I see where you're hearing: how cross-modal plasticity may exploit homologous brain structures

Bavelier, Daphné; Hirshorn, Elizabeth A.

How to cite

BAVELIER, Daphné, HIRSHORN, Elizabeth A. I see where you're hearing: how cross-modal plasticity may exploit homologous brain structures. In: Nature Neuroscience, 2010, vol. 13, n° 11, p. 1309–1311. doi: 10.1038/nn1110-1309

This publication URL: https://archive-ouverte.unige.ch/unige:103529
Publication DOI: 10.1038/nn1110-1309

a transcriptional code that determines the subtype identities of neuronal progenitors. This code is thought to then directly translate into the generation of specific neuronal subtypes. The work of Rouaux and Arlotta[1] shows for the first time that this sequence can be subverted by generating glutamatergic neurons from a progenitor or even a young postmitotic neuron specified originally to an entirely different fate. Thus progenitors expressing Gsx2 and Mash1 find themselves giving rise to glutamatergic neurons (**Fig. 1**). These data further inspire the hypothesis that neuronal identity might even be switchable at entirely postmitotic states. Will it be possible at some point to convert a fully differentiated medium spiny neuron into a glutamatergic pyramidal neuron?

Indeed, the current study may open new areas of research in the recent field of 'direct reprogramming'[9]. This term describes the concept that cells can be converted from one differentiated identity into a very distinct differentiated identity—without going all the way back to some undifferentiated progenitor state. Direct reprogramming was pioneered in the 1980s by the conversion of fibroblasts into muscle cells with MyoD, and in the hematopoietic system by converting cells from one lineage directly into cells of a different lineage[10]. In the nervous system, the first evidence for direct reprogramming was the conversion of postnatal astrocytes into fully functional neurons by a single transcription factor[11–13]. Moreover, whereas direct reprogramming of these lineage-related cells can be achieved by a single transcription factor with high efficiency, it is also possible to convert cells to a completely different germ layer fate with the manipulation of multiple transcription factors[14]. Thus, a rule of lineage relations emerges from these remarkable studies: the more closely cells are related, the easier they can be interconverted[9]. Direct reprogramming does not require cell division[10,13], so it may well be feasible to convert one type of differentiated neuron into another. Of course, a prerequisite of this is to know the right transcription factor, and Rouaux and Arlotta[1] in this issue have demonstrated that Fezf2 indeed seems to be sufficiently powerful to impose a very specific fate.

Fezf2 in this study converted neuronal identity at a relatively late stage in lineage progression and hence may indeed act as a 'terminal selector gene'[15]. Terminal selector genes are not only necessary and sufficient for final differentiation of a given neuron type, but they regulate all genes responsible for the function of the respective differentiated neuron subtypes in a concerted manner[15]. The next step forward will be to unravel Fezf2's exact molecular function and thereby identify the 'molecular signature' of layer 5 corticofugal pyramidal neurons.

One key open question in Rouaux and Arlotta's study[1] is whether and how these glutamatergic layer 5 neurons in the midst of the striatum actually wire up. They might cause the formation of entirely novel but possibly behaviorally relevant circuits. The authors have shown that the efferent projections of the Fezf2-induced glutamatergic neurons take the subcortical path appropriate for their new character, but whether they indeed form synapses and functional connections in the thalamus or even in the spinal cord (or whether they extend beyond the cerebral peduncle) remains to be determined. Moreover, which neurons will innervate these strangers in the striatum? Will they be innervated by fibers projecting into the striatum—that is, functionally integrate into the basal ganglia circuitry but then send output to the spinal cord? One wonders whether direct reprogramming of neuronal subtypes may in fact be exploited to generate entirely novel 'designer circuits', which may be interesting to examine in regard to their functional and behavioral consequences—eventually founding a field of 'synthetic neurobiology'. Although it remains to be seen how informative such new circuits might be, these considerations also highlight the need to learn more about the connectivity of neurons generated with the aim to repair brain function. Indeed, very little is yet known about the functional connectivity of any regenerated neuron, independent of its source, despite the urgent need to understand how neurons generated at odd places or after injury may indeed connect. For now, the work by Rouaux and Arlotta[1] provides us with an intriguing first glimpse into exciting new areas in the field of neuroscience.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Rouaux, C. & Arlotta, P. *Nat. Neurosci.* **13**, 1345–1347 (2010).
2. Shimizu, T. & Hibi, M. *Dev. Growth Differ.* **51**, 221–231 (2009).
3. Chen, B., Schaevitz, L.R. & McConnell, S.K. *Proc. Natl. Acad. Sci. USA* **102**, 17184–17189 (2005).
4. Chen, J.G., Rasin, M.R., Kwan, K.Y. & Sestan, N. *Proc. Natl. Acad. Sci. USA* **102**, 17792–17797 (2005).
5. Molyneaux, B.J., Arlotta, P., Hirata, T., Hibi, M. & Macklis, J.D. *Neuron* **47**, 817–831 (2005).
6. Chen, B. *et al. Proc. Natl. Acad. Sci. USA* **105**, 11382–11387 (2008).
7. Polleux, F., Morrow, T. & Ghosh, A. *Nature* **404**, 567–573 (2000).
8. Barnes, A.P. & Polleux, F. *Annu. Rev. Neurosci.* **32**, 347–381 (2009).
9. Zhou, Q. & Melton, D.A. *Cell Stem Cell* **3**, 382–388 (2008).
10. Graf, T. & Enver, T. *Nature* **462**, 587–594 (2009).
11. Heins, N. *et al. Nat. Neurosci.* **5**, 308–315 (2002).
12. Berninger, B. *et al. J. Neurosci.* **27**, 8654–8664 (2007).
13. Heinrich, C. *et al. PLoS Biol.* **8**, e1000373 (2010).
14. Vierbuchen, T. *et al. Nature* **463**, 1035–1041 (2010).
15. Hobert, O. *Proc. Natl. Acad. Sci. USA* **105**, 20067–20071 (2008).

I see where you're hearing: how cross-modal plasticity may exploit homologous brain structures

Daphne Bavelier & Elizabeth A Hirshorn

Sensory deprivation such as deafness or blindness leads to specific functional and neural reorganization. A new study gives insight into why and how certain abilities change, while others remain unaltered after the loss of a sense.

Tales of blind individuals having enhanced remaining abilities, often relating to poetry or music, as in the case of the Greek poet Homer, or even crime fighting, in the case of the superhero Daredevil, have long been told. These stories may not have been that far off. Psychophysical studies have revealed enhanced auditory abilities in the early blind and specific superior visual abilities in the early deaf. Even more surprising, the deprived unused visual cortex in blind subjects has been shown to be taken over by other senses, such as audition or touch[1]. Notably, blind individuals listening to speech engage their visual cortex and deaf individuals watching moving objects engage their auditory cortex. However, the principles for instantiation of such cross-modal plasticity are not well understood. In particular, it remains unclear why some functions are altered after early sensory deprivation while others remain unchanged. For example, in the

The authors are in the Department of Brain and Cognitive Sciences, University of Rochester, Rochester, New York, USA.
e-mail: daphne@bcs.rochester.edu or ehirshorn@bcs.rochester.edu

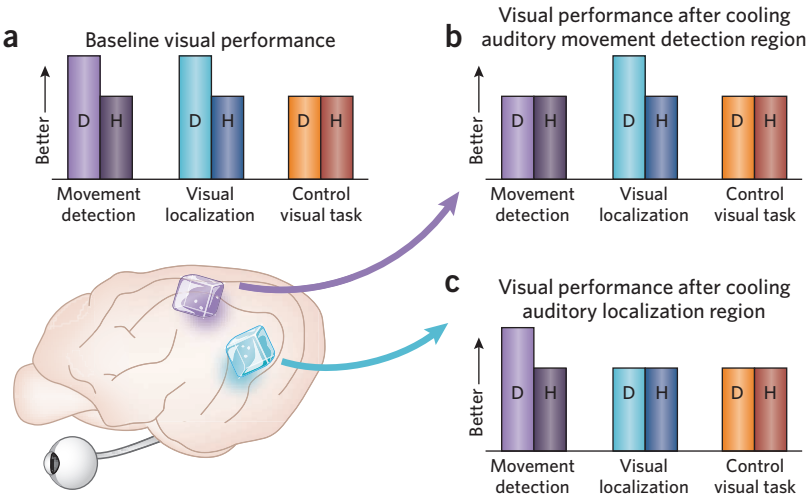


Figure 1 In congenitally deaf animals, homologous auditory cortex regions get recruited for enhanced visual processing according to their shared functionality: demonstration through a double dissociation using cooling probes. (**a**) Under normal conditions, deaf cats have better performance in supramodal tasks (movement detection and visual localization), but show no difference in control tasks. D, deaf cats; H, hearing cats. (**b**) Cooling in the auditory movement detection area leads to selectively decreased performance in visual motion detection in deaf cats. (**c**) Conversely, cooling in the auditory localization area leads to selectively decreased performance in visual motion detection in deaf cats.

case of deafness, low-level visual skills do not change, whereas attention to peripheral space or to moving objects improves[2]. In this issue, Lomber and colleagues[3] present an intriguing new hypothesis that proposes that 'supramodal' skills, or skills that are shared across senses, have greater potential to undergo enhancement and reorganization.

The intrinsic mechanisms that underlie this brain plasticity have interesting implications for learning, rehabilitation and simply understanding the limits of brain adaptation under a wide variety of circumstances. The study conducted by Lomber and colleagues[3] elegantly addresses the principles by which cross-modal plasticity may be regulated. The authors make the distinction that properties such as color or tone are specific to vision and audition, respectively. In contrast, vision and audition both contribute to the ability to locate information in surroundings in both humans and cats, such as when we first hear a mosquito buzzing on our left and then see the mosquito on our left arm. Our ability to locate an object is not uniquely linked to one modality, but is instead supramodal, with different modalities contributing to the computation of spatial location. Other supramodal functions include motion detection, such as when we identify a moving truck by its sound and then its sight, and shape recognition, such as when we search through a cluttered purse for our keys, feeling them before we can confirm by sight the nature of the object.

Lomber and colleagues[3] argue that, for such supramodal skills, the absence of one sense may be met by enhanced performance for that very skill when fed by the remaining senses. They measured a range of psychophysical visual abilities in congenitally deaf and hearing cats, contrasting supramodal skills to modality-specific skills. The performance of congenitally deaf cats was substantially better than that of hearing cats at visual localization in the periphery and motion detection, which are both supramodal functions. In contrast, there was no difference between deaf and hearing cats' performance in the vision-specific conditions. These results complement psychophysical data from humans showing no changes in basic visual threshold in congenitally deaf humans, but improved spatial localization in the periphery and an enhanced ability to selectively attend to moving stimulus[2].

A notable feature of Lomber and colleagues' study[3] is that it goes beyond this functional characterization and demonstrates that, for supramodal skills, auditory brain areas maintain their functional specialization after early deafness, but are driven by vision rather than audition. Using a cooling probe, which allows the temporary disabling of a small swatch of cortex, Lomber and colleagues[3] were able to test the functional specificity of brain areas with high precision. Four distinct bilateral auditory areas were chosen. A localization area and a motion processing area in the auditory cortex were chosen because of their functional involvement in supramodal tasks[3].The primary auditory cortex (A1), an obligatory relay in cortical auditory functions, was also included, as well as a control area chosen for its involvement in auditory pattern recognition, a modality-specific skill. Lomber and colleagues[3] found that cooling in the auditory movement detection area led to decreased visual motion detection performance in deaf cats. Conversely, cooling the auditory localization area decreased performance in deaf cats in the visual-localization task. Notably, cooling of these auditory areas had no effect on hearing cats as they performed these same visual tasks (**Fig. 1**). Cooling in the primary auditory cortex and the control area had no effect on either group, indicating that the effects were specific. To the best of our knowledge, this is the first demonstration that enhanced visual abilities in deaf individuals are not globally distributed throughout auditory areas, but are instead localized to specific and functionally homologous cortices. Furthermore, the degraded performance in the deaf cats in the two relevant tasks was equivalent to the performance of the hearing cats, demonstrating that the enhanced visual ability in the deaf cats can be attributed to processing in these distinct reorganized auditory cortices.

These elegant results lead to the proposal that supramodal functions may be more likely to engage cross-modal plasticity as a result of their functional reallocation in homologous areas of the brain. What remains to be further elucidated is why functions in the supramodal category may be more likely to be reorganized and how such changes may take place. The field of cross-modal plasticity provides converging evidence that sensory cortices, typically thought of as being unimodal, may have potential for multimodal functioning. Sensory cortex may receive inputs from several modalities early in development, whether through feedback connections or in a feedforward manner[4,5]. As development proceeds, each sensory cortex may come to be dominated by one modality, with inputs from other modalities being partially lost or masked[6]. Experiments in which normally sighted individuals were blindfolded for 5 d support this view. The visual cortex was recruited for auditory and tactile processing in these individuals, whereas no such activity was observed before blindfolding[7]. What is less well understood is how this multisensory potential in sensory cortices is engaged. The supramodal hypothesis may help in refining such views.

There are at least two ways in which deprived sensory cortices could be recruited by remaining senses in deaf or blind individuals[8]. The first is a 'bottom-up' process, assuming pre-existing direct cortico-cortical connections across sensory domains. For example, the auditory cortex has been reported to project directly to the primary visual cortex[9]. These auditory projections may remain stronger in

visually deprived animals[10]. A second way is through top-down attentional control from multisensory areas. Multimodal areas aid in orienting attention across modalities through feedback projections[11]. Shared multisensory feedback across the visual and the auditory areas that code for the same supramodal skill could guide cross-modal plasticity across homologous areas as proposed by Lomber and colleagues[3]. These two mechanisms are not mutually exclusive and both may very well be involved at different points in development.

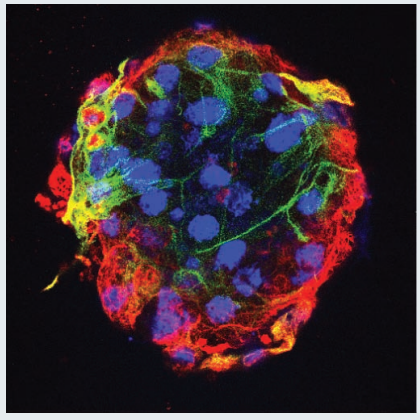
Although we have been talking about sensory cortices in general, one marked contrast between previous work and the current study is the absence of A1 reorganization. Cross-modal reorganization of primary sensory cortex is a well-documented phenomenon, especially in blind individuals. A host of studies document recruitment of the primary visual cortex (V1) in blind individuals in tasks as varied as Braille reading, listening to sentences, tactile discrimination or verbal memory[1]. The status of A1 in deaf individuals remains more controversial. Although all studies report cross-modal recruitment of secondary auditory areas, only one implicates A1 (ref. 12). In one of the rare animal models of cross-modal plasticity, congenitally deaf white cats, there is no sign of cross-modal plasticity in A1 (ref. 13). Lomber and colleagues[3] extend this finding and support the view that, unlike other auditory areas, top-down modulations to A1 are compromised following early deafness, preventing its recruitment in visual functions[14]. Following deafness, A1 may reorganize for other functions, such as somatosensory stimulation, as multisensory integration in A1 seems more weighed toward somatosensory signals[15]. However, evidence from deaf models is lacking so far. Clearly, the similarities and differences between A1 and V1 with respect to cross-modal reorganization remain to be elucidated.

A residual issue concerns the definition of supramodal itself. The enhancement of visual localization in the periphery and motion detection in deaf cats, contrasted with the lack of improvement in other clearly unimodal functions is clear-cut. However, it comes as a surprise, in the supramodal hypothesis, that discrimination of direction of motion and velocity were not enhanced. As an ambulance comes by, its siren provides much information about its direction and velocity, in addition to the visual information obtained from watching it drive by. Direction and velocity of motion are clearly supramodal skills. However, whether in deaf cats or deaf humans, these skills do not reorganize[2]. So, what exactly makes a function supramodal in regards to its potential for reorganization? Whether supramodal functions reorganize after deprivation may depend on the relative quality of the information each modality naturally contributes to that function. Cross-modal compensation may be more likely when the deprived modality is used to convey the most reliable information, as audition does for peripheral localization. Whether motion detection subscribes to that principle remains largely unknown. A prediction from this work is that deaf humans should show an advantage in a motion-detection task; this remains to be tested. Although unanswered questions remain, the supramodal hypothesis provides a welcome, principled approach as future research maps out the factors that foster or limit the ability of the brain to reorganize in the face of sensory deprivation.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Merabet, L.B. & Pascual-Leone, A. *Nat. Rev. Neurosci.* **11**, 44–52 (2010).
2. Bavelier, D., Dye, M. & Hauser, P. *Trends Cogn. Sci.* **10**, 512–518 (2006).
3. Lomber, S.G., Meredith, M.A. & Kral, A. *Nat. Neurosci.* **13**, 1421–1427 (2010).
4. Foxe, J.J. & Schroeder, C. *Neuroreport* **16**, 419–423 (2005).
5. Hunt, D.L., Yamoah, E.N. & Krubitzer, L. *Neuroscience* **139**, 1507–1524 (2006).
6. Dobkins, K.R. *Optom. Vis. Sci.* **86**, E583–E588 (2009).
7. Pascual-Leone, A., Amedi, A., Fregni, F. & Merabet, L.B. *Annu. Rev. Neurosci.* **28**, 377–401 (2005).
8. Bavelier, D. & Neville, H.J. *Nat. Rev. Neurosci.* **3**, 443–452 (2002).
9. Falchier, A. *et al. J. Neurosci.* **22**, 5749–5759 (2002).
10. Klinge, C., Eippert, F., Röder, B. & Büchel, C. *J. Neurosci.* **30**, 12798–12805 (2010).
11. McDonald, J.J. *et al. J. Cogn. Neurosci.* **15**, 10–19 (2003).
12. Finney, E.M., Fine, I. & Dobkins, K.R. *Nat. Neurosci.* **4**, 1171–1173 (2001).
13. Kral, A., Schröder, J.H., Klinke, R. & Engel, A.K. *Exp. Brain Res.* **153**, 605–613 (2003).
14. Kral, A.E. *Brain Res. Rev.* **56**, 259–269 (2007).
15. Lakatos, P. & Chen, C.-M. *Neuron* **53**, 279–292 (2007).

The importance of degradation



Neural stem cells can either self-renew, or differentiate into neurons, astrocytes and oligodendrocytes. How and why this decision is made is unclear. Hoeck *et al.* now show on page 1365 that Fbw7, a component of the SCF ubiquitin ligase complex, is a key regulator of the decision to differentiate. The cells in this neurosphere (red, GFAP; green, nestin; blue, DNA) lack Fbw7 and resisted differentiation even after 5 days in a differentiating medium.

Hoeck *et al.* found that, in the absence of Fbw7, the SCF substrates Notch and c-Jun are insufficiently degraded. Their ensuing accumulation inhibits differentiation and increases apoptotic death of neural progenitors. In the developing mouse brain, lack of Fbw7 increased the number of cells expressing immature progenitor markers and reduced neuron numbers by about half, but had no effect on glial numbers. Loss of one c-Jun allele reduced apoptosis in the Fbw7-depleted developing brain and partially restored cortical neuron numbers, but it did not normalize the number of immature progenitors. Conversely, inhibiting Notch signaling reduced immature progenitor numbers and also partially restored cortical neurons.

Fbw7 initiates the proteasomal degradation of several well-known mitotic molecules in addition to Notch and c-Jun, however none of these other known substrates were dysregulated in the Fbw7-depleted brain. *Fbw7* is an important tumor suppressor gene mutated in diverse cancers. Hoeck *et al.*, however, are the first to show that Fbw7 is also important for the development of the nervous system.

Annette Markus