EPIGENETICS

# A lingering smell?

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Studies in animals have shown that stressful experiences can be passed onto offspring, often in the form of a general anxious or stress-sensitive phenotype. A new study now shows that highly specific experiences can also be inherited by subsequent generations, in terms of behaviour and anatomy, and that this transmission occurs through parental gametes.

Dias and Ressler trained male mice (F0 mice) to associate mild footshocks with one of two odours: acetophenone (Ace) or propanol (Prop). The mice subsequently mated with females, and the resulting F1-Ace and F1-Prop male offspring underwent an odour-potentiated startle test to assess their sensitivity to the two odours. This test revealed that F1-Ace males displayed, on average, higher sensitivity to Ace (but not to Prop) than control mice, and that F1-Prop mice showed higher sensitivity to Prop (but not to Ace). Thus, mice whose fathers had undergone a painful experience associated with a particular odour were more sensitive to that odour, even though they had never been exposed to it themselves.

Ace is detected by M71 odorant receptors on neurons in the olfactory bulb and main olfactory epithelium (MOE). F1-Ace males had larger M71-specific glomeruli in the olfactory bulb and a greater number of M71 receptor-expressing olfactory sensory neurons in the MOE compared with control males. These anatomical changes might underlie the behavioural effects; however, the two could not be directly correlated because they were assessed in different sets of animals.

Interestingly, the male offspring of F1-Ace males and F1-Prop males (that is, F2 males) also showed increased sensitivity to Ace and Prop, respectively. Moreover, like their fathers, F2-Ace males had larger M71-specific glomeruli. These findings suggest that a specific olfactory experience had been transmitted down two generations. A crucial experiment provided evidence that this transmission occurred via the gametes: when sperm from F0-Ace males and F0-Prop males was used for *in vitro* fertilization of eggs from naive females, the offspring of F0-Ace males had larger M71-specific glomeruli than did the offspring of F0-Prop males.

The authors nevertheless examined whether social transmission — for example, through altered maternal behaviour — might also play a part. Here, they trained female mice to associate Ace with footshocks. The male offspring of these mice showed increased sensitivity to Ace and had enlarged M71-specific olfactory glomeruli, even if they had been fostered by control females. Conversely, the offspring of control mothers had no increased sensitivity to Ace, even if they had been fostered by Ace mothers. These findings indicated that the transmission of the olfactory sensitivity to Ace was not socially mediated and can also occur through the maternal line.

The authors reasoned that if F0-Ace mice transmit their olfactory experience through gametes, then DNA in sperm of F0-Ace males might show epigenetic changes in the gene encoding the M71 receptor (*Olfr151*). Indeed, *Olfr151* was hypomethylated in both F0-Ace sperm (compared with F0-Prop sperm) and F1-Ace sperm. Interestingly, however, there was no *Olfr151* hypomethylation in neurons in the MOE of F1-Ace and F2-Ace males.

This study is ground-breaking in that it shows that a specific sensory and/or learning experience can be transmitted — via the gametes — to the offspring, where it manifests as a specific behavioural sensitivity. Arguably, it raises more questions than it answers. For example, not all F1-Ace and F1-Prop offspring showed enhanced sensitivity to the relevant odour, and methylation in *Olfr151* was found in the gene itself rather than in a promoter region. Perhaps the greatest mystery is how an olfactory experience that is encoded in the brain can be transmitted to the gametes — an exciting challenge for future studies.

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**ORIGINAL RESEARCH PAPER** Dias, B. G. & Ressler, K. J. Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3594 (2013)

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