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Does Exposure to Persistent Maternal Depression Alter the Developing Brain's Empathetic Circuitry?

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It has been recognized for many years that maternal depression has significant consequences on the early social development of children living in the home. Such children often have poor emotional regulation, increased social withdrawal, reduced empathic responses to their mother and others, and additional maladaptive social behaviors.[1–2] An altered mother-child relationship is widely thought to be the origin of these social aberrations, as children learn empathy and other social responses through interactions with their caregiver, and depressed mothers are known to be more intrusive and less synchronous in their interactions with infants and young children.[3–5] However, while the impact of maternal depression on children's social behavior has been the focus of numerous studies, very little is known about how the underlying brain circuitry may be affected by such rearing conditions. Identifying the impact of maternal depression on the brain circuitry of social behavior is of major clinical importance, as such knowledge may help clarify the mechanisms underlying social withdrawal, vulnerability to psychopathology, reduced empathy, and other common outcomes.

In this issue of the *Journal*, Feldman et al.[6] report the first prospective longitudinal study investigating how brain circuitry and social behavior is altered in children exposed to maternal depression. They focused on the development of empathy, as empathic responses to the distress of others involves a multidimensional array of processes, including automatic sensorimotor arousal, cognitive appraisal, emotional regulation, and the capacity to consider multiple viewpoints simultaneously (e.g., first- vs. third-person). Their impressive study sample initially included almost 2000 healthy Israeli mothers who had at least a high school education, cohabitated, lived above the poverty line, and who had given birth to full-term healthy babies. Mothers were assessed for depression and anxiety six- and nine-months post-partum, and those who were in the highest and lowest quartiles on the Beck Depression Inventory and had no elevated anxiety according to the State-Trait Anxiety Inventory were followed up at six years. Following the six year visit, the mothers were divided into two groups: those who had been consistently depressed for the past six years and were diagnosed with major depressive disorder (MDD), and those who had not been depressed at any time point and were not diagnosed with any major psychiatric condition. Both of these groups were then followed up at eleven years. A total of 90 mothers agreed to participate in a

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brain imaging session using magnetoencephalography (MEG), and to complete emotional detection and empathy to pain tasks, among other neuropsychiatric measures.

MEG is an emerging method to study human brain function that is totally noninvasive, silent, and far less claustrophobic than functional MRI (fMRI). The method requires that the participant enter a vault-like magnetically-shielded room, sit a specially-designed chair, and place their head in a helmet-like structure that is attached to a large gantry. At all times, the environment is totally silent and the participant's face is exposed, with generally at least eight feet of open space in front of them. Under some circumstances, parents can be allowed inside the special room during the scan. These unique characteristics have made MEG a favorite imaging tool for investigators interested in pediatric studies, as the scanning session is typically well-tolerated by the vast majority of children. Although MEG systems have been around for many years, the instrumentation and analytical sophistication of the field have dramatically increased over the past decade,[7–8] and MEG methods like those used by Feldman and colleagues[6] are capable of temporal accuracy below a millisecond and, importantly, sub-centimeter spatial precision, especially in the cortex. Like fMRI, participants often complete a cognitive task during the MEG session, and children in the Feldman et al. study performed an empathy to pain task, which involved viewing hands and feet in painful and non-painful situations as MEG data was collected. The resulting MEG data were analyzed using cutting-edge methods to identify the involved brain regions and the specific time periods of active neural processing.

Several aspects of the results of Feldman et al.[6] are of major clinical importance for understanding the impact of maternal depression on brain and neuropsychiatric function. First, children with depressed mothers were twice as likely to have an Axis-I psychiatric diagnosis at age six than were children of non-depressed mothers. Interestingly, this difference decreased over the next three years and was no longer significant at age nine. Despite this apparent normalization of psychiatric symptoms in children of depressed mothers, significant differences in the brain circuitry supporting empathy persisted at least five more years to when the children were 11 years-old. Essentially, Feldman et al. found that viewing painful compared to non-painful stimuli resulted in stronger responses in the supplementary motor area (SMA) across both groups, as well as a significant group-by-condition interaction effect in the right posterior superior temporal gyrus (pSTG). This right pSTG effect was driven by the children of depressed mothers who exhibited stronger responses to pain versus non-painful stimuli in this region, while the non-depressed group showed the opposite pattern of responses (i.e., stronger for non-painful stimuli). Importantly, these differences were only present late in the time course, from approximately 1100 to 1300 ms after onset of the pain/non-pain images, and thus likely reflect differences in stimulus appraisal operations and not basic sensory processing. Finally, Feldman and colleagues were able to connect these differences in neural processing between pain and non-pain stimuli in the right pSTG to clinical characteristics of the mother-child interaction, as both maternal intrusiveness scores at nine months and dyadic synchrony at six years were significantly correlated with activity levels in the right pSTG. Basically, controlling for group, lower maternal intrusiveness in infancy and greater dyadic synchrony in early childhood uniquely predicted normal empathetic processing of other's pain at 11 years, which together forms a

critical bridge as both dimensions of the mother-child interaction are known to be negatively affected by maternal depression.

The findings of Feldman and colleagues[6] fill a major void in our understanding of how exposure to maternal depression during early childhood may alter empathetic processing and the underlying neural circuitry during preadolescence. The finding of differences in the right pSTG late in the time course is of particular interest, as this region has been implicated as part of the mentalizing network[9] and in other developmental disorders like autism.[10] The fact that this difference was only observed late in the time series helps us rule out basic sensory contributions, and look more toward higher-level appraisal processes. Furthermore, this finding also highlights the power of using temporally-resolved imaging methods like MEG, as such temporal precision can help us eliminate possible alternative interpretations (e.g., basic sensory processing), while also enabling unique differences to be discovered that may have otherwise been missed. Essentially, since the difference was only present from 1100 to 1300 ms, it is likely that it would not have been detected had the authors collapsed across the whole time course of stimulus processing, as is often done with other imaging methods.

Future studies in this domain are certainly needed and should identify whether such differences in brain circuitry are unique to the empathic processing of pain. At this juncture, it seems probable that such aberrations will extend to other social behaviors and brain circuits. Another area of major interest would be testing the developmental extent of these differences, as it is possible that some will persist through adolescence, and potentially even adulthood. Indeed, the study by Feldman and colleagues[6] fills a critical gap in our understanding of how maternal depression impacts the social development of children, but also inspires many new questions that future studies, both behavioral and neuroimaging, will need to tackle before we have a solid grasp on the long-term consequences. Nonetheless, such an understanding is definitely within reach and hopefully the best is yet to come.

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