BABY STIMULI AND THE PARENT BRAIN: Functional Neuroimaging of the Neural Substrates of Parent-Infant Attachment

by JAMES E. SWAIN, MD, PhD
Yale Child Study Center, Program for Risk, Resilience and Recovery, New Haven, Connecticut

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ABSTRACT

Interacting parenting thoughts and behaviors critically shape human infants' current and future behavior. Indeed, the parent-infant relationship provides infants with their first social environment, forming templates for what they can expect from others and how best to interact with them. This paper focuses on the functional magnetic resonance imaging (fMRI) experiments relevant to the study of the brain-basis of parenting. First there is a brief introduction to techniques and a selective review of functional neuroimaging studies that examine fMRI responses to infant stimuli: baby sounds or visuals. Next, there is a sample single-subject set of brain imaging data of brain response to own-baby-cry. Finally, there is a proposed model of how infant stimuli activate parent brain circuits, including sensory analysis brain regions, as well as corticolimbic circuits that regulate motivation, reward, and learning about their infants, and ultimately organize parenting impulses, thoughts, and emotions into coordinated behaviors. It is argued that an integrated understanding of the brain basis of parenting has profound implications for understanding long-term parent and infant mental health risk and resilience.

BRAIN IMAGING OF HUMAN PARENT-INFANT RELATIONSHIPS

This paper focuses on the use of brain imaging to understand the brain basis of human parental behavior and thoughts. In these experiments, infant auditory and visual stimuli are combined with the high resolution and noninvasive brain imaging technique of blood-oxygen-dependant functional magnetic resonance imaging (fMRI). fMRI assays brain activity by indirectly measuring changes in regional blood oxygenation. The differences between a region's oxygenated and deoxygenated hemoglobin, between states of action versus inaction for instance, provide characteristic magnetic signals localized to millimeters that are detected by scanners positioned around each subject's head. Functional neuroimaging research has provided researchers with tools to study the actual activity within the brain as a function of various states of mind elicited by sensory stimuli or associated with different cognitive tasks. This technique has already been used to study normal thinking and emotion as well as pathological psychological conditions, such as schizophrenia, depression, and substance abuse. Neuroimaging in psychiatry promises to provide new understandings of how the brain works in these different states and may provide new diagnostic and treatment planning possibilities for those having difficulties bonding with their infants. An important caveat throughout the interpretation of parenting fMRI studies, however, is that brain activity measurements represent an integration of electrical brain activity that may be instantaneous, yet the related blood flow change lags behind over seconds. Furthermore, experimental design captures brain activity over periods of a few seconds or tens of seconds. On the one hand, short blocks or events may capture

ADDRESS CORRESPONDENCE TO: Dr. James Swain, 230 South Frontage Road, New Haven, Connecticut 06520; Phone: (203) 785-6973; Fax: (203) 785-7611; E-mail: james.swain@yale.edu

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briefly held mental states, but miss bigger changes such as sustained emotion; on the other hand, longer blocks may capture more complex brain responses but also average them out, making subtle responses more difficult to detect. Brain activity during these blocks may then be measured and compared between periods of attending to stimuli of interest and control stimuli to generate maps of the brain, indicating differences in brain activity that may be important for one set of perceptions and thoughts versus another. So far, a small group of studies have been published in which parents have been the subjects and infant cries and pictures have been stimuli. In such studies, for example, comparisons of brain activity measured during baby cry versus control sound experience may yield significant differences in certain brain regions that may then be said to relate to the parental experience of a baby cry and therefore the associated parenting thoughts and behaviors. Some of these studies had small subject numbers and fixed effects analyses that do not take intersubject variability into account, while other studies use random effects analyses to account for intersubject variability and permit generalization of findings. I will first describe some aspects of the psychology and neurobiology of parenting (much of which comes from animal research) and human parenting studies with brain imaging published to date. I will then present single brain data from our own group, and conclude with a general model of the parenting brain.

PSYCHOLOGY AND BIOLOGY OF PARENTING

Forming enduring emotional bonds is critical to health. Parenting is a key foundational component of secure attachments. It is the first attachment for infants, and a key or even defining event in the life of adults that may be described in many ways: a stage in life, a personal choice, a psychological and biological transition, a cultural creation, a necessity for the species, and a state of mind. These varied and important characterizations underscore how the real and imagined roles of parents are woven through the tapestry of our developmental psychology. Given the importance of parenting, surprisingly little work has focused on how adults make psychological and biological adjustments to make room in their lives for infants. In 1956, Donald Winnicott, a pediatrician and psychoanalyst, drew attention to "primary maternal preoccupations." He described this state as "almost an illness" that a mother must experience and recover from in order to create and sustain an environment that can meet the physical and psychological needs of her infant. Winnicott[1] further speculated that this special state began toward the end of the pregnancy and continued through the first months of the infant's life. Although this concept has been incorporated into subsequent clinical formulations of disordered mother-infant interactions,[2,3] it has received relatively little scientific attention, especially in consideration of the normative developmental trajectory of parenting.[4–6] Rodent studies have pinpointed brain circuits crucial for maternal behaviors and suggest regions of likely importance for human parenting. Indeed, recent human brain imaging studies are showing that analogous circuits are active in human parenting.[41]

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Although the central nervous system events that accompany parenting relationships in humans are largely unknown, substantial conservation across mammalian species is likely.[7,8] Classical lesion studies in rodent model systems (rats, mice, and voles) have implicated the medial preoptic area (MPOA) of the hypothalamus, the ventral part of the bed nucleus of the stria terminalis (BNST), and the lateral septum (LS) as regions pivotal for regulation of pup-directed maternal behavior in rodents.[9–11] Other animal studies highlight the role of a variety of hormones and neuropeptides in parental care, including estrogen, prolactin, and oxytocin.[10,12,13] The central roles of the hypothalamus and oxytocin have also been highlighted with respect to adult social bond formation.[14,15] Behavioral studies have shown that maternal behavior in the days following birth serves to "program" the subsequent maternal behavior of the adult offspring as well as establishing the pups' levels of hypothalamic-pituitary-adrenal responsiveness to stress.[16–18] There is growing evidence that early-life programming of the mice pups' long-term parenting behavior[19] may be mediated through modulation of the stress-response system.[20] The observation that the effects of early adverse experiences on stress reactivity[21] appear to be reversible with environmental enrichment[22] may point the way to interventions in humans in which there may be neglect or abuse.

BABY CRY AND THE PARENT BRAIN

The process of using fMRI to explore the brain basis of these responses in parents began with Lorberbaum and colleagues[23,24] using standard baby cries as stimuli. Building on the thalamocingulate theory of maternal behavior in animals developed by MacLean,[25]

Lorberbaum and colleagues predicted that baby cries would selectively activate thalamus, cingulate, medial, and orbitofrontal cortex of parents. They first exposed mothers, who were less than 3.5 years postpartum, to blocks of 30 seconds of a standard baby cry versus white noise stimuli.[23] In this small (n=4) study, they found increased activity in anterior cingulate and right medial prefrontal cortex. In the follow-up study,[24] brain activity in breastfeeding first-time mothers (n=10) 4 to 8 weeks postpartum was measured while listening to standard baby cry compared with intensity and pattern matched white noise. In this more methodologically stringent study, with respect to subject selection and stimulus, all of the hypothesized regions as well as midbrain, hypothalamus, striatum, and septal regions—known to be important for rodent maternal behavior— were selectively more active in response to baby cry.[10,11]

It is interesting to consider whether parental neural responses to baby sounds would be different for mothers and fathers, whether parents are first-time or veteran, or at different times in the postpartum as the parent-infant relationship develops.[26] Hypothesizing that gender and experience would affect the neural responses to baby cry and laughter, Seifritz and colleagues[27] studied four groups: mothers and fathers of children under three years of age and nonparent men and women, with 10 subjects in each group. Using an event-related design, which measured localized brain responses to brief six-second events, it was found that over the entire sample, crying and laughing baby stimuli produced more activity in Heshyl's gyrus (auditory cortex). Further, it was reported that women have a decrease in activity to both baby cry and laughter in the anterior cingulate to these brief signals, which was not present in men. This is contrary to other studies,[23,24,26] which may mean that six-second stimuli have a different meaning to new parents compared to 30-second blocks. Finally, looking at parental status, Seifritz and colleagues[27] reported that nonparents activated right amygdala with baby-laugh stimuli but parents did not; while with baby-cry stimuli, nonparents activated right amygdala but parents did not. These data represent the first steps into the study of gender and experience-dependant aspects of parental brain circuitry. With the transforming experience of having a baby and the tendency for parents to be highly preoccupied in the immediate postpartum,[5,28,29] Swain and colleagues[26] hypothesized that parental responses to baby cries might produce activations in certain brain regions that might change over the first several weeks postpartum. These regions may include the thalamus-cortical-basal ganglia circuits akin to those seen in humans relating to ritualistic behaviors, such as with obsessive-compulsive disorder,[28,30] in addition to emotional alarm centers, including amygdala and insula. Using own baby-cry stimuli compared with other baby cry, Swain and colleagues[26] reported regions of relative activation in a group of first-time mothers (n=9) at 2 to 4 weeks postpartum, which included midbrain, basal ganglia, cingulate, amygdala, and insula. Preliminary analysis of the parenting interview data showed that mothers were significantly more preoccupied than fathers, which may be reflected in the relative lack of activation for fathers in amygdala and basal ganglia.[6] It is especially interesting that in the group of primiparous mothers, given the same stimuli at 3 to 4 months postpartum, amygdala and insular activations were not observed; instead, medial prefrontal cortical and hypothalamic activations[31] were seen, perhaps reflecting a change in regional brain responses as the parent-infant relationship develops. It would be interesting to see how measures of parenting behaviors and parent-infant interaction might be reflected in these changing brain activations as parent-infant attachment develops. In a pilot study, Swain and colleagues[32] found correlations between own versus other baby-cry brain activity, and measures of parental preoccupation in 14 first-time mothers at 2 to 4 weeks postpartum were in medial frontal cortex, basal ganglia, and hippocampus.[32] This kind of correlation analysis promises to reveal parenting circuits that are important in responding to baby cry proportional to specific dimensions of the relationship.

BABY VISUALS AND THE PARENT BRAIN

In addition to baby-cry stimuli, several groups are using baby visual stimuli.[26,33–35] Building on their neuroimaging of romantic love,[36] which showed areas of activation in the insula, anterior cingulate, and basal ganglia when adults are shown pictures of romantic partners versus control pictures, they are more recently studying parental love. Hypothesizing that reward and emotion circuits, which are important for aspects of romantic love, might also be involved in maternal love, Bartels and Zeki[33] exposed parents to photographs of own, familiar, and unfamiliar children (9 months to 6 years of age) to study parental brain circuits. They reported relative activations in anterior cingulate, insula, basal ganglia (striatum), and midbrain (periaqueductal gray). These regions may mediate the emotionally rewarding aspects of maternal behavior. Bartels and Zeki[33] also reported decreases in activity in areas important for negative emotions, avoidance behavior, and social assessment. They suggest a push-pull mechanism for maternal behavior in which child stimuli activate

reward and shut down avoidance circuits. Fisher and colleagues[37,38] are also looking at brain activity of romantic love, which is perhaps related to parental love. Using picture stimuli, they have differentiated brain responses corresponding to "wanting" and "liking," in which wanting was associated with dopaminergic circuits activations and involved medial frontal cortex. In addition, they found that length of relationship was related to cingulate and insular cortex activation.

Nitschke and colleagues[35] looked at primiparous mothers 2 to 4 months postpartum (n=6) responding to pictures of their own infants compared to age-matched control subjects. They reported bilateral orbitofrontal cortex activations, which were correlated with ratings of pleasant mood. These data point to the orbitofrontal cortex (OFC) as a center important for positive attachment of mother and child. Using photographs of older children (5–12 years old), Leibenluft and colleagues[34] found that own versus other comparison in a sample of seven mothers activated amygdala, insula, and anterior paracingulate regions, which they interpreted as emotion and theory-of-mind regions relating to the ability to predict and explain other peoples' behaviors. Using 40-second blocks of silent video of own versus other infants (4–8 months old) as stimuli for nine mothers, Ranote and colleagues[39] reported activations in amygdala, temporal pole, and occipital regions. While gazing at 30-second blocks of own versus other infant photographs, both mothers and fathers 2 to 4 weeks postpartum activated a familiar set of regions, including brainstem, amygdala, basal ganglia, cingulate, and occipital cortices.[26]

Thinking about the contribution of the infant's affect to maternal brain function prompted a recent study by Noriuchi and colleagues[40] that used silent video clips of their own and other infants in play or separation situations. First, they confirmed the increased activity, associated with recognizing own baby pictures, in certain brain regions, including cortical orbitofrontal, anterior insula, and precuneus cortical areas, as well as subcortical regions, including the periaqueductal gray and putamen. These are areas active in arousal and reward learning. Furthermore, they found strong and specific differential responses of mother's brain to her own infant's distress in substantia nigra, caudate nucleus, thalamus, posterior and superior temporal sulcus, anterior cingulate, dorsal regions of OFC, right inferior frontal gyrus, and dorsomedial prefrontal cortex. They interpreted OFC and related activations as part of circuits required for the execution of well-learned movements. This could also be interpreted as activation in emotion regulation and habitual behavioral response systems that are active in a range of normal and abnormal emotion-control states, including obsessive compulsive disorder.[41] They also found correlations in OFC with own baby response and happiness as well as to their own distressed baby response in the superior temporal regions. This is consistent with the importance of these areas in social thoughts and behaviors. Indeed, it seems that movies and other more complex stimuli may be used to stimulate parents' brains in ways that may be measured and combined with behavioral measures to better understand the functional architecture of parenting brain systems.

Finally, Strathearn and colleagues have also been studying healthy mother-infant dyads using fMRI to examine maternal brain regions activated in response to visual infant facial cues of varying affect (smiling, neutral, and crying). They have completed a pilot study of eight healthy, right-handed mothers without a history of psychiatric impairment or child maltreatment along with their infants aged between 3 and 8 months. They assessed serum oxytocin levels sequentially from the mothers during a standardized period of mother-infant interaction, during which they acquired infants' facial expression videotapes. Maternal brain activity was then assayed with fMRI in response to six-second exposures to the facial images of their own infants compared with familiar and unknown infant facial images.[42] Areas of significant activation (uncorrected $p<0.005$) unique to own-infant viewing included brain reward areas with dopaminergic projections (ventral striatum, thalamus and nucleus accumbens), areas containing oxytocin projections (amygdala, bed nucleus of the stria terminalis, and hippocampus), the fusiform gyrus (involved in face processing), and bilateral hippocampi (involved in episodic memory processing). Further, a positive, but nonsignificant, trend in this small sample was seen in serum oxytocin concentrations before and after mother-infant interaction (prior to scanning), suggesting a possible correlation between brain activation and peripheral affiliative hormone production. A further study using crying infant faces as fMRI stimuli revealed bilateral activation of the anterior cingulate and insula.[43]

While our group/composite data is under review elsewhere, I would like to present some provocative single-subject data that will give the reader an impression of the kind of work that is underway in a number of laboratories around the world. Replication in groups with reliable statistics and across research groups over the coming years may confirm some of these findings. The results of an experiment on a single primiparous mother and father at two early postpartum time points are presented next and suggest some of the parental circuits important for response to baby stimuli and how they may shift in

the early postpartum (Figures 1A–D).

The responses in the amygdala in a first-time mother 2 to 4 weeks postpartum are in keeping with animal studies, supporting its importance in fear and arousal.[44] Human imaging research supports the notion that the amygdala in humans, among other functions, serves in the detection of environmental threat[45] and emotional vigilance.[46] The basal ganglia have been implicated in obsessive thinking, and the frontal cortex is involved in planning. Thus, the involvement of amygdala, basal ganglia, and frontal areas could be interpreted to be part of an "own" baby-cry response circuitry that involves an alarm-like consideration of salience and fear of harm coming to the infant, activation of preoccupations to ensure that all considerations regarding the safety of the baby are reviewed, and planning to respond appropriately. Perhaps by 3 to 4 months postpartum (Figure 1B), the "own" baby-cry is less anxiety-provoking to a mother and more associated with responses in the hypothalamus and anterior cingulate—areas for hormonal regulation systems as well as emotional arousal.

Data from one first-time father, unlike that of one first primiparous mother presented in Figures 1A and B, did not appear to show activations in the amygdala in response to own baby-cry, but instead showed activity in the anterior cingulate and visual areas in response to own baby-pictures (Figure 2A). It is interesting that in this subject, baby cry appears to be activating visual areas—perhaps involving visualization of the subject's own baby. At 3 to 4 months postpartum (Figure 2B), additional activations are seen in medial frontal and parietal areas. Medial frontal activity (close to the anterior cingulate activity seen in the mother [Figure 1B]) in this experiment is consistent with number of studies for a range of emotional states.[47]

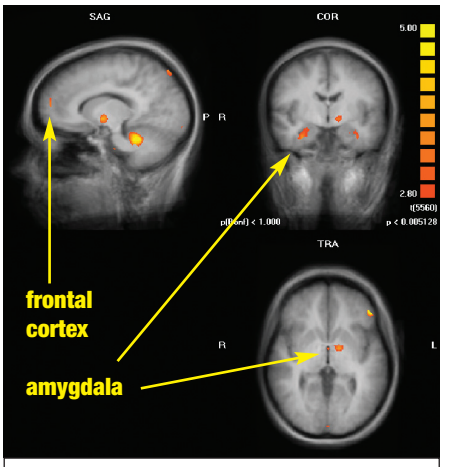

FIGURE 1A. First-time mother, 2–4 weeks postpartum, own vs. other baby cry

amygdala, basal ganglia, cerebellum, frontal cortex

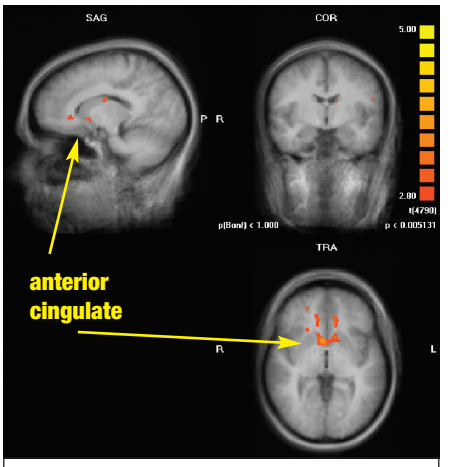

FIGURE 1B. First-time mother, 3–4 months postpartum, own vs. other baby cry

hypothalamus, anterior cingulate

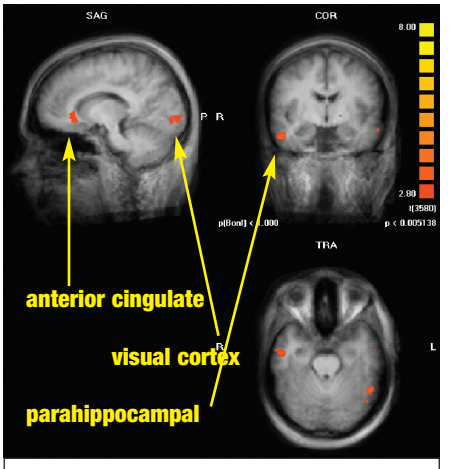

FIGURE 2A. First-time father, 2–4 weeks postpartum, own vs. other baby cry

anterior cinglate, visual, temporal/parahippocampal

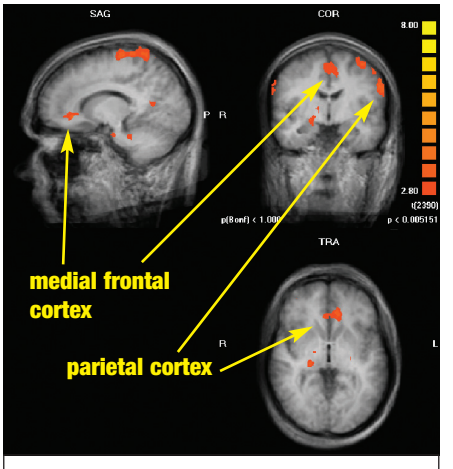

FIGURE 2B. First-time father, 3–4 months postpartum, own vs. other baby cry

anterior and cingulate, medial frontal, parietal

PARENTAL BRAIN MODEL

Based on brain imaging of human parents and informed by animal work,[41] the following rudimentary model is presented in Figure 3 in an attempt to begin to account for parenting behaviors with brain circuits. First, key parenting sensory signals, including cry, visuals as well as touch and smell , must be organized in sensory cortices, which appraise the input and interact with subcortical memory and motivation structures. With sufficient motivation, brain circuits are activated, that are designated as corticolimbic modules, that we have delineated as reflexive caring impulses, such as those studied in preclinical animal models and requiring little or no cortical input, such as licking, grooming, and nursing, in which the hypothalamus, MPOA, and other limbic and thalamocingulate circuits are of primary importance.[48] In humans, this might be a caring endophenotype[49] amenable to further study. In addition, cognitive circuits would be brought online, including those that regulate "mirroring," empathy, planning and further cognitive flexibility, including the inferior frontal, insular, and superior-temporoparietal cortical regions. These regions might allow accurate modeling

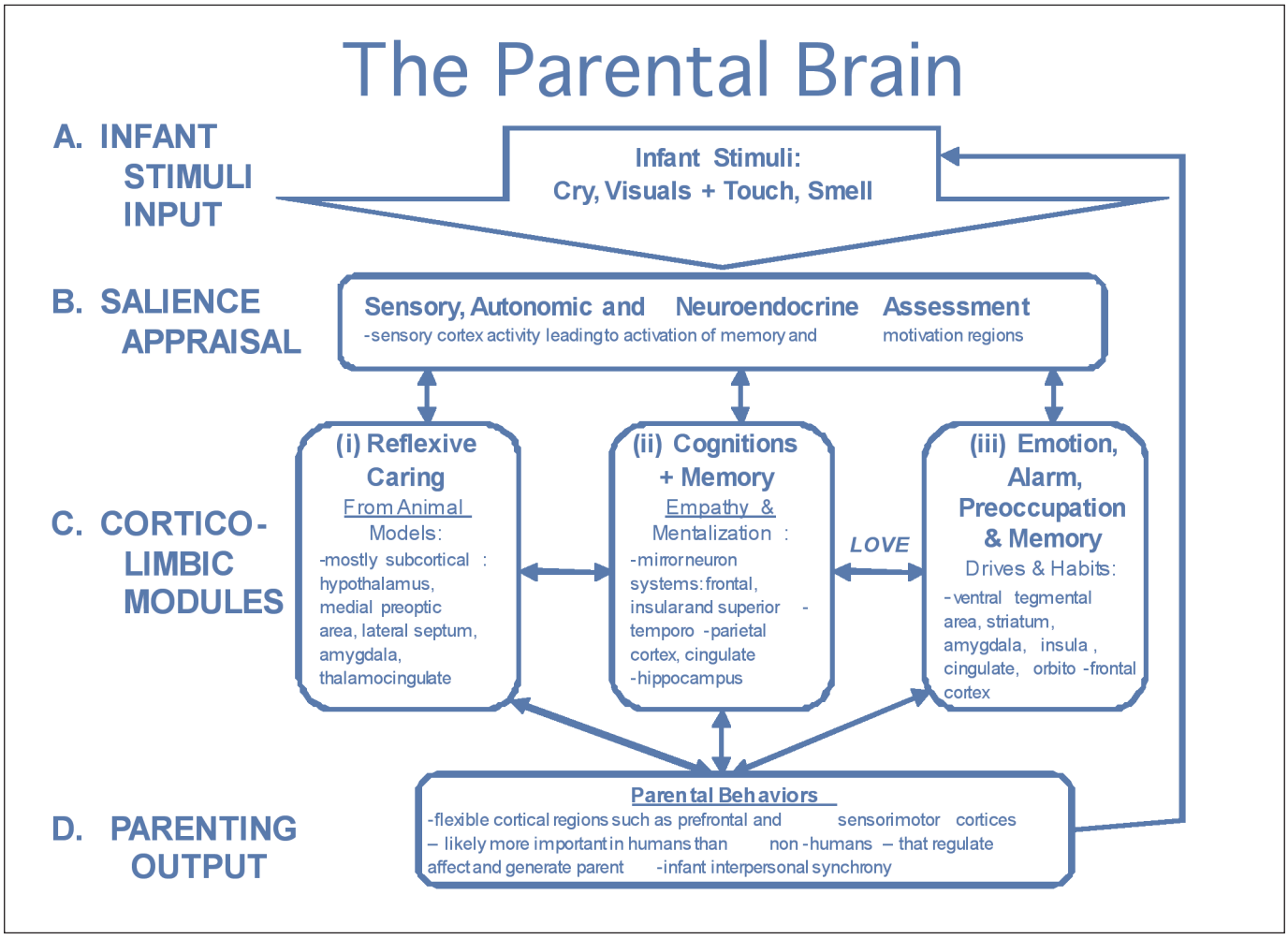

FIGURE 3. Baby stimuli are internalized and activate motivation and neurohormonal circuits that drive corticolimbic modules: (i) reflexive caring circuits from animal models of parenting of chiefly subcortical location, (ii) cognitive systems including mirroring and mentalization, and (iii) emotion and alarm systems from limbic circuits to cortical areas that regulate habitual behaviors. Figure adapted from Swain JE, Lorberbaum JF. Imaging the human parental brain. In: Bridges R (ed). *Neurobiology of the Parental Brain.* Burlington, MA: Academic Press, 2008:83–100.

of the baby's mind to predict needs and plan behavior.[50–53] Finally, other alarm/emotion-preoccupation anxiety systems might be activated to increase arousal and regulate parental worries and habitual responses in coordination with memory systems. These emotional circuits might include the ventral tegmental area, striatum, amygdala, insula, cingulate cortex, and OFC.[5,41] Thus, reflexive, cognitive, and emotional modules would interact with each other in the experience of parental love and attachment formation, and work together to generate coordinated hormonal, autonomic, and behavioral output required for parenting (via motor cortex and hypothalamus. The output would also feed back to sensory systems during dynamic interactions with the infant[2] to generate new input.

Each of these corticolimbic modules requires investigation with specific experiments.

Thus, it appears that some fundamental aspects of an "own" baby-response system begin to emerge in the first few weeks postpartum and include the anterior cingulate, amygdala, basal ganglia, parahippocampal areas, and frontal areas. This is under study in our lab in groups of first time and veteran parents of both genders. Combinations of well-controlled stimuli and sensitive psychometric data promise to clarify the specific importance of these brain circuits in mediating normal parental behavior, and promise to allow us to develop meaningful endophenotypes for improved early detection and treatment of peripartum mental health problems, such as postpartum depression and anxiety. Understanding the brain basis of risks and resilience to these postpartum conditions is of great importance because they can have profound effects on the quality of parent-infant interactions and long-term health of the infant.[54,55]

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