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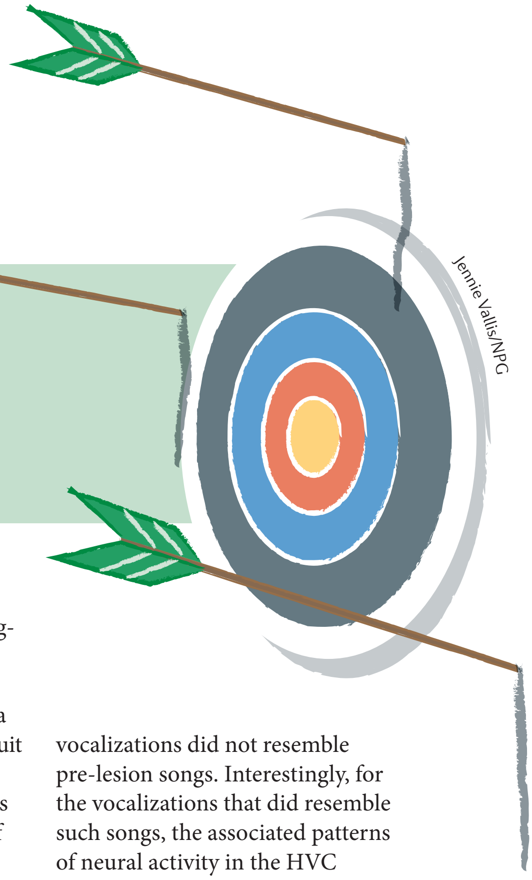

TECHNIQUES

Wide of the mark

The transient manipulation of neural activity by, for example, pharmacological means or optogenetics is widely used to investigate the role of specific neural circuits and brain areas in particular behaviours. A new study by Otchy *et al.* shows that such manipulations can sometimes have 'off-target' effects, rendering it difficult to establish meaningful mechanistic associations.

The authors reasoned that given the highly interconnected nature of many brain regions, transiently manipulating neural activity in one brain area might influence the independent functions of any connected areas. To test this hypothesis, they trained rats to press a lever twice, with a gap of 700 ms between presses. The authors had previously shown (and confirmed here) that although the motor cortex was necessary to learn this precise movement sequence, lesions in this brain area after learning did not affect the ability of the animals to perform it (as measured 10 days after lesioning). Interestingly, in unlesioned rats that had learned the task, muscimol-mediated transient inactivation of a portion of the motor cortex severely disrupted their ability to execute the task. Thus, the permanent and transient silencing of activity in the motor cortex appeared to have opposing effects on behaviour, suggesting that the transient manipulation of activity in the motor cortex has an effect in another brain area (an off-target effect) that is capable of generating this particular behaviour.

The authors next examined whether such effects could be observed in another system. In songbirds, a sensorimotor area known as the nucleus interface (Nif) sends excitatory projections to the HVC, a component of the song control circuit that is implicated in song timing. Previous studies showed that lesions to the Nif do not affect the ability of songbirds to perform a previously learned song, again a finding the authors confirmed. However, here, they found that transient inactivation of the Nif by muscimol considerably degraded the songs performed by the birds, again suggesting that acute manipulation of activity in one brain area can have an off-target effect.

The circuits responsible for vocal control in songbirds have been well investigated, which allowed the authors to examine why there are divergent outcomes of permanent and acute silencing of the Nif. They noted that the effect on singing from transient silencing of Nif was similar to that caused by lesions to the HVC itself, as reported in a previous study, suggesting that acute Nif inactivation affects the dynamics of the HVC. Given this finding, and the fact that song performance resumes 2 days after Nif lesioning, the authors examined the relationship between singing and HVC activity shortly after Nif lesions are made.

As the authors used an electrolytic as opposed to a surgical approach to make Nif lesions, singing resumed 1–2 hours after lesioning, although most of the vocalizations did not resemble pre-lesion songs. Interestingly, for the vocalizations that did resemble such songs, the associated patterns of neural activity in the HVC differed from those associated with pre-lesion songs. However, by the time most of the songs had recovered, these patterns had reverted to their pre-lesion structure. Together, these findings indicate that lesioning and transient inactivation of Nif both acutely affect HVC activity.

These results also suggest that the changes in HVC activity after Nif lesioning represented a period of homeostatic regulation of neural activity. In support of this idea, in a network model, the authors were able to rescue song termination deficits by homeostatically regulating HVC activity after Nif input loss.

Together, the findings indicate that the rapid, transient manipulation of neural activity in one brain area can have effects on connected, but functionally independent, brain regions, suggesting that caution should be exercised in the interpretation of findings from experiments that have involved such an approach.

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> "the permanent and transient silencing of activity in the motor cortex appeared to have opposing effects on behaviour"

ORIGINAL ARTICLE Otchy, T. M. *et al.* Acute off-target effects of neural circuit manipulations. *Nature* **528**, 358–363 (2015)

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