

News & views

Neuroscience

Becoming a mother leaves molecular memories

Frances A. Champagne

In mice, motherhood induces transcriptional changes in the brain that endure beyond short-term hormonal shifts. Postpartum stress disrupts these patterns. See p.465

The experience of pregnancy, childbirth and the postpartum period changes the brain. On page 465, O'Chan *et al.*¹ explore shifts in gene transcription and its regulation in the brains of female mice that have undergone a range of physiological and behavioural experiences that are associated with pregnancy and motherhood. The authors identify a brain region involved in learning and memory that exhibits particularly strong transcriptional changes in response to reproductive experience, and show that postpartum stress disrupts these effects. They also show that the neurotransmitter molecule dopamine is a key player in the regulatory process that maintains this transcriptional state.

The authors' work builds on the concept of 'matrescence', which refers to the profound changes to a person's brain and behaviour during the transition to motherhood. Although this concept was introduced in the 1970s, interest has resurged over the past few years. There is increasing evidence from studies that track participants over time that reproductive experience results in structural and functional changes in the human brain². These studies reveal enduring effects on the brain's anatomy, and raise crucial questions about the cellular and molecular pathways that underlie these changes. O'Chan *et al.* expand on this work, assessing transcriptional and behavioural traits (phenotypes) in mice to characterize the long-term effects of reproductive experience. They provide insights into the molecular mechanisms that underpin the transition to motherhood and its parallels with the neuronal adaptability (plasticity) seen in the developing brain³.

Studies of the maternal brain have typically focused on regions that respond to the rise and sharp decline of various hormones – namely, prolactin, oestradiol, cortisol, progesterone

and oxytocin – during the transition from pregnancy to the postpartum period². Many of these regions of the brain are part of the hypothalamus. O'Chan *et al.* performed gene-expression analyses in 11 brain areas, and compared the transcriptional profiles of reproductively inexperienced mice with those of mice that had experienced mating, pregnancy, parturition (giving birth), lactation and weaning of offspring. Notably, it was

the dorsal hippocampus, rather than a part of the hypothalamus, that emerged as the most 'transcriptionally sensitive' region, meaning that it had the highest number of genes with expression levels that were altered in response to reproductive experience.

The dorsal hippocampus has a key role in learning and memory, particularly in relation to spatial navigation. The apparent plasticity of this region could account for the long-term effects of motherhood on cognition. In humans, cognitive performance has been shown to decline in late pregnancy and the early postpartum period, but after weaning, it recovers considerably, or even improves⁴. O'Chan *et al.* observed this improvement in mice – reproductive experience was associated with an enhanced ability to acquire new memories and recall them later.

The other transcriptionally sensitive brain regions identified by the authors are responsible for diverse functions, including reward processing, motivation, stress responses, attention, emotion and social interactions. This suggests that a broad range of behavioural and cognitive outcomes could be affected by reproductive experience.

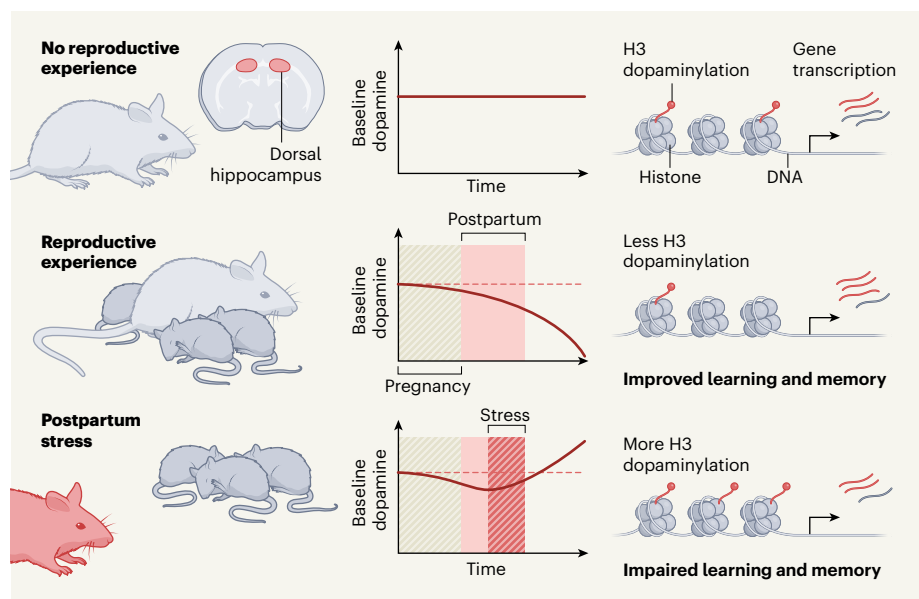


Figure 1 | The transition to motherhood induces enduring molecular changes. O'Chan *et al.*¹ show in mice that the molecular profiles of neurons in a region of the brain called the dorsal hippocampus are remodelled by reproductive experience (encompassing mating, pregnancy, giving birth, lactation, maternal care and weaning). Mice with reproductive experience have lower baseline levels of dopamine in the dorsal hippocampus than do reproductively inexperienced mice, and this results in a reduction in H3 dopaminylation – an epigenetic modification to histone H3 (one of the proteins that package DNA). These changes persist well after the postpartum period and after pups have been weaned. They result in alterations to gene transcription that lead to improved learning and memory. Postpartum stress caused by separation from offspring increases baseline dopamine in the dorsal hippocampus, increasing H3 dopaminylation and disrupting the transcriptional and behavioural effects.

Plasticity in the maternal brain is thought to serve an adaptive purpose, enhancing the mother's sensitivity to cues from the infant and promoting social and spatial abilities that are needed to support the child's survival. However, plasticity can carry risks when adverse experiences occur during this sensitive period of brain remodelling⁵. O'Chan *et al.* investigated this vulnerability using an experimental model of postpartum adversity in which female mice were separated from their offspring for three hours a day. This postpartum stress shifted the transcriptional profile of the dorsal hippocampus away from that of a reproductively experienced (parous) female and closer to that of a female with no reproductive experience.

This molecular shift might account for the impairments in spatial memory observed in stressed parous females relative to their non-stressed counterparts. In humans, the postpartum period is associated with a heightened risk of depression and anxiety. The molecular changes and their downstream biological pathways could provide mechanistic clues about how stress can have a lasting influence on mothers and on the social dynamic between mothers and their offspring.

What drives these shifts in gene transcription? Epigenetic modifications – chemical changes to DNA and the histone proteins that package it – have been implicated in a broad range of environmentally induced phenotypes. They are one of the mechanisms thought to underlie plasticity, and they can maintain long-lasting changes to the transcriptome (the full complement of transcripts expressed by a cell or tissue)³.

To understand the lasting influence of reproductive experience on the brain's transcriptome, O'Chan *et al.* examined an unusual modification to histone H3 by a chemical derived from dopamine. This 'H3 dopaminylation' has been implicated in the neuronal and behavioural adaptations that occur in rats after they are made to withdraw from self-administered heroin⁶, highlighting its possible role in transcriptional remodelling in the brain.

In the context of motherhood, O'Chan and colleagues saw that H3 dopaminylation in the dorsal hippocampus was lower in parous female mice than it was in reproductively inexperienced females or in parous females that had undergone postpartum stress. Similar effects were seen in humans: reduced H3 dopaminylation was observed in the dorsal hippocampus of individuals who had given birth, and the transcriptional profiles of human brains were highly concordant with those seen in mice.

One of the main challenges in understanding experience-dependent epigenetic variation is finding pathways that link broad physiological and environmental signals to

molecular changes in specific gene pathways. By focusing on H3 dopaminylation, O'Chan and colleagues provide a neurochemical connection between experience, epigenetic variation, transcription in the brain and behavioural phenotypes. They show that dopamine release into the dorsal hippocampus influences H3 dopaminylation, shaping the transcriptional landscape and behaviour (Fig. 1). Experimentally suppressing dopamine signalling in reproductively inexperienced mice mimicked the effects of reproductive experience on transcription and behaviour, as did reversing H3 dopaminylation directly in stressed parous females. Although transcriptional remodelling was not seen throughout the whole brain, these findings suggest that experiences that alter the tone (that is, the baseline levels) of dopamine during this window of plasticity can bring about enduring molecular and behavioural changes in mothers.

This work provides insights into how H3 dopaminylation – and perhaps epigenetic mechanisms linked to other neurochemicals, such as serotonin and histamine – contributes to the plasticity associated with matrescence. However, it is important to consider these effects as one of many possible pathways through which reproductive experience shapes the brain. O'Chan and colleagues' transcriptional analyses of cell types suggest that neuronal populations in the dorsal hippocampus decrease in parous female mice. Identifying when and how this occurs across brain regions could be essential for understanding molecular profiles associated with the transition to motherhood. For sensitive

periods in brain plasticity, timing is everything. Molecular profiling provides a snapshot of the state of the parous brain at a particular point in the lifespan, but it is unclear how molecular changes at one time point relate to those that occur earlier or later in life, or whether such changes can be used to predict cognitive and behavioural phenotypes.

Finally, a key challenge will be to disentangle the social, physical, physiological and hormonal features of reproductive experience. This will enable scientists to identify causal links between changes in these features and behavioural or cognitive outcomes. The fact that individuals experience pregnancy, parturition and the postpartum period differently to one another is a complexity that adds to this challenge, but it also creates opportunities for future studies of the neurobiological and behavioural trajectories of women across their reproductive life histories.

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Social science

Online child sexual abuse is widespread and invisible

Xiangming Fang & Greta M. Massetti

One in six Internet-using adolescents in parts of Africa and Asia faced technology-facilitated sexual abuse in 2020–21. As digital access expands globally, better protection is crucial. **See p.408**

Content warning: this News & Views contains information about child sexual exploitation and abuse, which some readers might find upsetting.

One in five women and one in six men worldwide report experiencing sexual violence during childhood, according to estimates that reflect mostly offline abuse¹. As Internet access expands, smartphones become widespread and social media deeply embeds itself in daily life, an urgent question

arises: how are these risks evolving in digital environments? On page 408, Ghai *et al.*² analyse survey data from nearly 12,000 adolescents across eastern and southern Africa and southeast Asia to examine technology-facilitated child sexual exploitation and abuse (TF-CSEA). Their findings are striking: roughly one in six Internet-using children experienced such harm in just one year and more than half of affected children never disclosed their experience to someone else.