Dissecting natural sensory plasticity: Hormones and experience in a maternal context

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Abstract

There is a growing consensus that the auditory system is dynamic in its representation of behaviorally relevant sounds. The auditory cortex in particular seems to be an important locus for plasticity that may reflect the memory of such sounds, or functionally improve their processing. The mechanisms that underlie these changes may be either intrinsic because they depend on the receiver's physiological state, or extrinsic because they arise from the context in which behavioral relevance is gained. Research in a mouse model of acoustic communication between offspring and adult females offers the opportunity to explore both of these contributions to auditory cortical plasticity in a natural context. Recent works have found that after the vocalizations of infant mice become behaviorally relevant to mothers, auditory cortical activity is significantly changed in a way that may improve their processing. Here we consider the hypothesis that maternal hormones (intrinsic factor) and sensory experience (extrinsic factor) contribute together to drive these changes, focusing specifically on the evidence that well-known experience-dependent mechanisms of cortical plasticity can be modulated by hormones.

Keywords

auditory cortex; estrogen; ultrasound communication; mouse; neurotransmitter; neuromodulation

Introduction

Early views of the adult auditory system describe it as a static processor organized as a series of filters for spectral and temporal characteristics of sound (Moore, 2003; Pickles, 2008). Ample evidence now demonstrates that the adult auditory system is actually dynamic in the way it encodes sound (Fontanini and Katz, 2008; Fritz et al., 2007; Weinberger, 2007; Weinberger and Diamond, 1987) – changing so that behaviorally relevant signals can be more "powerfully" represented. What mechanisms produce plasticity in sensory processing? Investigating this question is a rich and growing area in sensory neuroscience. Both extrinsic factors, such as experience with sounds, and intrinsic factors, such as the physiological state

of the receiver, have been shown to produce systematic changes in sensory representations. For example, the way in which sound experience is gained can affect its neural representation, according to a recent study in the ferret auditory cortex (AC) showing differences depending on whether an animal is trained by conditioned avoidance or positive reinforcement to detect a sound (David et al., 2008). Likewise, an animal's reproductive status can influence auditory neural responses – as demonstrated in fish (Sisneros and Bass, 2003), frogs (Goense and Feng, 2005; Hillery, 1984; Miranda and Wilczynski, 2009) and birds (Lucas et al., 2002; Lucas et al., 2007) – and improve the processing of species-specific mating calls. In the laboratory, both these extrinsic and intrinsic contributions can be straightforwardly studied in isolation. In natural contexts, however, both factors likely work together, potentially in nonlinear ways. Hence, to understand the natural means by which sensory representational plasticity arises, model systems in which both contributions can be dissected need to be investigated.

In this work, we describe a relatively new, ethologically-motivated model system that provides opportunities to specifically explore interactions between extrinsic sound experience and internal hormonal state. This model focuses on representational plasticity in the mammalian AC, a critical site for encoding behaviorally relevant stimuli in a plastic manner (Buonomano and Merzenich, 1998; Keuroghlian and Knudsen, 2007). Mechanistically, much is already known about the role that specific neurotransmitter systems play in driving experience-dependent cortical plasticity (Gu, 2002). Much less appreciated though is how hormones may modulate these neurotransmitter systems to affect this plasticity.

In our model, AC representational plasticity is observed in the female mouse for the ultrasonic vocalizations of mouse pups. Systematic differences in AC responses between virgin and maternal females lead to a more powerful representation of these calls that can improve their detection and discrimination. Here we will first review the nature of these changes, and then lay out a framework for studying the mechanisms by which they may have occurred. Given the focus of this special issue, we will synthesize what is known about how maternal hormones may interact with neurotransmitter systems underlying cortical plasticity to propose mechanisms for AC representational plasticity in this natural communication context. We aim for this to provide a more integrative framework within which the role of hormones in sensory cortical plasticity may be explored.

The mouse maternal model of auditory cortical plasticity

Species-specific vocalizations are one of the most important acoustic signals that any auditory system must process. Hence, to understand the natural, integrative mechanisms of AC plasticity for behaviorally-relevant signals, we have adopted a natural communication context in the mouse as a behavioral model. Specifically, mouse pups emit bouts of high ultrasonic vocalizations (USV), depicted in Fig. 1, that carry communicative significance (Ehret, 2005). These USVs are produced by pups when they are isolated from their nest. The sounds elicit a directed search and retrieval response in the mother. Playback of the call itself has been shown to initiate this behavior, provided the mother is suitably maternally motivated (Haack et al., 1983). In fact, two-alternative choice playback tests indicate mothers prefer to approach to a 50-kHz tone model of a pup call about twice as often as to a neutral sound. Importantly though, virgins that have never cared for pups approach both sounds equally often (Ehret et al., 1987). In other words, these USVs become behaviorally relevant to and are recognized by mothers, but not virgins.

Behavioral studies suggest that both experience with pups and ovarian hormones are involved in acquiring and retaining this call recognition. Circulating estrogen levels in the mouse are generally elevated at parturition (Fig. 2), a time when a mother receives the first sensory stimulation from her own pups. However, estrogen by itself does not enable recognition: if

ovariectomized females are given estrogen implants but have no interaction with pups, they do not exhibit pup call recognition (Ehret and Koch, 1989). After five days of pup experience though, these females, like intact virgins with the same amount of pup experience, do prefer the pup-like tone. Ovariectomized females without hormone replacement do not, although continued experience with pups for 21 days can lead to pup call recognition when tested within one week of separation from pups (Ehret and Koch, 1989). These results suggest that estrogen facilitates the acquisition of pup call recognition over short periods of pup experience (Ehret and Koch, 1989), and that long-term pup experience may be able to compensate for its absence. Interestingly, recent studies in estrogen receptor-α and -β knockout mice lend further support for this (Choleris et al., 2006). They found impaired conspecific recognition in both knockout animals, and argued that the learning deficit was specific to social contexts.

Acquiring the behavioral relevance and specific recognition of pup calls must therefore involve both intrinsic (hormonal) and extrinsic (experiential) factors. The same appears to be true of the retention of call recognition. Ovariectomized females tested one month after separation from pups did not prefer pup calls whereas mothers still did. Moreover, experienced mothers that were ovariectomized *after* pup separation and tested one month later also did not show a preference, in contrast to experienced mothers that were kept gonadally intact (Ehret and Koch, 1989). These data suggests that without gonadal hormones, ovariectomized females have reduced long-term recall of pup call recognition. Thus, hormones present during either pup experience or during retention after separation from pups helps to stabilize the acquired call recognition.

These intrinsic and extrinsic factors could alter just the neural circuitry driving the motivation (component 3 in Fig. 3) or behavioral decision to respond to pup calls (between components 3 and 4). In other words, the sensory perception, and its underlying neural representation, would not necessarily have to change between virgins and mothers to explain these differences in behavioral preference for pup calls. In fact though, recent studies in intact female mice demonstrate that the sensory cortical representation of pup calls also changes, consistent with the idea that plasticity occurs which may improve the encoding of behaviorally relevant signals. The first hint of this came from an immunolabeling study comparing mothers (actively caring for postnatal day 7 pups) and virgins in AC expression of the immediate early gene c-Fos that was induced by playback of pup call models (Fichtel and Ehret, 1999). A significant difference in the spatial pattern of activation of AC neurons was found between animal groups in both hemispheres, concentrated in the ultrasound field (UF) and the secondary auditory field (AII).

Since the expression of c-Fos correlates, but is not synonymous, with synaptic stimulation, this result does not necessarily imply differences in how neurons in virgins and mothers actually respond to pup calls. That has been explored in two recent electrophysiological works in ketamine-anesthetized mice that compared similarly aged, gonadally-intact females with different physiological and experiential histories (Liu and Schreiner, 2007; Liu et al., 2006). One group (1–2 week post-weaning mothers) gave birth to pups and cared for them for 21 days, and the other (virgins) had never been pregnant and never cared for pups (although they probably heard pup calls as background noise in the vivarium). Experiments were conducted at a time point when both mothers and virgins had normal estrus cycles, although the precise estrus state of each female was not determined. Both studies relied primarily on multiunit (MU) spiking activity sampled across most regions of the left AC, including UF, primary auditory field (A1) and anterior auditory field (AAF).

Results suggest that AC spiking activity in response to pup calls changes from virgins to mothers in a way that is better adapted for processing the acoustic structure of these natural vocalizations. First, Liu et al. (2006) demonstrated that MUs in mothers follow the temporal modulations in real call bouts better than in virgins. Pup calls naturally occur at a ~5 Hz rate,

as Fig. 1 shows. The mother's AC neural population responded to each component call in a bout fairly well at this modulation rate. This was true regardless of the specific acoustic features of the call, making the AC entrainment less susceptible to natural call variation. This could provide a robust distributed neural representation for downstream detection of pup calls, even in the presence of natural acoustic variability. On the other hand, AC neural populations in virgins could only follow repeated vocalizations if they were presented at rates slower (i.e. 3 Hz) than typically produced by pups naturally. Moreover, this entrainment depended more on the specific acoustic structure of a call (e.g. long or short duration). These results provide the first indication that AC neural population responses to the same infant communication sounds can vary systematically depending on different maternal histories, and that the differences could improve call processing.

A second study provided rigorous quantification of this idea, focusing on the neural response to a variety of individual calls presented in isolation. Liu and Schreiner (2007) found that MU responses in mothers can actually carry more Shannon information (Cover and Thomas, 1991) for both detecting and discriminating pup calls. Loosely speaking, improved detection arises if a MUs call-evoked spiking activity (analyzed here in 2 ms time bins across the duration of the response) is more similar for the different calls and significantly different from spontaneous spiking. Improved discrimination occurs if this call-evoked activity can be more reliably used to distinguish between specific calls, irrespective of the spontaneous activity. Across the population, MU spiking in mothers was better than in virgins at providing information for both these call processing functions. Importantly, mothers and virgins did not differ for a non-behaviorally relevant ensemble of sounds presented at the same average sound level, suggesting a relative specificity in the coding changes for pup USVs. Moreover, the plasticity resulted from a change in the timing of spikes evoked in MUs across the entire auditory cortex, with the improved information in mothers arising earlier in the neural response. This is consistent with a recent study in awake guinea pigs suggesting the temporal discharge pattern of AC neurons is important for conveying information about species-specific vocalizations (Huetz et al., 2009). Experiments in the mouse are now also being extended to the awake preparation (Galindo-Leon et al, submitted).

These studies provide clear evidence for AC plasticity in a natural communication context. Hence, even though the behavioral response to pup calls could have simply been due to changes in a mother's motivation or decision to respond to calls, we now know that its sensory cortical representation is in fact altered. This result raises two types of questions. First, what does this mean for the "quality" of call perception by virgins and mothers? The behavioral experiments that would be needed to explore this have not been done, and would be challenging to pursue without invoking some operant training paradigm that risks altering the cortical representations. Hence, behavioral analysis may not be able to provide a definitive explanation for the role this plasticity has in maternal care. On the other hand, the computational analyses described in the cited studies at least provide evidence that the neural changes can improve functional processing for downstream decisions to act.

Second, what caused these sensory cortical differences between virgin and mother mice to appear and persist, even weeks after the last experience with pups? We know that hormones alone can affect neural activity throughout the auditory system (see various examples in this special issue). Auditory experience alone can also alter neural representations of sound, particularly at the level of the cortex (Norena et al., 2006; Weinberger, 2004). In this maternal context though, where hormone levels and pup interactions are changing throughout parturition and lactation, these intrinsic and extrinsic factors are probably not independent. Indeed, the behavior itself indicates that both maternal hormones and pup experience contribute to the acquisition and retention of call recognition. Hence, in considering possible experience-dependent mechanisms for natural sensory representational plasticity, the question of how

hormones may modulate this should be addressed. In the next section, we begin this by drawing on the neural plasticity and hormone literature to synthesize an understanding of how well-known sites responsible for AC plasticity may be susceptible to hormonal influences during maternal behavior.

Interaction sites between hormones and cortical plasticity

Several hormones are associated with pregnancy and maternal behavior, including estrogen, progesterone and oxytocin. We focus first on estrogen, since a great deal is known about its role in neuroplasticity and its influence on brain areas that mediate auditory cortical plasticity. Estradiol, a naturally-occurring form of estrogen, can generally increase dendritic spine density and neural excitability, enhance long term potentiation, promote neurotrophin activity and increase neurogenesis (Raz et al., 2008; Spencer et al., 2008; Toran-Allerand et al., 1999; Wise et al., 2001). As noted earlier, estrogen levels peak during the latter third of pregnancy (Fig. 2), fall after birth towards baseline, and remain low throughout lactation (Atkinson and Leathem, 1946; Rosenblatt and Siegel, 1981; Taya and Greenwald, 1982). Thus, sensory stimulation by pups actually begins just as estrogen starts to drop. Through the long timescale structural changes it promotes though (Wise et al., 2001), the high pre-parturitional levels of estrogen likely still help prime neural circuits for plasticity during these first several days of pup experience.

The mechanism for these neural changes is believed to involve the engagement of various neurotransmitter systems, including the dopaminergic, noradrenergic, serotonergic and cholinergic systems (Edeline, 2003; Gu, 2002; Thiel, 2007; Xerri, 2008). The main sources of these neurotransmitters lie in brain regions that overlap considerably with those activated during maternal and social behaviors: the ventral tegmental area (VTA), the locus coeruleus (LC), the dorsal raphe nuclei (DR) and the nucleus basalis (NB), respectively. Each of these areas is: 1) significantly activated during maternal behavior and/or sensory learning, 2) important in the mechanisms of AC plasticity and 3) sensitive to estrogens or other hormones. These three characteristics make these neural sites prime candidates for integrated endocrine and neural mechanisms of sensory plasticity in the maternal context.

Dopamine

Dopamine, a neurotransmitter usually associated with operant reinforcement and pleasure, has a well-known role in both maternal responsiveness and AC plasticity. Pups are known to be reinforcing (Hauser and Gandelman, 1985; Lee et al., 1999) and rewarding (Ferris et al., 2005; Mattson et al., 2001) to rodent mothers, and pup-directed behaviors such as retrieval, licking and nursing activate the mesocorticolimbic reward system originating in the VTA (Ferris et al., 2005; Hernandez-Gonzalez et al., 2005). In humans, the VTA is activated while listening to cries or viewing emotional images of an infant (Lorberbaum et al., 2002; Strathearn et al., 2008). This documented role of the VTA in maternal responsiveness opens the possibility that it may also influence infant recognition through projections to sensory processing areas (Campbell et al., 1987; Gu, 2002). Indeed, the dopaminergic system can modulate auditory associative learning in reward contexts to produce persistent perceptual changes. For instance, sound stimuli paired with fluid reward results in discrimination between reinforced and non-reinforced sounds for up to two weeks (Watanabe et al., 2001), and requires dopamine D2 receptor activation in primary AC (Kudoh and Shibuki, 2006). In fact, one study has demonstrated long-term representational plasticity in the AC by electrically stimulating the VTA in conjunction with acoustic tone presentation (Bao et al., 2001), an effect that is blocked by dopamine antagonists. Put together, these results suggest VTA dopamine activity may facilitate sensory cortical plasticity in the maternal context.

Importantly, the hormones of pregnancy and parturition also modulate VTA dopaminergic activity. Estrogen receptors (ER) are found in VTA dopamine neurons (Creutz and Kritzer, 2002; Shughrue et al., 1997) and estradiol administration to ovariectomized female rats stimulates dopaminergic activity by elevating VTA dopamine neuron activity (Zhang et al., 2008). In female rhesus macaques, an ovariectomy reduces the cortical innervation of tyrosine hydroxylase (TH), the enzyme responsible for converting the amino acid L-tyrosine to DOPA, the precursor for dopamine; estradiol replacement maintains it (Kritzer and Kohama, 1998). Similarly, male rats show a decrease in cortical TH innervation shortly after gonadectomy that is attenuated by estrogen treatment (Kritzer, 2000). However, the effect of gonadectomy is time-dependent and region-specific since levels of TH innervation weeks after gonadectomy either return to intact levels, or in some cortical areas, significantly surpass intact levels.

This last result hints that estrogen modulation of dopamine activity is complicated by temporal factors. Elevated dopamine activity after extended periods of low hormone levels may explain some contradictory results found in females where high estradiol is actually correlated with low VTA activity (Dazzi et al., 2007; Sakamoto et al., 1993; Zhang et al., 2008). Hence, in considering how estrogen interacts with the dopamine system around birth, it is important to keep in mind the changing levels of estrogen. Perhaps the elevation in estrogen primes the mesocortical pathway by increasing cortical dopaminergic fiber innervation that then influences sensory cortical plasticity during early mother-pup interactions.

Norepinephrine

Norepinephrine (noradrenaline) – a neurotransmitter generally involved in arousal, attention and vigilance – has an established role both in forming memories of maternal experiences and in AC plasticity. An early study found that pharmacologically activating the noradrenergic system in mothers after a brief maternal experience at birth facilitates the long term retention of the experience (Moffat et al., 1993). More recently, mouse mothers lacking the gene for dopamine beta-hydroxylase (Dbh), which synthesizes norepinephrine, show a profound deficit in maternal responsiveness, resulting in the loss of pups (Thomas and Palmiter, 1997). This can be rescued only if the norepinephrine precursor, DOPS, is given to mothers shortly before birth so that it is present at parturition. Amazingly, once rescued for one litter, a subsequent litter from the same mother also survives, even though she is not given a further injection of DOPS. This suggests norepinephrine may help consolidate the long-term memory of the first maternal experience. What normally drives the release of norepinephrine in the maternal context? Intriguingly, LC neurons have dendrites extending into the rostromedial peri-LC region (Rizvi et al., 1994), which receives a dense, focal input from the medial preoptic area, a key nucleus required for maternal behavior (Numan and Insel, 2003). Medial preoptic area activation may thereby help modulate activity in LC, which provides a major source for noradrenergic afferents to the cortex (Gu, 2002). This anatomical pathway may therefore provide a substrate for the motivational components of maternal behavior (component 3 in Fig. 3) to affect cortical processing.

Indeed, cortical norepinephrine release has been found to induce plasticity in sensory processing (Gu, 2002). In primary auditory cortex, iontophoretic application of norepinephrine inhibits both spontaneous and evoked activity (Manunta and Edeline, 1997;Manunta and Edeline, 1998;Manunta and Edeline, 1999), thus sharpening neural receptive fields without changing the overall signal-to-noise ratio across the population. Moreover, pairing of norepinephrine with tones mostly leads to frequency-selective suppression in the tuning curve (Manunta and Edeline, 2004). These changes could conceivably support neural improvement in frequency discrimination by creating greater differential responses to varying frequencies. Indeed, enhanced information for ultrasound frequency discrimination was observed in post-weaning mothers compared to virgins (Liu and Schreiner, 2007). For norepinephrine to be

involved in this, its effects would have to survive much longer than current studies have explored (Manunta and Edeline, 1999).

Evidence does point to the possibility that the noradrenergic system can be facilitated by hormones. LC neurons in the rat concentrate estradiol (Heritage et al., 1980) and contain ER-α and ER-β (Helena et al., 2006; Mitra et al., 2003; Shughrue et al., 1997; Zhang et al., 2002). In fact, estradiol regulates Dbh mRNA expression in LC neurons (Serova et al., 2002) and therefore may help control norepinephrine levels. Hence, the noradrenergic system could be an additional site for hormonal augmentation of sensory plasticity.

Serotonin

Serotonin – a neurotransmitter commonly associated with different moods (stress, anger, aggression, anxiety, depression, sexuality, sleep and appetite) – also affects a mother's degree of maternal care and facilitates representational plasticity in AC. Normally, serotonin activity and serotonin receptor function vary systematically across pregnancy and the postpartum period (Glaser et al., 1990). In humans, abnormalities in these time courses have been implicated in postpartum mood disorders (Doornbos et al., 2008), and are perhaps a physiological reflection of problems dealing with the stresses of motherhood. Furthermore, a direct role for serotonin in maternal care was recently demonstrated by genetically disrupting the development of serotonergic neurons in the mouse DR (Lerch-Haner et al., 2008). Pups born to these mothers survived less than three days, unlike those of wild type controls. Mothers had a specific deficit in pup retrieval, even though measures of their olfactory, locomotive and fear-related behaviors were normal. Hence, serotonin released through the projections of DR neurons must normally be involved in maternal responsiveness, although the precise site of action is unknown. Nevertheless, since DR projects widely to all areas and layers of the cortex (Campbell et al., 1987; Gu, 2002), its activation during maternal behavior likely also impacts auditory cortical processing of infant cues.

The effects of serotonin on sensory cortical activity are quite varied. Under normal conditions, evoked responses in primary auditory cortex are inversely related to DR serotonergic cell activity (Juckel et al., 1999), and to local serotonin levels in primary auditory cortex (Ji and Suga, 2007). However, exogenous application of serotonin or a serotonin receptor agonist directly onto the AC can produce myriad changes in frequency tuning, which are dose-dependent (Ji and Suga, 2007). This is hypothesized to reflect a changing balance between excitation and inhibition, depending on which serotonin receptors on which types of neurons are activated. As with the noradrenergic system though, we do not yet know the long-term effects of serotonergic modulation of cortical activity.

A wealth of evidence supports the hypothesis that the DR serotonergic pathway is modulated by pregnancy hormones (Bethea et al., 2002; Bodo and Rissman, 2006). Many of the serotonergic neurons in the DR contain ER-α and ER-β (Sheng et al., 2004; Shughrue and Merchenthaler, 2001) suggesting that estradiol could modulate serotonin activity in the synaptic targets of these neurons. Estrogen acts to increase serotonin activity by modulating synthesis, reuptake and degradation, as well as neural firing (Bethea et al., 2002). Thus, the DR may be yet another site for the hormonal changes associated with motherhood to potentially affect sensory cortical plasticity during experience with pups.

Acetylcholine

The basal forebrain NB cholinergic system has not been commonly linked to maternal responsiveness, but is strongly implicated in general associative learning (Gu, 2002). Thus, we consider it here for its potential involvement in the acquisition and memory of sensory cues from infants. The NB contributes to the long-term retention of various forms of conditioned

auditory associations (McLin et al., 2002;Miasnikov et al., 2006;Montero-Pastor et al., 2001). It is specifically hypothesized to organize the learned behavioral significance of sounds at the level of the AC (Suga and Ma, 2003;Weinberger, 2003), and thus could play a key role in its plasticity within the maternal context. Indeed, many studies have shown that electrical stimulation of the basal forebrain paired with an acoustic tone can drive frequency-specific changes in AC receptive fields and long-term reorganization of the AC's map of sound frequency (Bakin and Weinberger, 1996;Chen and Yan, 2007;Kilgard and Merzenich, 1998;Kilgard et al., 2007;Kilgard et al., 2001a;Kilgard et al., 2001b;Yan and Zhang, 2005).

Less well-known is the potential effect that estrogen may have on the NB cholinergic pathway (Gibbs and Aggarwal, 1998). NB neurons contain both ER-α and ER-β in mice (Mitra et al., 2003), rats (Shughrue et al., 1997; Shughrue et al., 2000) and humans (Ishunina and Swaab, 2001; Osterlund et al., 2000). This could allow estradiol to modulate associative learning via the NB cholinergic pathway, as a recent study suggests (Horvath et al., 2002). Rats were conditioned using foot-shock in a two-way active avoidance learning paradigm to move from one compartment of a test box to another upon hearing an auditory stimulus. Estrogen replacement in ovariectomized rats improved the rate of acquisition in this active avoidance task (although retention after 24 hours was not affected). The improved acquisition rate in estrogen treated animals was accompanied by an increase in cholinergic fiber density in the somatosensory cortex (no measurements in AC). This result hints that estrogen may prime the NB to accelerate sensory associative learning, at least in the case of active avoidance responses. If this also applies in the maternal context, perhaps it contributes to the more rapid acquisition of pup call recognition in estrogen-replaced compared to ovariectomized females.

Potential influence of other hormones

Besides estrogen, other hormones are also changing during the maternal experience and can affect the neuromodulatory systems involved in cortical plasticity. For example, progesterone levels in the maternal mouse peak during the latter third of pregnancy, rapidly decrease during the days before birth and peak midway through the lactation period (Fig. 2), which is consistent with other rodents (Atkinson and Leathem, 1946;Rosenblatt and Siegel, 1981;Taya and Greenwald, 1982;Tomogane et al., 1969). Behaviorally, administering progesterone to rats has been found to improve their performance on cognitive and memory related tasks, including those mediated by the prefrontal cortex and hippocampus (Frye, 2007;Frye and Walf, 2008a;Frye and Walf, 2008b). While such behavioral changes do not require any sensory cortical changes, progesterone can nevertheless modulate the same neuromodulatory systems discussed above that affect cortical plasticity. Progesterone receptors and receptor mRNA have been demonstrated in VTA, DR and LC (Curran-Rauhut and Petersen, 2002;Helena et al., 2006). In fact, progesterone along with estradiol can increase dopamine release in several dopamine target areas (Frye, 2007).

Finally, the neuropeptide oxytocin also functions during maternal behavior, peaking at birth and remaining high throughout lactation. Besides its effects on parturition and lactation, oxytocin is hypothesized to play a more general role specifically in social, but not nonsocial, recognition (Bielsky and Young, 2004). This has been mainly tested using olfactory recognition tasks, where male oxytocin-knockout mice fail to recognize a familiar female but not a familiar nonsocial odor (Ferguson et al., 2000). Oxytocin acting in the medial amygdala is believed to mediate this recognition (Ferguson et al., 2001). Whether oxytocin might play a similar role for other sensory modalities, such as the recognition of conspecific vocalizations, is currently unknown. In terms of a potential influence on neuromodulation though, oxytocin fibers do innervate VTA and LC in rodents (Hermes et al., 1988; Rosen et al., 2008) and receptors are present in human NB and DR (Gimpl and Fahrenholz, 2001).

Summary and future

It is clear from decades of research that hormones play an important role, along with infant experience, in regulating the acquisition and retention of maternal responsiveness. Less well appreciated is the influence hormones and experience may have on purely sensory aspects of maternal behavior, such as the recognition and discrimination of behaviorally significant infant cues. In particular, experiments in the auditory system demonstrate that the internal cortical representation of infant stimuli changes over the course of motherhood, irrespective of changes in the neural circuitry for raising motivation or deciding to respond to infants.

This paper draws attention to the potential means by which such changes might naturally occur. We presented a synthesis of known experience-dependent mechanisms for sensory cortical plasticity with known influences by maternal hormones on these mechanisms. On balance, the dopaminergic and cholinergic systems may be the most relevant for driving the documented sensory cortical plasticity. Each has been shown in other contexts to generate long-term physiological or behavioral changes in auditory processing, and both can be directly influenced by estrogen or other hormones. Looking forward, to better understand how these neuromodulatory centers might function in natural contexts to drive sensory representational plasticity, future experiments will need to directly test the effects of hormonal modulation on these areas.

Acknowledgments

Abbreviations

A1

primary auditory field

AAF

anterior auditory field

AC

auditory cortex

AII

secondary auditory field

Dbh

dopamine beta-hydroxylase

DR

dorsal raphe nuclei

ER

estrogen receptor

LC

locus coeruleus

MU

multiunit

NB

        nucleus basalis

TH

        tyrosine hydroxylase

UF

        ultrasound field

USV

        ultrasonic vocalizations

VTA

        ventral tegmental area

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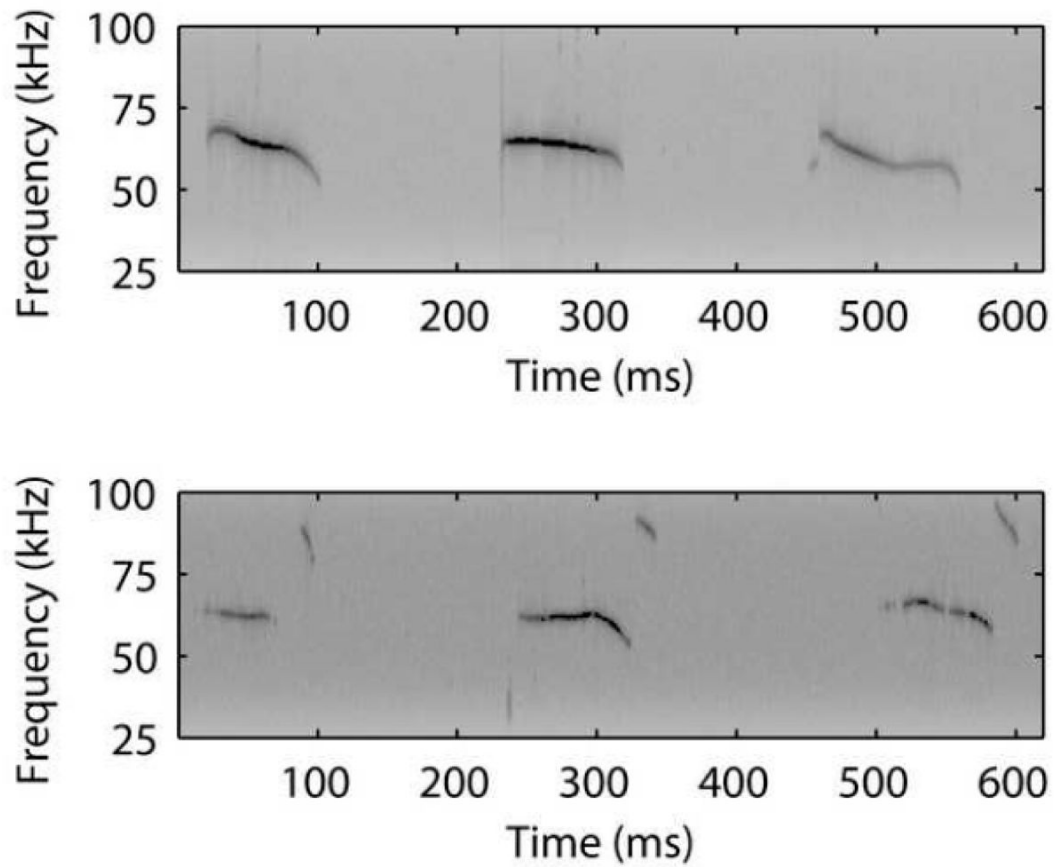
Fig. 1.
Sample spectrograms of two bouts of natural ultrasonic calls emitted by postnatal day 7 pups. Note the rhythmic nature of the calls, which are typically separated by ~180–200 ms (onset to onset).
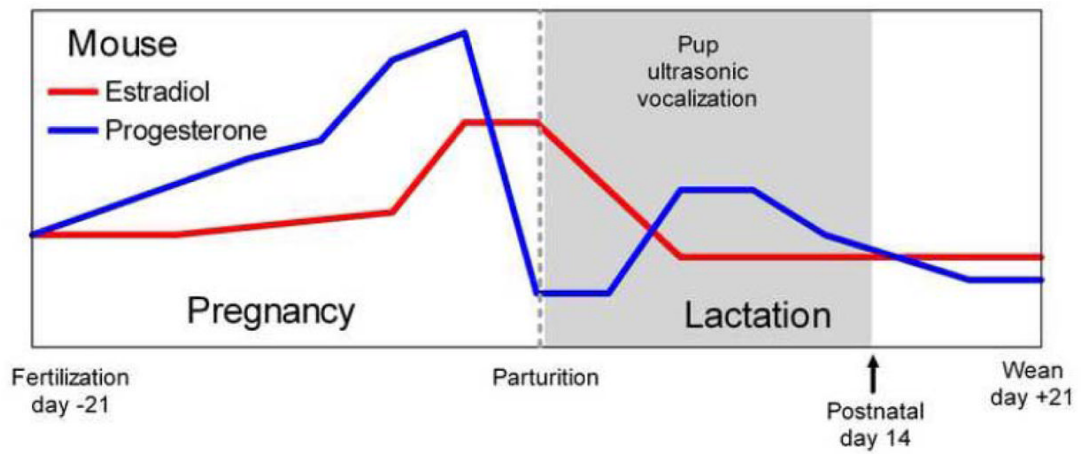
Fig. 2.
Schematic representation of estradiol and progesterone profiles during pregnancy and lactation in the mouse (Atkinson and Leathem, 1946; Barkley et al., 1979; Bell and Dawson, 1983; Critser et al., 1982; McCormack and Greenwald, 1974). The vertical dashed line denotes the time of parturition. The grey shaded area encompasses the period in which pups produce ultrasonic vocalizations (Elwood and Keeling, 1982; Graham and Letz, 1979; Pontet et al., 1989; Vieira and Brown, 2002).
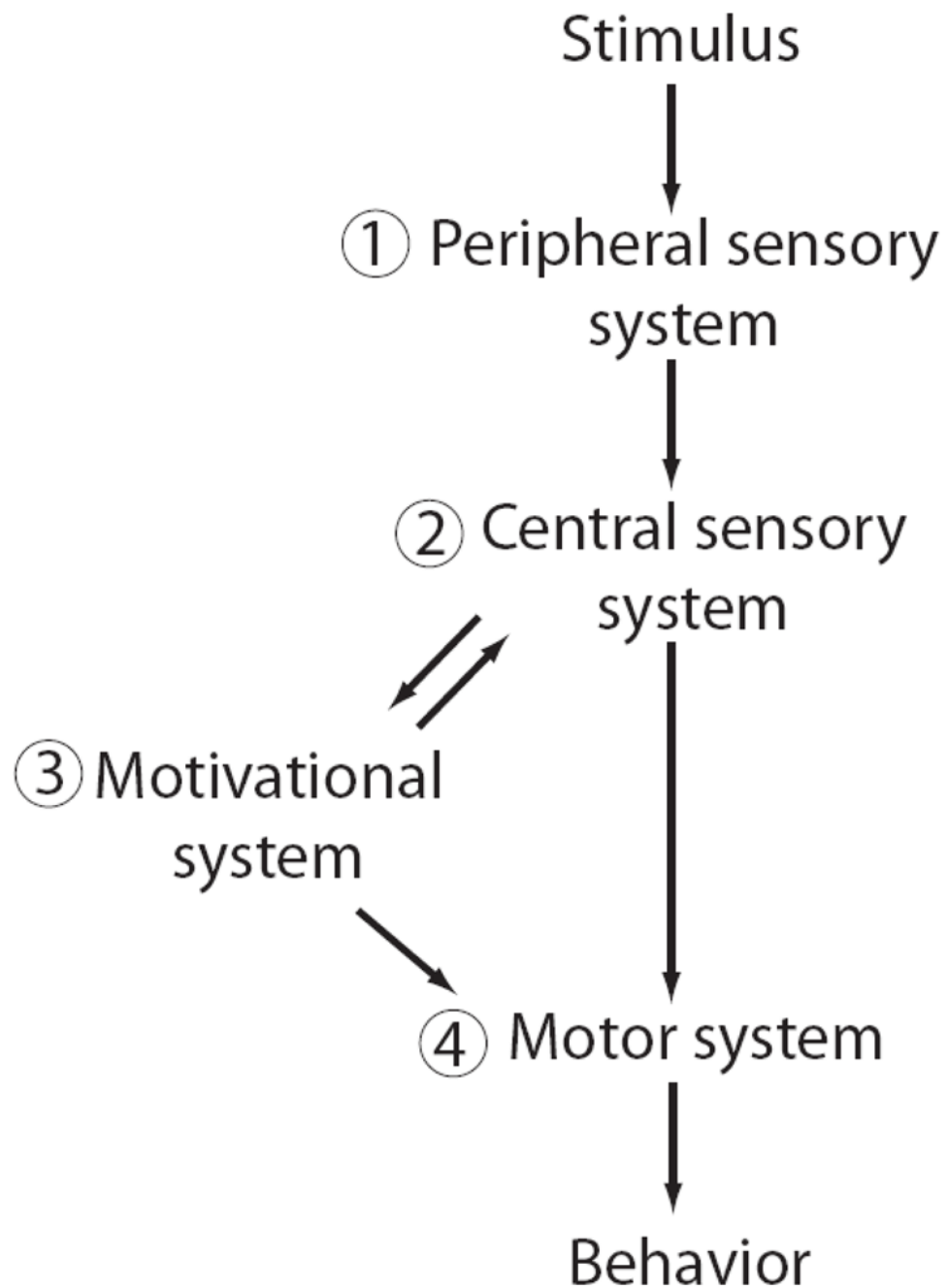
Fig. 3.
Neuroanatomical model for information flow leading to maternal behavior. Numbers denote components that are referred to in the text. Hormones can act at the numbered levels (1–4).