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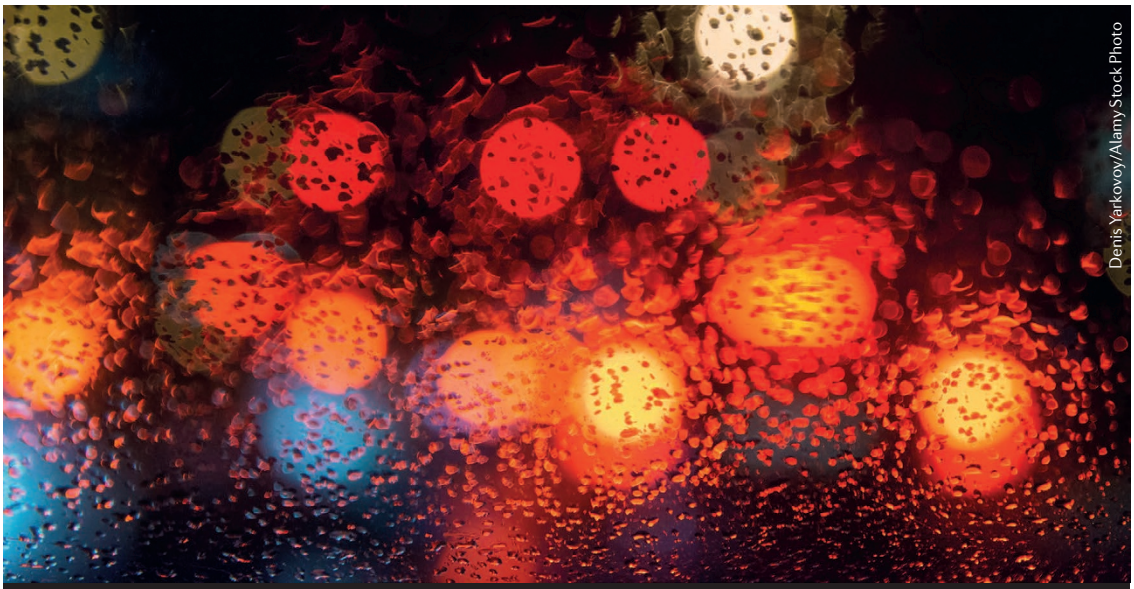

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PSYCHIATRIC DISORDERS

A sensitive window

Early-life stress renders animals more likely to exhibit depression-like behaviours following exposure to stress in adulthood. Previous work has implicated the reward circuitry, including the ventral tegmental area (VTA), in this priming process; however, the exact mechanisms remain unclear. In a new study, Nestler and colleagues demonstrate that exposure to stress within a specific postnatal period leads to long-lasting transcriptional changes in the VTA that are mediated by a transient, local downregulation of orthodenticle homeobox 2 (OTX2) expression.

The authors stressed male mouse pups by separating them from their mothers for 4 hours a day either between postnatal day 2 (P2) and P12 (early postnatal stress) or between P10 and P20 (late postnatal stress). In adulthood, these mice were subjected to chronic social defeat stress and subsequently tested for depression-like behaviours — including anhedonia on the sucrose preference test, social avoidance behaviour, and immobility in the forced swim test. Following adult stress exposure, mice in the late (but not the early) postnatal stress group were more likely to develop depression-like symptoms than were standard-reared controls. Thus, in mice, exposure to stress in the developmental window between P10 and P20 sensitizes the brain to exposure to stress in adulthood.

To investigate the transcriptional changes that underlie this sensitization, the authors carried out RNA sequencing in VTA tissue from adult mice exposed to either late postnatal stress or chronic social defeat stress in adulthood. Each type of stress altered the expression of many genes, and interestingly, both types of stress led to similar changes (that is, increases or decreases) in the expression of 69 genes. Statistical analysis of the transcriptomic data revealed that these genes are co-regulated, suggesting that both types of stress induce a 'depressive' transcriptional state in the VTA.

Gene pathway analysis identified OTX2 as a key upstream regulator of several genes that were found to be downregulated in the VTA by both types of stress. At P21, but not at later time points, *Otx2* mRNA levels and OTX2 binding at active enhancer regions (characterized by the presence of methylated H3K4) were lower in mice that were subjected to late postnatal stress than in standard-reared mice. These findings led the authors to propose that transient downregulation of *Otx2* expression during a sensitive period could enhance the susceptibility of postnatally stressed mice to later exposure to stress.

Consistent with this hypothesis, transient virus-mediated overexpression of *Otx2* — between P17 and ~P24 — in the VTA of mice that had been exposed to late postnatal stress prevented the downregulation of OTX2 target genes and the development of depression-like symptoms following exposure to stress in adulthood. In addition, transient knockdown of the expression of endogenous *Otx2* (by virally expressed microRNA) in the VTA of standard-reared mice between P17 and ~P24 increased the sensitivity of these mice to stress in adulthood. Thus, OTX2 expression in the VTA during the window P17–P24 is both necessary and sufficient to sensitize the brain to later stress.

Together, these results suggest that, in mice, late postnatal stress transiently disrupts OTX2-mediated regulation of transcription in the VTA to induce a life-long depression-like-primed state.

Natasha Bray

> "both types of stress induce a 'depressive' transcriptional state in the VTA"

ORIGINAL ARTICLE Peña, C. J. *et al.* Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. *Science* **356**, 1185–1188 (2017)