News & views

Neuroscience

Pups' cries shape neural circuits in mothers

Flavia Ricciardi & Cristina Márquez

All newborn mammals cry. The neural circuit that stimulates mothers to look after crying offspring has been identified in mice – along with a mechanism that promotes maternal behaviour only after prolonged calls from pups. **See p.788**

We have all probably had the experience of being on a flight with a crying baby. Most passengers would probably respond by putting on headphones and hoping that the baby will fall asleep, but the parents' reaction is to try to work out a helpful way to soothe the infant and attend to its needs. Why is there a difference? In the case of mothers, it is well known that pregnancy induces substantial changes in the body, but the brain also undergoes major alterations that we are only now starting to understand. On page 788, Valtcheva *et al.*[1] report the discovery of a neural circuit in mice that is active only in the brains of mothers, and which promotes sustained and efficient maternal care in response to their pups' distress calls.

The study concerns oxytocin, a small neuropeptide molecule that is highly evolutionarily conserved across species. It is crucial for inducing uterine contractions during labour and the release of milk during nursing, but it also has a key role in parental care and bonding. Previous studies by researchers from the same group as Valtcheva *et al.* have revealed much about when, where and how neural circuits involving oxytocin influence maternal behaviour in mice.

For example, a seminal study[2] investigated the role of oxytocin-producing neurons in the hypothalamus – which, evolutionarily, is one of the most ancient parts of the brain, specialized in regulating various fundamental functions that ensure survival. The study revealed that, in maternal mice, oxytocin released by the neurons in the paraventricular nucleus (PVN) region of the hypothalamus is crucial for modulating the activity of the auditory cortex (AuCX), one of the main brain regions that processes auditory information. Oxytocin released from the PVN to the auditory cortex causes nursing mothers to become attuned to their pups' calls. Importantly, the oxytocin neurons are also activated in virgin female mice that observe nursing activities when co-housed with mothers, thereby promoting maternal behaviours in the virgin mice[2–4].

Valtcheva and colleagues' study now addresses an unexplored question: how are oxytocin neurons activated by pup distress calls? To answer this question, the authors recorded the neural activity of maternal mice whose heads were fixed in position as pup calls were played from a speaker. This approach gave the authors full control of the source of auditory information and allowed them to perform highly sophisticated neural recordings and manipulations, which would have been more challenging in freely behaving animals.

The authors found that oxytocin neurons in the PVN did not respond immediately to pup calls. Instead, the neurons' activity increased only after repeated playback of the calls. Oxytocin neurons in other contexts have previously been reported to require strong stimulation and to exhibit delayed responses[5]. However, the current study suggests a temporal correlation: only continued or prolonged cries, such as those that might happen before and during episodes of maternal care, were able to activate these oxytocin neurons in mothers. Remarkably, these responses were specific to pup calls (there was no response to other sounds) and were not observed in virgin females.

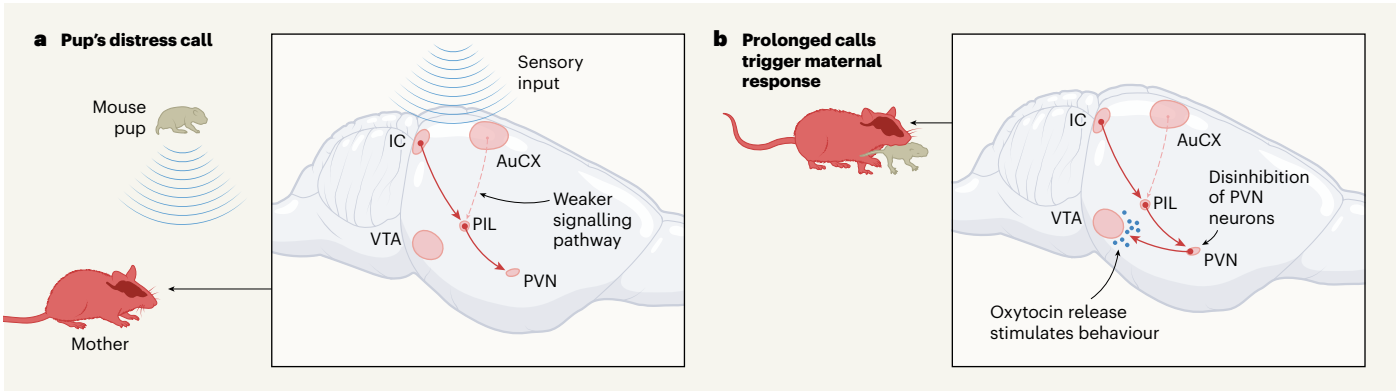

Figure 1 | How pups' cries trigger maternal behaviour in mice. Valtcheva *et al.*[1] report the neural circuit that stimulates maternal mice to respond to their pups' distress calls. **a**, The calls trigger activity in brain areas that process conscious responses to auditory information (the inferior colliculus, IC, and the auditory cortex, AuCX). These areas, especially the IC, signal to the posterior intralaminar (PIL) nucleus – part of the posterior thalamus (a region where sensory information is organized and redirected towards other parts of the brain). The PIL then signals to neurons in the paraventricular nucleus (PVN; part of the hypothalamus, a region that regulates various fundamental functions that ensure survival). However, the PVN neurons are initially strongly inhibited, and do not activate immediately. **b**, Sustained activity of PIL neurons in response to prolonged cries eventually overcomes the strong inhibition of the PVN neurons, which then release the neuropeptide oxytocin. This stimulates maternal behaviour, such as fetching unprotected pups back to the nest.

Valtcheva *et al.* went on to inject viral tracers into the PVN oxytocin neurons of maternal mice; these viruses move through upstream neurons in neural circuits, thereby allowing the authors to label the brain areas that send auditory information to the oxytocin neurons. Intriguingly, areas that process conscious responses to auditory information, such as the AuCX and the inferior colliculus (IC), are not directly connected to PVN oxytocin neurons. Instead, the AuCX and IC send pup-call information through the posterior thalamus, a brain area in which sensory information is organized and redirected towards other regions (Fig. 1).

Specifically, the authors found dense projections from the posterior intralaminar (PIL) nucleus of the thalamus to the PVN. The PIL belongs to the non-lemniscal auditory pathway, which has been suggested to mediate unconscious perception of sounds, such as attention, emotional responses and reflexive reactions[6]. Recent studies have also highlighted the role of the PIL and its projections to hypothalamic areas in the processing of other social cues in mice[7] and in the recognition of social signals in evolutionarily conserved circuits in zebrafish[8].

Valtcheva and colleagues propose a new role of the PIL in the oxytocin PVN circuit that mediates the perception of pup distress calls, and which could therefore influence the quality of maternal care. Indeed, when the authors silenced signalling of the PIL to the oxytocin PVN neurons, using a technique known as chemogenetic suppression, they observed reduced willingness of freely behaving mothers to make sustained efforts to protect their pups from potential dangers.

The PIL neurons responded to pup calls with sustained activity, sometimes firing for several seconds after the pup calls had ended. But although the projections to PVN oxytocin neurons were dense, direct and functional, the synaptic connections from the PIL to the PVN were not strong enough to induce direct firing of oxytocin neurons. Instead, the authors report an intriguing mechanism in which strong inhibition of oxytocin-neuron activation is overcome by the sustained activity of PIL neurons, thereby aiding the response of oxytocin neurons to pup calls (see Fig. 3i of ref. 1).

Finally, the authors hypothesized that the activated PVN neurons cause oxytocin to be released in downstream brain areas, thereby promoting maternal behaviour. To test this, they used a genetically encoded sensor[9,10] that enabled the labelling of oxytocin molecules bound to their receptor protein in selected brain areas when mothers were listening to the pup distress calls. This approach revealed that oxytocin is indeed released after pup calls, in a region called the ventral tegmental area (VTA). The VTA is one of the core nodes of the brain's reward system, and is known to produce motivated behaviour and process reward information. Interestingly, when signalling from the PIL to the oxytocin PVN neurons was silenced, oxytocin release in the VTA after pup calls was negligible.

One of the strongest points of this work could be also seen as its main limitation. The highly controlled experimental setup, in which head-fixed mice listened to pre-recorded pup calls, allowed the authors to obtain unprecedented mechanistic knowledge of how oxytocin neurons in this circuit process information that is highly relevant to natural animal behaviour. However, the dynamics of these neurons' activity during actual natural behaviour are still unknown. For example, do these cells fire differently in response to pup calls from a mother's own progeny compared with the recorded calls?

Overall, Valtcheva *et al.* provide a mechanistic understanding of how sensory cues from offspring are integrated at the level of neural circuits to activate the release of neuromodulators such as oxytocin and promote maternal care. The demonstration that the activation of the pathway from the PIL to the oxytocin PVN neurons is necessary to induce maternal care raises questions for future research. For example, is the activation of this pathway sufficient to drive maternal behaviour in virgin mice?

It is also tempting to think that this circuit is altered in some postnatal conditions that affect many women, such as postpartum depression. If so, then this work might eventually help to elucidate the biological mechanisms of these conditions and potentially open up strategies for drug discovery.

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Optics

Organic lasers go electric

Stéphane Kéna-Cohen

An organic light-emitting diode has been integrated with an optically driven organic laser to produce laser light from electricity. The design bypasses many of the challenges posed by direct electrical input in such devices. **See p. 746**

Thin layers of organic molecules can be fabricated over large areas at low cost, and their electrical and optical properties can be chemically tuned with ease. These characteristics make organic molecules ideal materials for thin-film lasers. The first such lasers[1,2] were developed in the late 1990s, but these devices needed to be driven optically by a second laser, which limited their usefulness. On page 746, Yoshida *et al.*[3] demonstrate an organic laser that can be driven electrically when integrated with a very bright organic light-emitting diode (OLED) — creating an all-organic package that is both powerful and versatile.

A key component of every laser is a material called the gain medium, which uses energy to amplify the intensity of light in the laser. The use of organic molecules as a gain medium dates back to the invention of the dye laser[4,5], in which a jet of organic dye solution provided the amplification (gain) that is essential to laser operation. In that case, the excess energy came from exciting the dye with a second laser, which prompts the question: why use a laser to make another laser? One reason is that there are many molecules to choose from, so the wavelength of the outgoing light could be easily tailored by using the right molecule. Organic molecules also tend to amplify light over a broader range of wavelengths than inorganic media do — a property that enabled dye lasers to be readily tuned and capable of generating ultrafast light pulses.

But using organic gain media poses some challenges. The absorption of light by a molecule raises the energy of one of the molecule's electrons, while leaving a second, identical, electron behind, unexcited. Importantly,