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The yin and yang of cortical oxytocin

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Abstract

Female mice can learn to respond to distress calls from young mice — an ability that has now been found to be improved through signalling by the hormone oxytocin in the left auditory cortex of the brain.

When newborns cry in the night, they capture the attention of sleepy parents, who become suddenly alert, ready to comfort their babies. This response might seem like instinct, but our ability to recognize social cues from infants is heavily shaped by experience^{1,2}. Mothers and fathers of many species, including humans, learn over time to recognize the cries of their own babies³. In a paper published on *Nature's* website today, Marlin *et al.*⁴ investigate how the brain learns this information. They report that oxytocin, a well-studied hormone released in the brain in social situations, acts in an unexpected manner to help to create memories of infant cues.

Oxytocin is a neuropeptide molecule produced in the brain's hypothalamus. It acts in both the peripheral and central nervous systems, exerting prosocial effects on behaviour by promoting pair bonding, parental care, social reward, and attention to and memory of social cues^{5–7}. But how oxytocin actually acts on neurons to affect social behaviours is only just beginning to be explored^{8,9}, with much still unknown about the mechanisms by which it influences sensory-information processing and memory in social contexts.

To address this gap in knowledge, Marlin and colleagues studied how female mice react to the ultrasonic cries made by pups. Mothers and virgin 'nanny' mice (which have experience of caring for pups) recognize the cries as distress calls and respond by approaching calling pups, picking them up and carrying them to the nest. By contrast, inexperienced (naive) mice fail to recognize the cue and do not retrieve pups. There is evidence¹⁰ that memories of the pups' cries in maternal mice are linked to the activity of neurons in the auditory cortex of the brain — part of the neocortex, which controls higher brain functions, including sensory perception (Fig. 1). Marlin *et al.* used pharmacological inactivation to demonstrate that, without left-auditory-cortical activity, pup retrieval is severely impaired in most experienced female mice. Inactivating the right auditory cortex had little effect, adding neuronal evidence to other work¹¹ suggesting that control of communication processing in mice is dominated by one side of the brain (lateralized), much as it is in other species.

Systemically delivered oxytocin facilitates maternal behaviours such as pup retrieval^{2,7}, but it has been presumed to act on evolutionarily conserved circuits for maternal responsiveness

that are located in subcortical brain regions beneath the neocortex. Oxytocin-receptor proteins have previously been discovered in the prefrontal region of the neocortex⁹, but Marlin *et al.* found that both oxytocin receptors and projections from hypothalamic oxytocin-producing neurons are present in the auditory cortex of mice, with the former (but not the latter) being more numerous on the left side than on the right.

Amazingly, naive virgins that had been injected with oxytocin in the left auditory cortex began retrieving pups earlier than counterparts that received saline. It remains to be seen whether oxytocin's cortical effect on pup retrieval is lateralized, because the authors did not repeat the experiment in the right auditory cortex. Blocking oxytocin-receptor activation in the left auditory cortex of experienced retrievers did not impair performance, which perhaps indicates that oxytocin in the auditory cortex facilitates learning about calls rather than maintaining memories of them. If so, blocking auditory-cortical oxytocin receptors during endogenous systemic oxytocin release in naive mice should prevent them from learning pup-retrieval behaviours.

What is the role of oxytocin in the auditory cortex? In technically challenging experiments, Marlin and colleagues analysed the neuronal inputs to auditory-cortical neurons, and showed that oxytocin can alter the balance between inhibitory and excitatory inputs, which are both activated by pup calls — they are the yin and yang of neuronal signalling. The team found that inhibitory and excitatory inputs were not well balanced in naive females, whose neurons fired less consistently in response to calls than did those of their experienced counterparts. By applying oxytocin to the left auditory cortex, the authors could transiently weaken inhibitory currents in naive females. This disinhibited the excitatory response, resulting in a gradual balancing of yin and yang through strengthening of both types of input. The change led to more-robust signalling in response to calls, similar to that observed in the left auditory cortex of mothers and nannies. This neuronal effect was long-lasting, suggesting that it might provide a key mechanism for establishing memories of socially relevant sounds in the auditory cortex.

Marlin and colleagues' data show that the effect of oxytocin on behaviour varies substantially between individuals. Could this be related to natural variation in the oxytocin-receptor gene, affecting either the protein's function or how much of it is present in each individual^{5,6}? Sound-evoked cortical responses and their susceptibility to oxytocin manipulations also vary from neuron to neuron. It will be important to understand whether this variation also arises from differences in oxytocin-receptor expression, or whether it can be explained by other differences between cortical neurons that have yet to be considered in depth. For example, could it be due to the types of cortical neuron that express oxytocin receptors, the sound features that cortical neurons respond to, or where in the auditory cortex the cry-responsive neurons are found?

This study supports recent hypotheses about how hormones and sensory experience interact to shape the function of the maternal cortex¹². Such 'oxytocin-experience' interactions have been implicated in the recognition of social odours through subcortical neurons^{6,13}, but the current work breaks ground by showing that such interactions also act at the level of the sensory neocortex. The authors' findings suggest that oxytocin can behave in a similar

manner to other neuromodulator systems that are involved in attention and learning, by instigating an enduring neuronal plasticity that increases responsiveness to social stimuli.

Human imaging studies have enabled us to expand our models of the neuronal circuits in the maternal brain that respond to infant cues, from primarily subcortical circuits to those that include neocortical regions¹⁴. Using mice alongside these studies opens the door to dissecting the mechanisms that underpin hormone–experience interactions in the neocortical areas that process infant cues. The potential relevance of these combined experimental strategies to investigating disorders such as postpartum depression and autism, in which the salience of social cues is diminished⁶, adds a translational element to the promise of Marlin and colleagues' work.

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Figure 1. From cryo cortex

Ultrasonic distress calls made by young mice act as social cues that elicit a maternal response in females that have experience of caring for pups. Memories associated with this cue seem to be linked to neurons in the auditory cortex, part of the neocortex region of the brain. The hormone oxytocin, which is produced in the hypothalamus, can be released in the neocortex. Marlin *et al.*⁴ report that oxytocin can act directly in the left auditory cortex to facilitate the behavioural response to the cries of pups, which are relayed to this brain region through a sound pathway.