segments of pyramidal cells rather than on the terminals[8]. In exceptional cases, a short section of initial segment has been observed to synapse on an inhibitory axo-axonic terminal in a serial arrangement[9], but this in no way explains the results of Ren *et al.*[3]. Perhaps the most unusual observation is of apparent excitatory terminals making contact with dendro-dendritic synapses between inhibitory interneurons[10] (that is, synaptic triads). Alas, even this observation cannot account for the results of Ren *et al.*[3].

Electron micrographs of neocortical neuropil are exceedingly complex images, and an observer's expectations strongly guide his perceptions. As George Orwell said, "To see what is in front of one's nose needs a constant struggle[11]." Visualizing these unusual synaptic arrangements will require directed ultrastructural analyses, starting perhaps with the isolated, immuno-labeled pyramidal cells prepared by Ren *et al.*[3].

It is also curious that other electrophysiologists have rarely observed interpyramidal IPSCs resembling those described in this study. Two recent studies in neocortex show that activity in one pyramidal cell can evoke inhibition in another pyramidal cell[12,13]. In both cases, however, the first cell has to fire multiple spikes at a high frequency (>30 Hz) before inhibitory currents are elicited. Fast interpyramidal IPSPs triggered by single spikes are exceptionally scarce (only 4 out of 1,450 cell pairs in one study[13]). Both of these investigations were done on pyramidal cells in somatosensory cortex of rats, whereas Ren *et al.*[3] studied cells in visual cortex of mice; perhaps these inhibitory circuits vary between cortical areas or species. An intriguing earlier study of the hippocampal CA3 region[14] found that about 30% of pyramidal cell pairs generated short-latency inhibition, but these seemed to be explained by a classical disynaptic pathway.

The computational implications of an inhibitory circuit that bypasses most of the interneuron are exciting. The classical disynaptic inhibitory pathway allows for considerable integration of synaptic inputs onto interneurons. In general, one spike in one pyramidal cell is not nearly enough to trigger spikes in the interneurons. Rather, convergent, coincident excitatory inputs are usually required before inhibition appears in downstream pyramidal cells (**Fig. 1b**, left). Classical disynaptic inhibition also tends to be more variable. In contrast, the interpyramidal pathway proposed by Ren *et al.*[3] requires no synaptic integration. With high reliability and short latency, a spike in one pyramidal cell ($P_2$) can trigger GABA release from one or more terminals onto neighboring pyramidal cells (**Fig. 1b**, right). This is not merely a more efficient system, but it also turns the usual communication between pyramidal cells on its head. Instead of weakly exciting one another, pyramidal cells arranged in this way can strongly inhibit one another.

The inhibitory circuit described by this study[3] implies that pyramidal cell synapses, acting via kainate and AMPA receptors, strongly excite GABAergic terminals to evoke transmitter release. It seems a good bet that this process also triggers action potentials in inhibitory terminals[5,15]. If so, spikes might propagate antidromically throughout an interneuron's arbor, inhibiting all downstream targets of that cell. Thus, by using the interneuron-bypass pathway, a single pyramidal cell could potentially trigger an unusually powerful cascade of local inhibition.

The work of Ren *et al.*[3] suggests both a new inhibitory function and its surprising cellular mechanism. Further studies will be illuminating. Are there actually synaptic triads with specialized sites of contact? How common is this type of circuit across cortical areas and laminae? Is it exploited by other cortical pathways, such as thalamocortical afferents? When does it appear in development and how is it regulated? Which interneuron subtypes are involved? What is the relationship between classical inhibitory pathways and interneuron-bypass circuits? Whatever the answers may be, one thing is certain. Neocortical inhibition will never again seem simple.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

1. Markram, H. *et al. Nat. Rev. Neurosci.* **5**, 793–807 (2004).
2. Shepherd, G.M. *The Synaptic Organization of the Brain. 5th ed.* (Oxford University Press, Oxford, UK, 2003).
3. Ren, M., Yoshimura, Y., Takada, N., Horibe, S. & Komatsu, Y. *Science* **316**, 758–761 (2007).
4. Ali, A.B., Rossier, J., Staiger, J.F. & Audinat, E. *J. Neurosci.* **21**, 2992–2999 (2001).
5. Semyanov, A. & Kullmann, D.M. *Nat. Neurosci.* **4**, 718–723 (2001).
6. Jones, E.G. *The Thalamus. 2nd ed.* (Cambridge University Press, New York, 2007).
7. Colonnier, M. *Brain Res.* **9**, 268–287 (1968).
8. Somogyi, P., Tamas, G., Lujan, R. & Buhl, E.H. *Brain Res. Brain Res. Rev.* **26**, 113–135 (1998).
9. Sloper, J.J. & Powell, T.P. *Phil. Trans. R. Soc. Lond. B* **285**, 173–197 (1979).
10. Sloper, J.J. & Powell, T.P. *Proc. R. Soc. Lond. B* **203**, 23–38 (1978).
11. Orwell, G. *The Collected Essays, Journalism and Letters of George Orwell: In Front of Your Nose, 1945–1950* (eds. Orwell, S. & Angus, I.) (Harcourt Brace Jovanovich, New York, 1968).
12. Kapfer, C., Glickfeld, L.L., Atallah, B.V. & Scanziani, M. *Nat. Neurosci.* **10**, 743–753 (2007).
13. Silberberg, G. & Markram, H. *Neuron* **53**, 735–746 (2007).
14. Miles, R. *J. Physiol. (Lond.)* **428**, 61–77 (1990).
15. Pinheiro, P. & Mulle, C. *Cell Tissue Res.* **326**, 457–482 (2006).

# The highs and lows of being tone deaf

Petr Janata

**Representations of pitch and space seem to interact. A new study now reports that people with amusia, a pitch processing deficit, do not show the interference between these concepts that is found in control subjects.**

When we talk about the stunning high note from the soprano at the opera or the deep sound of the bass at a jazz club, we use spatial concepts to describe sounds. These descriptors do not seem to be mere metaphors that have established themselves idiosyncratically in numerous cultures. Instead, experiments suggest that there are cognitive correspondences between representations of pitch and space[1,2]. For example, people are slower and less accurate in deciding whether the second of two notes is lower or higher in pitch than the first if they have to respond to the higher pitch by pressing the lower button than if the response is spatially compatible[2] (**Fig. 1a**).

A prediction of this hypothesis is that 'amusics', individuals with severely impaired ability to tell whether notes in melodies go up or down, should also have difficulty with tasks that depend on spatial relationships. This prediction is provocative because amusia or 'tone-deafness' has largely been considered a perceptual impairment that is restricted

Petr Janata is in the Center for Mind and Brain, Department of Psychology, University of California, Davis, 267 Cousteau Place, Davis, California 95618, USA.
e-mail: pjanata@ucdavis.edu

to music, stemming from difficulties in making fine pitch discriminations[3,4], rather than a broader impairment of higher-order processes. In this issue, Douglas and Bilkey report that amusics indeed show deficits, relative to musicians and nonmusicians, in tasks that involve spatial processing[5].

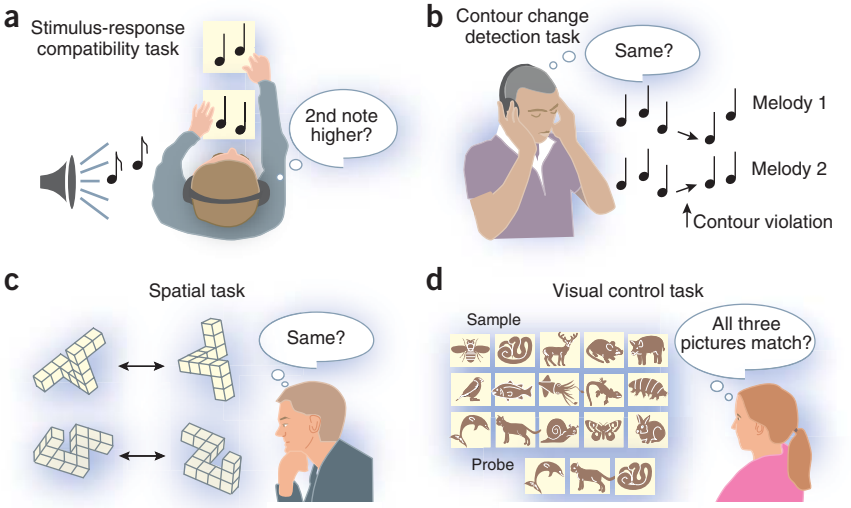
Their conclusions derive from two sets of observations. First, they found that impaired performance on one of the tests for amusia, a contour-change detection task drawn from the Montreal Battery for the Evaluation of Amusia[6] (**Fig. 1b**), was accompanied by poor performance on a classic task involving mental rotation of geometric figures[7] (**Fig. 1c**). Individuals classified as amusics by this test stood apart from both control groups in terms of the number of mental rotation errors that they committed. Notably, all three groups performed comparably well when asked to determine whether a set of three animal pictures was contained in a larger set of 15 animal pictures—a task with modest working memory and visual search demands (**Fig. 1d**).

In a second set of task comparisons, Douglas and Bilkey[5] showed that representations of pitch and space are dissociated more strongly in amusics than in control subjects. They examined performance on the stimulus-response compatibility (SRC) task discussed above[2] (**Fig. 1a**) under both single- and dual-task conditions. In the compatible condition, subjects responded to lower and higher tones, respectively, by pressing the lower (closer) and higher (farther) buttons on a computer keyboard. The response mapping was reversed in the incompatible condition. When carrying out the SRC task alone, amusics showed no difference between compatible and incompatible response configurations, either in terms of their accuracy or of their response speed. Although they were not slower than either control group in the incompatible conditions, they did not show the same benefit of a compatible mapping as did musicians and, to a lesser extent, nonmusicians.

The most intriguing results were obtained in the dual-task condition, which is a tried-and-true method for determining whether psychological processes interact with each other or proceed independently. Subjects carried out the SRC task concurrently with either the animal-matching or mental-rotation task. As expected when the secondary task does not interact with the primary task, concurrent animal matching slowed SRC task performance to a similar extent in all groups. However, in concurrent mental-rotation and pitch-discrimination tasks, musicians and nonmusicians showed a greater interference effect than did amusics. Both control groups were about half a second slower than amusics in making the pitch judgments, and also made more errors and completed fewer trials in the mental-rotation task. Thus, the results supported the hypothesis that space and pitch share a common representation in normal subjects, but not in amusics. Perhaps the most remarkable result, though, was the effect that the dual-task condition had on the amusics: they actually improved in their mental-rotation performance, committing fewer errors and completing more trials than when mental rotation was their sole task. It remains unclear why amusic subjects benefited from having to perform both tasks simultaneously.

Linking amusia to the growing literature on the relationship of pitch to the mental representations of other dimensions or spaces provokes new sets of questions. For example, many amusics also show significant rhythmic impairments, thus implicating higher-order representations of time and temporal structure. To what extent are amusics impaired in other tests of spatiotemporal processing? Do pitch and space interactions depend on training? Although the amusics in the current study were significantly impaired in the spatial tasks, the degree of their impairment on the SRC task was pretty minor in terms of absolute numbers of errors. In terms of reaction times, they mainly failed to show the benefit that the musicians showed in the compatible trials. Given that the difference between amusics and nonmusician controls on the SRC task did not quite reach statistical significance, the SRC results overall raise the possibility that conjoint pitch and space representations are as much a consequence of training and experience as they are of some underlying congenital difference. Are amusics impaired on other abstract spatial tasks, and would melody-discrimination training help spatial abilities or vice versa? Aficionados of the Mozart effect may discern the haunting echoes of the relationship between music and spatial skills.

A second set of questions follows the search for the anatomical locus of amusia. Several neuroimaging and lesion studies have documented the role of the auditory areas along the superior temporal gyrus in pitch discrimination and melodic contour processing (summarized in ref. 8). These studies, together with the focus on amusia as a perceptual deficit[3,4], would seem to root the neuroanatomical causes of amusia squarely along the superior temporal gyrus, even without evidence of any gross morphological differences[4]. However, the representations of abstract spaces and multiple coordinate systems, such as those that guide mathematical




Ann Thomson

**Figure 1** The link between musical and spatial processing was investigated via a set of tasks. (**a**) In a stimulus-response compatibility task, subjects press either the closer or farther of two buttons on a computer keyboard to indicate whether the second of two pitches is higher or lower than the first. The response that the second pitch was higher was made more quickly, on average, when the answer "higher pitch" was mapped to the 'higher' (farther) of the two response buttons, than when the response "lower pitch" was mapped to the higher button. (**b**) In the contour violation task from the Montreal Battery for the Evaluation of Amusia, subjects have to detect whether a single note in the repetition of a melody changed direction. Amusic individuals have extraordinary difficulty with this task. (**c**) In the Shepard and Metzler mental rotation task, subjects must determine whether two geometric figures are the same or different. (**d**) In the animal matching task, a large set of 15 animal pictures is shown to the subject along with a set of three probe pictures. Subjects must determine whether all three pictures from the small set are in the large set.

reasoning, spatial attention and translating perception into action, are largely the province of the parietal cortex[9,10]. Taken together, the results surrounding interactions between pitch and space suggest that the neuroanatomical correlates of amusia might be found in the parietal lobes. Unfortunately, this prediction was not borne out by a magnetic resonance imaging and morphometry study of two populations of amusics that found a reduction in white matter concentration in amusics relative to controls in the right inferior frontal cortex, but no difference in the parietal cortex[11]. Thus, amusia may be a condition that arises in a brain network involving temporal, parietal and frontal cortices. These regions are involved in pitch processing and attentive tracking of melodies[12–14], along with other functions.

The scant evidence for gross morphological correlates of amusia raises the possibility that the deficit may derive from changes in neural functioning that are invisible to the tools that have been applied to date. For example, Douglas and Bilkey[5] point to literature on the interactions between hormones, gender and spatial abilities as a means of understanding the link between musical and spatial processing. With sex and drugs as part of the show, it is highly unlikely that the search for the biological basis of amusia will fall flat.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

1. Repp, B.H. & Knoblich, G. *Psychol. Sci.* **18**, 6–7 (2007).
2. Rusconi, E., Kwan, B., Giordano, B.L., Umilta, C. & Butterworth, B. *Cognition* **99**, 113–129 (2006).
3. Ayotte, J., Peretz, I. & Hyde, K. *Brain* **125**, 238–251 (2002).
4. Peretz, I. *et al. Neuron* **33**, 185–191 (2002).
5. Douglas, K.M. & Bilkey, D.K. *Nat. Neurosci.* **10**, 915–921 (2007).
6. Peretz, I., Champod, A.S. & Hyde, K. *Neurosciences and Music* Vol. 999 (eds. Avanzini, G. *et al.*) 58–75 (New York Academy of Sciences, New York, 2003).
7. Shepard, R.N. & Metzler, J. *Science* **171**, 701–703 (1971).
8. Stewart, L., von Kriegstein, K., Warren, J.D. & Griffiths, T.D. *Brain* **129**, 2533–2553 (2006).
9. Hubbard, E.M., Piazza, M., Pinel, P. & Dehaene, S. *Nat. Rev. Neurosci.* **6**, 435–448 (2005).
10. Walsh, V. *Trends Cogn. Sci.* **7**, 483–488 (2003).
11. Hyde, K.L., Zatorre, R.J., Griffiths, T.D., Lerch, J.P. & Peretz, I. *Brain* **129**, 2562–2570 (2006).
12. Gaab, N., Gaser, C., Zaehle, T., Jancke, L. & Schlaug, G. *Neuroimage* **19**, 1417–1426 (2003).
13. Janata, P., Tillmann, B. & Bharucha, J.J. *Cogn. Affect. Behav. Neurosci.* **2**, 121–140 (2002).
14. Zatorre, R.J., Evans, A.C. & Meyer, E. *J. Neurosci.* **14**, 1908–1919 (1994).



# Numb, neurogenesis and epithelial polarity

Seonhee Kim & Chris A Walsh

**Numb's function in mammalian neural progenitors has been unclear. A paper in this issue shows a crucial role for Numb in the maintenance of radial glia adherens junctions and, consequently, the integrity of the neurogenic epithelium.**

Although there is some neurogenesis in the adult brain, the vast majority of neurons are born during the embryonic period. What signals the end of this neurogenesis? This long-standing question generates intense interest as evidence accumulates for adult neurogenesis, raising hopes that it might be possible to reactivate neurogenesis in the mature brain for the treatment of neurodegenerative diseases. However, the molecular mechanisms that determine the timing of neurogenesis remain poorly understood.

In the embryo, neurons are generated from an ordered neuroepithelium composed largely of highly polarized radial glial cells (RGCs). Wilhelm His and Santiago Ramón y Cajal observed in the 19th century that these radial cells disappear at the end of neurogenesis. Only over the last decade have researchers realized that RGCs are direct neuronal progenitors, and that their terminal differentiation into astrocytes indicates the loss of the normal neuronal progenitor population[1]. Put another way, the loss of the polarized, radial neuroepithelial structure might be a major mechanism for ending neurogenesis. The study by Rasin *et al.* in this issue[2] convincingly supports this link between neurogenesis and epithelial morphology. The authors show that *Numb* and *Numbl*, genes implicated in neurogenesis[3–5], are also required for maintaining the polarized structure of radial glia, through the correct targeting of adherens junction components, such as cadherins, that maintain epithelial integrity.

The Numb protein was first identified in the fruit fly, *Drosophila melanogaster*, as a cell fate determinant in neuroblasts and sensory organ precursor cells, where 'asymmetric' cell divisions generate two daughter cells with distinct (asymmetric) cell fates. Fly neuroblasts, which are akin to neuronal stem cells, divide to regenerate a neuroblast and to produce a ganglion mother cell, which is a short-lived, intermediate progenitor that generates a pair of neurons or glial cells. This asymmetric cell division is controlled by asymmetric distribution of specific proteins. The apical polarity proteins Baz, Par6 and aPKC localize to one side of the neuroblast, whereas Lgl,

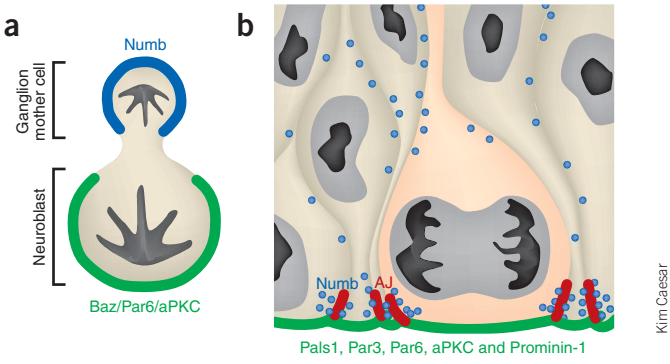



**Figure 1** Numb localization is evolutionarily conserved in fly neuroblast and mammalian neuroepithelium. (**a**) In the fly neuroblast, the localization of apical complex protein composed of Baz, Par6 and aPKC (green) is restricted to the apical side, and Numb (blue) is localized on the basal side and segregated to the small ganglion mother cell. (**b**) In the mammalian neuroepithelium, the apical membrane (green) includes apical complex proteins, such as Pals1, Par3, Par6, aPKC and Prominin1. Numb (blue) is localized to vesicular structures of the basolateral membrane and is especially enriched near the adherens junction (AJ) of apical endfeet of interphase cells.

Seonhee Kim and Chris A. Walsh are at the Division of Genetics, Children's Hospital Boston, Howard Hughes Medical Institute, Beth Israel Deaconess Medical Center, and the Program in Neuroscience, Harvard Medical School, New Research Building, Room 266, 77 Avenue Louis Pasteur, Boston, Massachusetts 02115, USA.
e-mail: cwalsh@bidmc.harvard.edu