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Review

Storing maternal memories: Hypothesizing an interaction of experience and estrogen on sensory cortical plasticity to learn infant cues

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ABSTRACT

Much of the literature on maternal behavior has focused on the role of infant experience and hormones in a canonical subcortical circuit for maternal motivation and maternal memory. Although early studies demonstrated that the cerebral cortex also plays a significant role in maternal behaviors, little has been done to explore what that role may be. Recent work though has provided evidence that the cortex, particularly sensory cortices, contains correlates of sensory memories of infant cues, consistent with classical studies of experience-dependent sensory cortical plasticity in non-maternal paradigms. By reviewing the literature from both the maternal behavior and sensory cortical plasticity fields, focusing on the auditory modality, we hypothesize that maternal hormones (predominantly estrogen) may act to prime auditory cortical neurons for a longer-lasting neural trace of infant vocal cues, thereby facilitating recognition and discrimination. This couldthen more efficiently activate the subcortical circuit to elicit and sustain maternal behavior.

1. Introduction

Parental behaviors are an evolutionarily conserved social behavior observed across vertebrate species (Numan and Insel, 2003). These behaviors first arise after birth when parents respond to sensory cues from their offspring and are maintained until infants reach independence. In mothers, these behaviors are facilitated by a slew of hormonal changes that alter her overall physiological state during parturition. The major hormonal changes that accompany parturition are a surge of steroid hormones, namely estrogen and progesterone, which in turn modulate the release of other key neurochemicals like oxytocin and prolactin (Kendrick, 2000; Kinsley, 2008; Neumann, 2009). Changes in the levels of these steroid hormones and neurochemicals can then alter neural activity, gene expression, synaptic plasticity and neuronal structure within the circuitry of the maternal brain, ultimately initiating and retaining a mother's behavioral responsiveness to infant cues.

Much of the work to understand the brain mechanisms of maternal behavioral has led to the delineation of a canonical hypothalamic-limbic circuit involved in the onset and maintenance of maternal responsiveness. This circuit – with key nodes in the medial preoptic area (MPOA), amygdala, ventral tegmental area (VTA), and nucleus accumbens (NAcc) – is critical for the motivational aspects of motherhood (Numan and Sheehan, 1997; Numan and Insel, 2003; Numan, 2007). However, even though some studies suggest a further role of this circuit in consolidating maternal memories (Lee et al., 1999b; Li and Fleming, 2003; Numan and Insel, 2003), we still do not completely understand where the long-term engram of offspring cues are stored. In particular, a usual assumption of the canonical model is that the neural input forward from sensory cortices representing these stimuli enters the subcortical circuit in the same way regardless of whether or not a female has been or is a mother. The main reason why mothers respond more positively to those cues than females that have never had or raised infants is then explained by intrinsic processing differences within the canonical circuit arising in part from hormonal modulation (Numan and Insel, 2003; Numan and Stolzenberg, 2009). However, this model does not fully incorporate the role of plasticity in the sensory input itself, which could arise as the cues from offspring become more salient. In fact, such sensory plasticity, possibly aided by hormonal priming in the maternal context, could be an important contributor to the formation and retention of maternal memories by providing a more efficient activation of the subcortical maternal circuit to more readily elicit the maternal responsiveness of experienced mothers.

The role of experience-dependent sensory cortical plasticity and its interplay with hormonal effects on neural circuits is a relatively

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new topic in the neurobiological research of both maternal behavior and sensory processing (Miranda and Liu, 2009; Pinaud and Tremere, 2012). Here, we make the argument for the view that sensory plasticity contributes to the establishment of maternal memories in order to facilitate the recognition of and differential response to infant cues. Since this topic lies at the intersection of otherwise separate bodies of research on sensory processing and maternal behavior, we try here to review the literature that may be unfamiliar to one or another side in the hopes that it helps explain the mutual interest in the topic, and spurs a deeper integration of the two. We begin by briefly reviewing work illustrating the importance of infant cues in triggering maternal behaviors, and the function of the canonical maternal motivation circuit in responding to those cues. We then discuss classic as well as recent studies implicating the cortex as a whole, and sensory cortex in particular, in maternal behavior and maternal memory. Although the processing of proximal sensory cues from offspring, such as olfactory and tactile stimuli, has been studied in more depth in the context of maternal behaviors, little is known about the processing of distal cues such as vocalizations that draw approach behavior. Hence, we focus here on the auditory cortex and its processing of vocal cues from offspring, using mice as a primary model, where more research has been conducted, and to which we have also contributed. We argue that experience-dependent plasticity, whose underlying neurobiology has been studied widely using (non-maternal) laboratory learning contexts, is likely a key mechanism in the maternal context through which a neural memory trace of offspring vocalizations is created in a mother's auditory cortex. Finally, we discuss some recent data that leads us to hypothesize that this memory trace of offspring cues might be more robustly established in mothers through a combined role of rearing experience paired with a facilitatory action from steroid hormones like estrogen at parturition.

2. Importance of sensory processing for maternal behavior

Sensory stimulation by offspring is essential for the performance of maternal behaviors (Kinsley and Amory-Meyer, 2011; Lambert and Kinsley, 2012; Okabe et al., 2012). For example, olfactory cues from offspring act as powerful overall inhibitors or stimulators of maternal behavior in mammals. Female sheep are repelled by amniotic fluid throughout their estrous cycle and gestation, but for a few hours following parturition, they become attracted to it (Levy et al., 2004; Nowak et al., 2011). In fact, parturient ewes are more attracted to a fake lamb smeared with amniotic fluid than to one without amniotic fluid (Vince et al., 1985; Gonzalez-Mariscal, 2001), while anosmic female sheep are neither repelled by nor clearly attracted to amniotic fluid (Levy et al., 1983). Rabbits also display similar olfactory preferences in the maternal context: an absence of placentophagia in female rabbits is observed during estrus and pregnancy, whereas most females become placentophagic at parturition (Melo and Gonzalez-Mariscal, 2003). Even human mothers show olfactory preferences associated with motherhood. In one study, new mothers, 1-month postpartum mothers and nulliparous women were presented with a variety of infant and control odors, and were asked to provide hedonic ratings ranging from very pleasant to very unpleasant. In comparison to the other women, new mothers gave significantly more positive ratings to the infant body odors (Fleming et al., 1993). Finally, in some rodents like rats, offspring odors are initially aversive to virgins, but acquire a positive valence in mothers after parturition (Fleming et al., 1979; Kinsley and Bridges, 1990; Levy and Keller, 2009), when they become important cues for motivating maternal behaviors (Smotherman et al., 1974). In fact, changes in the interactions between olfactory and maternal systems are thought to underlie this new-found attractiveness by suppressing an intrinsic neural circuit for avoiding unfamiliar odors, which we describe further in Section 3.

As another example, vocal cues from offspring have also been shown to be key triggers for maternal behaviors, particularly for the distal recognition and localization of infants. For instance, when isolated from their mothers, lambs will emit bleats that vary in duration, mean frequency and spectral density of the calls. Ewes can use these acoustic features to individually recognize their own offspring from alien lambs (Searby and Jouventin, 2003). Similarly, sows can recognize and respond to their piglets by their calls (Maletinska et al., 2002). In humans, baby cries often reflect an infant's different needs, and in response to these cries, both limbic and auditory processing areas of first-time mothers can show enhanced activation as measured by functional MRI (Lorberbaum et al., 2002; Swain et al., 2007, 2008; Del Vecchio et al., 2009; Landi et al., 2011; Montoya et al., 2012).

In rodents, which this review focuses on, pups from many species emit bouts of ultrasonic vocalizations (USVs) known as isolation calls when separated from the nest and fellow littermates (Sewell, 1968) (Fig. 1). Such vocalizations have been argued to arise as a result of dropping body temperature, since pups cannot fully thermoregulate until they reach approximately two weeks of age (Okon, 1970; Blumberg and Alberts, 1990; Blumberg et al., 1992). Others have made the case that they indicate anxiety or distress in the pup (Winslow and Insel, 1991; Hofer, 1996), or more general emotional arousal (Shair et al., 2003; Ehret, 2005). Regardless of their proximal cause, the calls are clearly communicative to those who have learned their meaning. Mothers and even pup-sensitized virgin female mice can recognize USVs and will respond by searching for pups and returning them to the nest (Sewell, 1970; Ehret et al., 1987). In the mouse maternal model, the playback of the calls alone is sufficient to elicit this approach behavior in motivated mothers (Haack et al., 1983; Lin et al., 2013), illustrating a key function for the auditory modality in the maternal context. On the other hand, virgin female mice do not naturally prefer the USVs and must learn their meaning through pup sensitisation (Ehret, 1987), since even if they are instrumentally trained to respond to ultrasounds, they do not process them like communication sounds (Ehret, 1987). Furthermore, mouse pups are also known to emit other, lower frequency vocalizations known as wriggling calls when they are in the nest and trying to attach to the mother's teats (Ehret and Riecke, 2002; Geissler and Ehret, 2002). These calls require different maternal responses (e.g. adjusting the nursing position, nest building and licking) from the search-and-retrieval elicited by USVs. This demonstrates that the auditory system needs

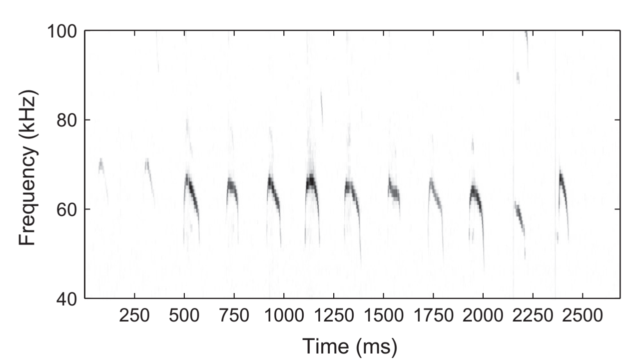

Fig. 1. Example spectrogram of a USV bout from an individual postnatal day 7 mouse pup. Darker colors correspond to higher intensities in the sound signal at corresponding frequencies. These calls concentrate in the 60–80 kHz range, and feature moderate frequency modulation, as well as temporal structure in the form of a $\sim$5 Hz repetition rate, which for comparison, is comparable to the typical syllable rate in human speech.