression showed enhanced alpha rebound to pain in the right posterior superior temporal gyrus, which was unrelated to emotion detection abilities, pointing to decreased late processing of others’ overwhelming experiences in socio-cognitive areas. Alpha power in the posterior superior temporal gyrus was predicted by higher maternal intrusiveness and lower synchrony across early childhood.

Conclusion: These findings, from the first study to examine maternal depression and early caregiving as long-term predictors of children’s neural empathic response, pinpoint a decrease in top-down socio-cognitive mechanisms as potential pathways for the cross-generational transfer of vulnerability from mothers with depression to their offspring and highlight the need for early interventions focused on enhancing maternal attunement.

Key words: maternal depression, mother–child interaction, empathy, magnetoencephalography, alpha oscillations
relationship and its specific disruptions in cases of maternal depression. Child empathy develops based on attuned parenting; higher maternal synchrony with the infant’s nonverbal signals has been shown to predict greater empathy at 6 and 13 years of age. Mothers with depression are more intrusive and less synchronous during interactions with their infants and young children, and these maladaptive patterns have been associated with deceased empathy to others’ distress in their offspring. However, the effects of these relational impairments on the neural mechanisms underpinning the expression of empathy have not yet been studied in prospective longitudinal research. Understanding the impact of maternal depression on social brain development can shed new light on the mechanisms implicated in the lifetime vulnerability to psychopathology, social withdrawal, and loneliness observed in offspring of mothers with depression. Moreover, because the ability to process others’ distress signals and respond in prosocial ways is critical for social learning and psychological adjustment, charting the pathways by which maternal care supports the brain basis of empathy and its disruptions in cases of maternal depression is of theoretical and clinical importance.

In assessing the effects of maternal depression on the brain basis of empathy, it is important to understand how the age-appropriate neural response to others’ pain is expressed. Empathic response to the distress of others involves a multidimensional constellation of processes ranging from automatic increase in sensorimotor arousal, an evolutionary ancient process observed in rudimentary form in rodents, to higher-order mechanisms implicating emotion regulation, cognitive appraisal, and the capacity to engage multiple perspectives and oscillate between first- and third-person viewpoints. Developmental studies have indicated that although empathic response to others’ distress is observed already in early infancy, the ability to show empathic concern, not only personal distress, unfolds gradually across childhood and adolescence and requires maturation of emotion regulation capacities. Functional magnetic resonance imaging studies testing developmental changes in children’s neural response to others’ pain have shown an age-related decrease in amygdala activation and increase in frontal regions’ activations alongside increased prefrontal-amgydala connectivity that correlate with the degree of perceived pain. An electroencephalographic (EEG) study of children’s and adults’ event-related brain potentials to others’ pain has found that children display stronger response in the early components combined with weaker response in the later components, suggesting that age-related changes in neural responsivity to others’ pain stem from maturation of top-down control mechanisms.

In light of these findings, the present study examined, for the first time, the long-term effects of early and chronic maternal depression on preadolescents’ neural response to others’ pain using magnetoencephalography (MEG). MEG uniquely combines high temporal resolution with good spatial localization and is particularly suited to examine the integration of automatic and higher-order processing implicated in vicarious empathy. To specify pathways by which maternal depression shapes the brain basis of empathy, we used a large birth cohort (N = 1,983) of women with no comorbid contextual risk who were repeatedly assessed for maternal depression across the first years of life (Figure 1 presents a description of the cohort). At 9 months and at 6 years, mother–child interactions were observed and relational behaviors were examined as predictors of children’s neural response at 11 years.

MEG studies assessing adults’ brain response to others’ pain have found greater alpha suppression in response to painful compared with nonpainful stimuli in the sensorimotor cortex. Alpha oscillation is the predominant frequency in humans during rest and is suppressed while processing relevant information, thus, greater alpha suppression to painful stimuli is believed to index greater processing in areas of the brain’s pain matrix. Only 1 study examined developmental changes in alpha suppression to others’ pain using EEG and found that up to 9 years of age children show no differentiation in alpha suppression to pain versus no pain within the first post-stimulus second. This is surprising in light of brain and behavioral studies using other techniques that showed that school-age children exhibit differential response to others’ pain. Because age-related improvements in empathic response during preadolescence depend on maturation of regulatory processes, examination of later time windows that reflect top-down cognitive control of the initial non-differentiated response might be required. Thus, we hypothesized that differences between response to pain and no pain would emerge at later post-stimulus time windows in areas repeatedly shown to comprise the brain’s pain matrix: the anterior cingulate cortex, the anterior insula, the supplementary motor area (SMA), and the sensorimotor cortex. Consistent with behavioral studies, we expected a less mature response to others’ distress in children exposed to maternal depression across the first 6 years. Zahn-Waxler et al. found that children of mothers with depression are more distressed by the pain of others, which decreases their other-oriented response, but are no less cognizant of it. Thus, we hypothesized that group differences might be found in socio-cognitive areas, such as the temporal pole, posterior superior temporal gyrus (pSTG), and medial prefrontal cortex, and that it might be dissociable from children’s emotion detection abilities. Further, we expected that mother–child relational patterns across the first 6 years of life, particularly increased maternal intrusiveness and decreased synchrony, would predict the altered neural response to others’ pain in children of mothers with depression.

**METHOD**

**Participants**
Participants were recruited in 7 waves of data collection (Figure 1), and a detailed description of recruitment appears in Supplement 1 (available online). During the second day after birth, 1,983 women who were healthy, completed high school, were older than 21 years, above the poverty cutoff, cohabiting, and whose infants were at...
term, healthy, and singletons were recruited in 3 maternity wards in a large metropolitan area. Mothers were assessed for symptoms of depression and anxiety at 6 and 9 months postpartum, and families of mothers in the highest and lowest quartiles of the Beck Depression Inventory and with no increased symptoms of anxiety in the State-Trait Anxiety Inventory were visited at home at 9 months and at 6 years. Mothers with comorbid anxiety disorders were excluded because of previous findings showing that mothers...
with anxiety and depression display different patterns of maternal behavior\textsuperscript{46} and different patterns of brain activity.\textsuperscript{35} and the focus in this study was on the relation between maternal behavior and child neural development in mothers with depression. At 6 years of age, families were divided into 2 cohorts: 46 mothers who reported high depressive symptoms at birth, 6, and 9 months were diagnosed with Axis I major depressive disorder at both 9 months and at 6 years, and reported being depressed throughout much of the child’s first 6 years (depressed group) and 103 mothers who reported no increased symptoms at any time point and were free of any psychiatric diagnosis across the first 11 years (control group).

At 11 years of age, 90 families were contacted and participated in an MEG session. Full MEG data were available for 72 participants, and exclusion was due to excessive muscle artifact, movement, or inability to finish a session, leading to the present cohort of 27 children in the depressed group and 45 in the control group (mean age 11.25, 42 boys). In the group with depression, 14 mothers still received a major depressive disorder diagnosis and 13 remitted. Demographic information showed no group difference (Table S1, available online).

The study was approved by an institutional review board, procedures were explained to the accompanying parent before the beginning of the study, and all signed an informed consent form. Families received a gift certificate for participation.

**Measurements**

Maternal psychiatric diagnosis was conducted by a clinical psychologist at 9 months and at 6 and 9 years using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).\textsuperscript{36} Child psychiatric diagnosis was conducted by a clinical psychologist at 6 and 9 years using the Development and Well-Being Assessment (DAWBA).\textsuperscript{32} SCID and DAWBA diagnoses were supervised by a child psychiatrist, with reliability exceeding 85%, and cases were conferred every few weeks (SCID κ = 0.85, DAWBA κ = 0.86).

*Mother–Child Interaction.* Ten minutes of mother–child free play with age-appropriate toys were filmed at 9 months and at 6 years.\textsuperscript{39} Interactions were coded with the Coding Interactive Behavior manual.\textsuperscript{39} Two coders, trained to 85% reliability and blinded to all other information, coded the interactions, with inter-rater reliability computed for 20% of interactions exceeding 87% (intraclass r = 0.91, range 0.87–0.99). We used the constructs of maternal intrusiveness, including codes addressing maternal overriding, forcing, anxiety/hostility, parent-led interactions, and inconsistent parenting, and dyadic synchrony, including codes assessing give-and-receive reciprocity, mutual adaptation, synchrony, and fluency.

*Emotion Detection.* A series of pictures depicting emotional expressions of sad, happy, and neutral faces was presented to the children at 11 years of age. Pictures were taken from the FG-net Facial Expressions and Emotions Database (FEED; http://www.mmkn.ei.tum.de/~waf/fgnet/feedtum.html) and were presented for 200 ms. Next, children were asked to rate whether pictures displayed happy, sad, or neutral expressions, and the proportion of correct responses was used to index emotional accuracy.

*Empathy to Pain.* A series of 180 digital color pictures showing right hands and right feet in painful and otherwise similar nonpainful situations was presented in 2 blocks (Figure 2).\textsuperscript{41} The pictures were presented for 1.5 seconds followed by 1.5 seconds of a gray fixation screen, consistent with previous research.\textsuperscript{25} Pictures were presented on a 17-inch screen located 60 cm in front of children using e-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA). To confirm attention, 10% of the stimuli depicted twisted movement (Photoshop, Adobe Systems Inc., San Jose, CA), and children were asked to press a button when these stimuli appeared.\textsuperscript{26} All participants with MEG data fully detected all twisted images.

**Data Acquisition and Analysis**

MEG recordings were conducted with a whole-head 248-channel magnetometer array (Magnes 3600 WH, 4-D Neuroimaging, San Diego, CA) in a magnetically shielded room with a sample rate of 1,017 Hz and online 1- to 40-Hz bandpass filter in a supine position. Reference coils located a short distance (~30 cm) away from the 248 sensors and oriented by the x, y, and z axes were used to record environmental noise. Five coils were attached to the participant’s scalp for recording of the head position relative to the 248-channel sensor array. External noise (e.g., powerlines, mechanical vibrations) and heartbeat artifacts were removed from the data as previously described.\textsuperscript{31} Signal preprocessing at the sensor level was carried out using MATLAB (MathWorks, Natick, MA) and the FieldTrip toolbox.\textsuperscript{32} Data were segmented for the time window surrounding the stimulus (−0.8 to 2.2 seconds). Trials containing muscle artifacts and power jumps were discarded by visual inspection, resulting in a total mean of 129 viable trials (standard deviation [SD] 22) per participant, with a mean of 67 trials in the pain condition (SD 11.6) and 68 trials in the no-pain condition (SD 11.2) for the control group and 60 trials in the pain condition (SD 9.1) and 58 trials in the no-pain condition (SD 10) for the depressed group. No significant difference was found between conditions (F\textsubscript{1,20} = 0.25, not significant [NS]), but a significant difference was found between groups (F\textsubscript{1,20} = 11.92, p < .01). No significant group-by-condition interaction was found (F\textsubscript{1,20} = 2.64, NS). Next, the remaining trials were bandpass filtered in the 1- to 40-Hz range, and independent component analysis was used to remove eye movement, blinks, and other remaining artifacts from the data. Then, the segmented trials were baseline corrected.

To measure alpha activity, each data segment was subjected to spectral analysis. A Hanning taper was applied to each epoch to calculate the fast Fourier transform for sliding time windows of 800 ms in 50-ms steps in the 1- to 40-Hz frequency range, resulting in a spectral resolution of 1.25 Hz.

For source estimation, a template magnetic resonance image (Colin27, McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, Canada) was modified to fit each participant’s digitized head shape using SPM\textsuperscript{8} (Wellcome Department of Imaging Neuroscience, University College London, London, UK). A synthetic aperture magnetometry beamformer\textsuperscript{43} was applied with a spatial resolution of 0.5 cm to estimate the neural source of the measured MEG signal. Covariance estimates were calculated using the full raw data throughout the entire paradigm and were uniform for the 2 conditions. Then, the spatial filter was applied on the time segments and frequency bands that
were found to show the most significant difference in condition statistics in the sensor level. The spatial filter was applied to each trial of the segmented data and then averaged across trials, and synthetic aperture magnetometry estimates were noise-normalized by division by the mean square of the active weights. Then, the data were presented as functional maps on each participant’s modified template, and these templates were used to transform the beamforming functional images into a common Talairach space to allow group comparisons.

Statistical Analysis
Sensor-level statistics were implemented in the FieldTrip toolbox\textsuperscript{42} by applying cluster-based permutations on the time-frequency data and assessing regions of significance across all times, epochs, and frequencies in the alpha band (8–12 Hz). We first examined main effect of pain (pain versus no pain) for the entire sample and then addressed group differences in the pain effect.

Source-level statistics were calculated using Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni). To estimate the regions from which the pain effect and the group differences in the pain effect were elicited, a 2-way mixed analysis of variance was used with 1 within-subject variable (condition 2 levels: pain versus no pain) and 1 between-subject variable (group 2 levels: depressed versus control) using the 3dMVM function of AFNI. To control for multiple comparisons, we applied a nonparametric permutation approach\textsuperscript{44} in which analysis of variance was repeated 1,000 times, with condition and group randomly assigned within a subject at each permutation. The critical cluster size corresponded to the 50th maximal cluster size (5%) among the largest significant cluster from each permutation and contained 53 voxels for the condition main effect and 168 voxels for the interaction effect. For each participant, the average value of significant voxels in each cluster in each condition was selected for statistical analysis, including Pearson correlations and linear regression.

RESULTS

Preliminary Analysis
As a preliminary analysis, 2 \( \chi^2 \) tests examined the prevalence of child psychiatric disorders at 6 and 9 years for the final sample participating in the MEG study. At 6 years of age, 52% of children of mothers with depression received an Axis I psychiatric diagnosis compared with 24% of children of controls, and the difference was significant \( (\chi^2 = 5.59, p < .05) \). This difference was expressed in higher levels of internalizing \( (\chi^2 = 14.51, p < .001) \) and externalizing \( (\chi^2 = 5.69, p < .05) \) disorders. Of the children receiving a clinical diagnosis, 40% displayed externalizing disorders, including attention-deficit/hyperactivity disorder and conduct disorder, and 68% showed affective disorders (mainly anxiety disorders). At 9 years of age, 29% of children in the control group received some psychiatric diagnosis compared with 41% of the depressed group, and the difference was not significant \( (\chi^2 = 0.94, \text{NS}) \). Of the children receiving a clinical diagnosis, 50% exhibited externalizing disorders and 50% had affective disorders.

As a preliminary step in analyzing the MEG data, task effects were examined by collapsing the data across all groups and conditions and conducting a 1-sample \( t \) test to examine what frequencies and times were most significant compared with baseline. As expected, there was a significant difference between trial and baseline from 50 ms to the end of stimuli presentation. This difference was most significant at 400 to 800 ms post-stimulus at 8 to 11 Hz. Thus, source analysis examining the origins of this difference was conducted eliciting 2 significant clusters: the first included visual and temporal areas (i.e., occipital lobe, pSTG and anterior STG, and temporal pole bilaterally) and the second included the dorsolateral prefrontal cortex bilaterally.

Pain Effect on MEG Activity
Figure S1 (available online) shows the root mean square of the entire timeframe of the trial, collapsed on group in the 2 conditions, and exhibits that neural activity returned to baseline before stimulus presentation. Figure 3 shows the global effects at the sensor level. As presented in the right panels, the temporal dynamics of the alpha band includes initial suppression in power compared with baseline followed by rebound starting at approximately 500 ms. There were no differences found between conditions during the peak of alpha suppression; instead, differences were found in the rebound phase, with pain stimuli eliciting significantly greater alpha power than non-pain stimuli at the 1,100- to 1,300-ms time window and centered on 10 Hz (9–11 Hz). Children of mothers with depression showed a greater difference between conditions (lower panels).

Source-level analysis examining group and condition differences at 400 to 800 ms and 8 to 11 Hz was conducted, and no significant clusters were found. Source-level analysis, focused on 1,100 to 1,300 ms and 9 to 11 Hz, showed 1 significant cluster eliciting the main effect for condition and 1 eliciting the interaction effect (Figure 4). There were no significant clusters found for the main effect for group. Thus, similar to the findings at the sensor level, differences were not found in the time window of peak alpha suppression, but in the time window of alpha rebound. Exact coordinates and sizes of the clusters that reached significance are presented in Table S2 (available online). The main effect for condition was localized in the SMA, with higher alpha activation for pain (Figure 4A), whereas the interaction effect was localized in the right pSTG (Figure 4B), with lower alpha activation for pain versus no pain in controls \( (t_{44} = -2.04, p < .05) \) compared with higher alpha activation to pain in the depressed group \( (t_{26} = 2.49, p < .05) \). To better understand this result, group differences at baseline were examined, and no significant cluster was found. Because group differences were found in the number of viable trials, we ran a sanity check examining correlations between alpha power in the pSTG and the number of viable trials for each condition and group. These analyses yielded nonsignificant results (control: pain \( r = -0.17 \), NS; no pain \( r = -0.10 \), NS; depressed: pain \( r = 0.01 \), NS, no pain \( r = -0.17 \), NS), suggesting that alpha power in the pSTG was not related to the number of viable trials.

Post hoc \( t \) test of pSTG alpha activation within the depressed group showed no differences in the pain effect in children of mothers with current versus remitted depression \( (t_{26} = -0.46, \text{NS}) \). Similarly, no differences were found in children with or without Axis I psychopathology \( (t_{69} = -0.08, \text{NS}) \).
Correlation With Longitudinal Data

Pearson correlations were calculated between the average value of alpha power in significant clusters in pain minus no-pain conditions with mother–child interaction patterns and emotion detection accuracy (Table S3, available online). Lower maternal intrusiveness at 9 months ($r = 0.38$, $p < 0.05$) and higher dyadic synchrony at 6 years ($r = -0.25$, $p < 0.05$) were related to stronger alpha power in no pain compared with pain in the right pSTG. Emotion detection was unrelated to pSTG activation.

Hierarchical multiple regression predicted individual differences in pSTG activation to pain versus no-pain stimuli by maternal intrusiveness at 9 months and dyadic synchrony at 6 years after controlling for group (Table 1). Results show that lower maternal intrusiveness in infancy and greater mother–child synchrony in preschool each uniquely predicted preadolescents’ processing of others’ pain.

**DISCUSSION**

This decade-long study—the first to test the role of maternal depression in predicting preadolescents’ neural empathic response—demonstrates the pervasive, long-term interrelation between early and chronic exposure to maternal depression and the maturation of children’s vicarious empathy and suggests one pathway of risk through patterns of maternal care. We found that preadolescents show a differentiated response to others’ pain at a late time window in the SMA, a core structure of the “pain matrix.” This suggests that the development of top-down mechanisms that regulate the initial sensorimotor response to pain in others could underpin maturation of the brain basis of empathy. Exposure to maternal depression predicted a decreased late response to others’ distress in the pSTG, a key structure of the mentalizing network, indicating that deficits in empathic response in children with depression could stem from aborted socio-cognitive processing. Activation in this region was individually predicted by maternal relational patterns across early childhood, suggesting that attuned early caregiving is associated with maturation of the brain’s top-down regulatory processes.

Consistent with prior research, preadolescents did not show a differentiated brain response to others’ pain (compared with no pain) at the time window found in adults and the pain effect emerged at a later time window, possibly reflecting slower, less efficient processing in children compared with adults and underscoring the importance of including longer time frames in research on children’s brain oscillations. Unlike several EEG and MEG studies in adults, the pain effect in preadolescence was expressed...
as stronger alpha power to the painful versus nonpainful stimuli in sensorimotor areas. This pain effect was found in a time window that was characterized by alpha rebound, with alpha power gradually increasing from 500 ms post-stimulus, particularly to the painful stimuli. Alpha “rebound” refers to the increase of cortical synchronization of alpha oscillations in sensorimotor regions after own or observed movement. Studies have shown that when individuals produce own movement or observe others’ movement, there is a decrease in alpha synchronization followed by a gradual increase in alpha synchronization until return to baseline. Hence, this phenomenon is believed to index increased cortical inhibition and restabilization of the sensorimotor cortex. Our findings are consistent with those of an EEG study in adults by Mu et al. who also found stronger alpha synchronization to painful stimuli. In this study, negative correlations between subjective ratings of painfulness and alpha power elicited by each picture emerged, indicating that the stronger alpha power in response to pain represents cognitive control and regulation of the painful stimuli in the brain’s pain matrix. This accords with theoretical models postulating that alpha oscillations represent a specific top-down inhibitory mechanism, and the temporal pattern of our data tapping top-down processes lends further support to these perspectives. Indeed, developmental studies found that children experience the stimuli presented in this study as more painful than adults. Thus, preadolescents can experience others’ pain as more overwhelming than adults and modulate their initial sensory response, and this could manifest as stronger alpha power in the rebound phase to the painful compared with nonpainful stimuli in the SMA. However, because many factors contributing to the development and functioning of alpha oscillatory activity remain unknown, such interpretation should be considered preliminary, and much further research is required to fully understand the data.

Children of mothers with depression showed greater difference between pain and no pain in the rebound phase compared with controls, which was localized to the pSTG. The pSTG is a critical node in the mentalizing network and plays a key role in socio-cognitive abilities, including biological motion, inferring intentions, causality, and...
theory of mind, and understanding nonverbal socio-cognitive cues. Thus, alpha power in the rebound phase in pSTG could imply that children of mothers with depression decrease mentalizing-related processing of others’ pain earlier than children of healthy mothers. This could suggest that such children not only abort late sensory-motor processing, as seen in the SMA, but also terminate socio-cognitive processing of the distressing stimuli. As seen in this study, pSTG activation was unrelated to emotion detection, suggesting that maternal depression interferes not with the child’s ability to classify social cues but with top-down social processing, potentially interfering with higher-level processing of negatively arousing social stimuli. However, it is important to note that pSTG activation has been related to multiple brain functions, and more studies are required to verify our interpretation.

The nature of our sample, which was otherwise low risk, was as follows: mothers were healthy, educated, older than 21 years, and cohabiting, and the long-term predictions of maternal caregiving patterns might suggest a “sensitive period” in maturation of the social brain. Although the nature of our sample, as most studies performed in humans, cannot allow us to determine the causality of this correlation, it is consistent with much previous research on the effects of maternal depression on child development. Mainly, research has shown that infancy and toddlerhood are critical periods in the effects of maternal depression on propensity to psychopathology in offspring. It is possible that early and chronic maternal depression and the mother’s uncontained style lead to overwhelming the children’s neural response to highly arousing negative stimuli and weakness of top-down mechanisms to process intense social information. Indeed, the development of top-down mechanisms, including emotion regulation, executive functions, and effortful control, have been shown to be disrupted in children of mothers with depression. The neural structures supporting these functions, such as white matter development, amygdala size, and cortical thickness in prefrontal regions, are also altered in such children. Importantly, the adaptive development of emotion regulation and socio-cognitive competencies is codependent during preadolescence. For instance, social motivation underpins adolescents’ capacity to use cognitive control, which in turn enables them to act in a prosocial manner and maintain peer relationships. As such, our data, pinpointing decreased late processing in children of mothers with depression in an area related to socio-cognitive functions is alarming, particularly because preadolescence marks a sensitive period for the onset of psychological disorders that are often of a chronic, lifetime course.

We found that early caregiving patterns—mother’s intrusive, inconsistent, and uncontained style in infancy and decreased give-and-receive reciprocity at preschool age—predicted greater alpha power in the pSTG at 11 years of age above and beyond maternal depression. This is consistent with animal studies demonstrating the lifetime effects of the maternal species-specific behaviors during the early sensitive period on offspring brain maturation, particularly on systems implicated in social affiliation and stress management. In rodents, maternal licking and grooming carries a unique effect on shaping pups’ hypothalamic-pituitary-adrenal reactivity above and beyond the effects of nursing and maternal presence. These differences in stress reactivity lead to alterations in brain development that remain stable throughout life. Our biobehavioral model suggests that in humans, these species-specific behaviors are embedded within the experience of mother–child synchrony, the online coordination of maternal and infant nonverbal cues, and maternal attunement to the infant’s changing needs. These patterns of maternal behaviors, disrupted in cases of maternal depression, have been shown to predict the development of emotion regulation and hypothalamic-pituitary-adrenal reactivity in children. Interestingly, in the present sample, at 6 years we found that maternal intrusiveness predicted children’s inability to decrease the cortisol response during a home visit, which in turn was associated with children’s lower empathic response to the experimenter’s distress, further supporting the hypothesized link among maternal intrusiveness, children’s unregulated stress, and decreased capacity for empathy. Overall, our findings underscore the importance of early life stress, associated with exposure to maternal depression and its concomitant disruptions to maternal caregiving, for maturation of the neural basis of empathy and highlight the need for early interventions that focus on maternal attunement and consistent parenting.

Several study limitations should be mentioned. It is important to emphasize that although our study is prospective and longitudinal and the groups are carefully matched, no causality can be inferred, and some unmeasured variable could have contributed to the findings; thus, the term “effects” used here refers to statistical, not causal, effects. In addition, although studies found links between the individual’s neural response to others’ pain, in particular modulations of alpha oscillations, with behavioral measurements, the associations between the neural and behavioral substrates require much further research. Because it is not possible to conduct magnetic resonance imaging in participants younger than 18 years for research purposes in Israel, we did not have individual anatomic data, limiting our ability to fully ensure the accuracy of the source estimates. We also did not include a wide age range of children, and much further research is required to cover the entire transition from childhood to adolescence.

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<thead>
<tr>
<th>B</th>
<th>SE</th>
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<tbody>
<tr>
<td>Group (depressed/controls)</td>
<td>17.26</td>
<td>7.46</td>
</tr>
<tr>
<td>Maternal intrusiveness—9 mo</td>
<td>8.09</td>
<td>3.8</td>
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<tr>
<td>Dyadic synchrony—6 y</td>
<td>7.43</td>
<td>3.6</td>
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<tr>
<td>$R^2 = 0.33, F_{3,36} = 5.77^{**}$</td>
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Note: SE = standard error.
* $p < .05$, ** $p < .01$. 

**TABLE 1** Regression Analysis Predicting the Difference Between Average Alpha Power in Pain and Average Alpha Power in No Pain in the Cluster Located in the Right Posterior Superior Temporal Gyrus.
Moreover, although fathers in our sample reported below clinical levels of anxiety and depressive symptoms, we did not conduct full psychiatric diagnosis on fathers. Although our sample is large for an imaging study, the depressed group is relatively small, highlighting the tradeoffs of a well-selected sample. The group difference in the number of viable trials poses an additional limitation; children of mothers with depression moved more than controls, and this could have resulted from their lower regulatory capacities or attention span; because these abilities were not measured, we could not control for their potential impact. However, because no significant correlations were found between the number of viable trials and alpha power in the pSTG, the group difference found in activation in this area is probably unrelated to the number of viable trials. Much further research is needed to test the interplay between cognitive control and social processing in children of mothers with depression to further understand the exact disruption to maturation of the social brain and its infancy precursors. Much further effort is required to untangle the cross-generational transmission of vulnerability from mothers with depression to their offspring; understand how patterns of maternal care implement in the child’s brain, endocrine systems, behavior, and relationships; and examine how these children meet the next life transitions, such as the pubertal transition, leaving home, forming intimate relationships, and eventually parenting their own children. &

REFERENCES


SUPPLEMENT 1

METHOD

Participants were recruited in 7 waves of data collection.

First Wave of Data Collection: Birth
The initial cohort included 1,983 women who were consecutive admissions to 2 university hospitals and were recruited on the second day after birth. Research assistants visited the maternity wards of 2 tertiary care hospitals in a large metropolitan area and invited women who were physically healthy by their own account, delivered a healthy term singleton infant (excluding genetic disorders and infants requiring specialized medical care or neonatal intensive care unit hospitalization), completed at least 12 years of education, and were cohabitating with the infant’s father to participate in a study on maternal post-partum mood. Women completed demographic questionnaires and the Beck Depression Index (BDI)\(^1\) and the State-Trait Anxiety Inventory (STAI)\(^2\) questionnaires. Recruitments were conducted twice a week in each ward, and 39.8% of the women approached refused participation. Hospital records showed no systematic differences on demographic variables between participating and declining women or between women in the 2 hospitals. Only mothers who were free of physical illness, completed high school, were older than 21 years, were married or cohabitating, and their infants, who were healthy, term, and singleton, were included. In all families, the mother was the primary caretaker for the child. Families were above the poverty line as indexed by income above the poverty cutoff (6000 NIS per month, approximately $1,800).

Second Wave of Data Collection: 6 Months
Of the 1,983 women recruited at birth, we selected women in the high (BDI scores \(>11\)) and low (BDI \(<9\)) ends of the depressive symptom continuum at birth to complete measurements of anxiety and depression at 6 months (n = 900 approached, n = 680 responded, 75.5%). No differences related to demographic, medical, or mood factors at birth were found between responding and nonresponding mothers.

Third Wave of Data Collection: Questionnaires at 9 Months
Of the 680 women who responded at 6 months, we sent questionnaires to those at the high and low ends of the BDI scores at 9 months (n = 350 approached, n = 254 responded, 72.5%). No differences related to demographic or medical factors or mothers’ mood at 6 months were found between those who did and did not respond.

Fourth Wave of Data Collection: Home Visit at 9 Months
Of the 254 mothers who responded at 9 months, we contacted 210 mothers at the high and low ends of the depressive symptomatology who did not report high anxiety symptoms (STAI score \(<43\)). Of those, 192 agreed to participate in the home visit (91.4%), with no differences in mood variables at 9 months between those who agreed and those who declined. These 192 mothers were assessed by a clinical psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).\(^3\) Ten minutes of mother–child free-play interaction were filmed.

Fifth Wave of Data Collection: Home Visit at 6 Years
Of the 192 families seen at 9 months, we contacted all families we were able to locate at 6 years. One hundred fifty-six families (81.3%) including mothers, fathers, and children were diagnosed by a clinical psychologist using the SCID-I,\(^3\) and children were diagnosed using the Development and Well-Being Assessment (DAWBA).\(^4\) Ten minutes of mother–child free-play interaction were filmed.

Sixth Wave of Data Collection: Home Visit at 9 Years
Of the 156 families seen at 6 years, we contacted all families we were able to locate at 9 years. One hundred twenty-seven families (81.4%) including mothers, fathers, and children were diagnosed by a clinical psychologist using the SCID-I,\(^3\) and children were diagnosed using the DAWBA.\(^4\)

Seventh Wave of Data Collection: Magnetoencephalography at 11 Years
Of the 127 families seen at 9 years, we contacted 113 families at 11 years and then excluded 14 families because of comorbid disorders (e.g., anxiety and eating disorders). Of these, 90 families (79.6%) were found and were willing to participate. Those families were invited to the magnetoencephalographic laboratory, and attrition was mainly related to inability to locate families. There were no significant demographic or psychopathologic differences between those who dropped out and those who continued. At 9 years, mothers were diagnosed by a clinical psychologist using the SCID-I,\(^3\) and children were diagnosed using the DAWBA.\(^4\)
FIGURE S1  Root mean square of power in pain and no-pain conditions throughout the trial.

![Graph showing root mean square of power in pain and no-pain conditions throughout the trial.]

<table>
<thead>
<tr>
<th></th>
<th>Without Depression</th>
<th>With Depression</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Mother education</td>
<td>14.24</td>
<td>2.54</td>
<td>13.97</td>
</tr>
<tr>
<td>Mother age (y)</td>
<td>42.46</td>
<td>4.07</td>
<td>41.5</td>
</tr>
<tr>
<td>Father education</td>
<td>13.42</td>
<td>3.24</td>
<td>13.93</td>
</tr>
<tr>
<td>Father age (y)</td>
<td>45.45</td>
<td>4.73</td>
<td>43.14</td>
</tr>
<tr>
<td>Child age (mo)</td>
<td>133.67</td>
<td>12.37</td>
<td>137.35</td>
</tr>
<tr>
<td>Child gender: Male, %</td>
<td>66.67</td>
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<td>55.17</td>
</tr>
<tr>
<td>Child birth order: First, %</td>
<td>34.15</td>
<td></td>
<td>41.67</td>
</tr>
</tbody>
</table>

Note: NS = not significant.
$^a$61.97% of the sample were male.
$^b$36.92% of the sample were firstborns.
TABLE S2  Coordinates and Sizes of Significant Clusters

<table>
<thead>
<tr>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Cluster Size</th>
<th>F</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main effect for condition</td>
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<td></td>
<td></td>
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<tr>
<td>Supplementary motor area</td>
<td>B</td>
<td>−7.5</td>
<td>17.5</td>
<td>62.5</td>
<td>43</td>
<td>9.49</td>
</tr>
<tr>
<td>Interaction effect group x condition</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior superior temporal gyrus</td>
<td>R</td>
<td>−32.5</td>
<td>37.5</td>
<td>37.5</td>
<td>199</td>
<td>10.36</td>
</tr>
</tbody>
</table>

Note: B = Bilateral; R = Right.

TABLE S3  Correlation Matrix Between Study Variables

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<tr>
<th></th>
<th>2</th>
<th>3</th>
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<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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</thead>
<tbody>
<tr>
<td>Alpha activation to pain minus no pain</td>
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<td></td>
<td></td>
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<tr>
<td>1. SMA</td>
<td>0.04</td>
<td>0.01</td>
<td>0.21</td>
<td>−0.06</td>
<td>0.06</td>
<td>−0.14</td>
<td>0.004</td>
<td>−0.14</td>
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<tr>
<td>2. R pSTG</td>
<td>0.38*</td>
<td>0.04</td>
<td>0.19</td>
<td>−0.25*</td>
<td>0.02</td>
<td>−0.21</td>
<td>−0.06</td>
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<tr>
<td>Interaction behaviors at 9 mo</td>
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<td>3. Maternal intrusiveness</td>
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<td>0.04</td>
<td>−0.09</td>
<td>−0.10</td>
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<tr>
<td>4. Dyadic synchrony</td>
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<td>0.16</td>
<td>0.03</td>
<td>0.19</td>
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<td>Interaction behaviors at 6 y</td>
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<tr>
<td>5. Maternal intrusiveness</td>
<td>0.05</td>
<td>0.02</td>
<td>0.03</td>
<td>−0.16</td>
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<td>6. Dyadic synchrony</td>
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<td>0.20</td>
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<td>Emotion recognition at 11 y</td>
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<td>7. Neutral</td>
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<td>8. Sadness</td>
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<td>9. Happiness</td>
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</tr>
</tbody>
</table>

Note: Alpha power is calculated by the average power within the significant clusters in pain minus the average power within the significant clusters in no pain. R pSTG = right posterior superior temporal sulcus; SMA = supplementary motor area.

*p < .05; **p < .001.

SUPPLEMENTAL REFERENCES