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,

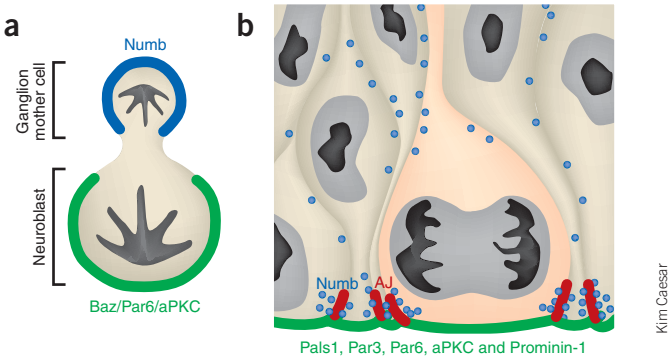

Figure 1 Numb localization is evolutionarily conserved in fly neuroblast and mammalian neuroepithelium. (**a**) In the fly neuroblast, the localization of apical complex protein composed of Baz, Par6 and aPKC (green) is restricted to the apical side, and Numb (blue) is localized on the basal side and 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

Dlg and Numb localize to the basal pole (**Fig. 1a**). Consequently, Numb segregates to the basally budding ganglion mother cells, but not to the apical neuroblasts. Numb thereby defines the different fates of the two daughter cells, apparently by modulating Notch signaling[6]. The same molecular components are well conserved in the mammalian neuroepithelium (except that mammals have at least two Numb orthologs, Numb and Numblike), but the function of Numb in asymmetric cell division of mammalian neural progenitors seems to be somewhat different than in fly neuroblasts. Conditional inactivation of Numb (in mice also lacking Numblike) provides some evidence that Numb and Numblike promote progenitor cell fate, rather than neuronal fate[4,5]. Also, the localization of Numb in mice seems to be opposite to that in flies. Numb seems to localize at the ventricular (apical) surface, apparently overlapping with the apical location of Baz, Par6 and aPKC homologs, instead of occupying the opposite pole of the cell as it does in flies.

Work using Emx1-Cre (where expression starts at E9.5 in dorsal cortex) to inactivate Numb on a Numblike null background[3] provided somewhat unclear results about cell fate determination, possibly because the neuroepithelium was structurally disturbed, with more severe hydrocephalus than in the other mutant mice[4,5]. Thus, this study provided a clue as to a potential role of Numb in maintaining neuroepithelial integrity. Further support for the importance of Numb and Numblike in epithelial integrity came from work reporting that these genes are involved in the integrity of the ependymal layer in the adult neural stem-cell niche[7].

Rasin *et al.*[2] now report several surprising observations concerning Numb expression in the neuroepithelium and its function. Whereas previous studies localized Numb to an apical crescent in progenitors[8], Rasin *et al.* show that Numb is mainly localized to the ventricular endfeet of interphase cells, but is actually excluded from the apical-most membrane of mitotic RGCs. Indeed, the authors demonstrate by immuno-electron microscopy that Numb accumulates in basolateral membranes of both dividing and nondividing cells, and is excluded from the apical membrane in between the adherens junctions (**Fig. 1b**).

Other reports support the basolateral localization of Numb in Madin-Darby canine kidney cells[9], and in chick neuroepithelial cells[10], suggesting that Numb localization may be evolutionarily conserved after all. It remains unclear, however, how Numb localization is regulated in the dividing cells, although one report implicates the Golgi-associated protein ACBD3 in regulation of Numb through the cell cycle[11]. More sensitive approaches, maybe using *in vivo* time-lapse imaging of tagged Numb or antibodies against different epitopes of Numb protein, might tell us more about its asymmetric distribution during RGC division. Nonetheless, Numb mainly localizes to the basolateral portion of radial glia endfeet near the adherens junctions.

Rasin *et al.* went on to show that there were direct interactions between Numb and adherens junction components. Several adherens junction proteins, including Cdh1 (E-cadherin), Cdh2 (N-cadherin) and catenins (α-E-catenin, β-catenin) could be co-immunoprecipitated with endogenous Numb. Numb is an endocytic adaptor protein that interacts with AP2 and Eps15 to regulate clathrin-mediated endocytosis of Notch[12], is directly associated with the Rab11-positive pool of recycling endosomes containing Cdh1, and is regulated by a Golgi-associated protein, ACDB3 (ref. 11). In *Numb*- and *Numblike*-deficient cells, cadherins were mistargeted to the apical membrane, causing the loss of adherens junctions. Thus, Numb might function in the trafficking of adherens junction components.

To directly address the outcome of a loss of Numb, Rasin *et al.* used *in utero* electroporation of shRNA to knock down Numb and Numblike in a subset of progenitors, circumventing the potential secondary consequences of the severe structural defects previously seen in knockout studies. In accordance with these studies, the shRNA-mediated knockdown of Numb and Numblike led to a loss of adherens junctions and the release of RGC endfeet from their anchor on the ventricular surface. Interestingly, shRNA against cadherins (Cdh1 and Cdh2) generated a phenocopy of the defects seen in the knockdown of Numb and Numblike, which further supports their direct relationship.

Conversely, overexpression of Numb isoforms or cadherins (Cdh1 and 2) prolonged radial morphology beyond the normal end of neurogenesis. The prolonged maintenance of radial morphology by forced Numb expression was dependent on cadherin-mediated cell adhesion, as it could be blocked using shRNA to cadherins. Somewhat surprisingly, the forced expression of Numb and cadherins in neural stem cells did not increase the production of neurons, although it did decrease the production of astroglia. This result suggests that there may be additional intrinsic or extrinsic mechanisms that limit the production of neurons.

Although the adherens junction defects were evident, there were no obvious cell fate changes in Numb-inactivated progenitors. In the mice lacking forebrain Numb and Numb-like[3], all the cortical layers were formed, and the sequential generation of neurons was not affected, although neuron numbers, especially of late-born neurons, were reduced. In these mice, it is possible that the extensive structural defects of the neuroepithelium may have occluded changes in cell fate. The shRNA knockdown experiment, in turn, might have left enough residual Numb and Numblike proteins for proper regulation of cell fate determination.

The Rasin *et al.* study is particularly interesting because it connects the body of work on Numb in neurogenesis with reports suggesting that adherens junctions affect the fate of progenitors. For example, conditional inactivation of α(E)-catenin in the nervous system causes hyperproliferation of progenitors with an accelerated cell cycle and suppression of cell death[13]. A mouse model expressing a constitutively active form of the adherens junction component (and Wnt signaling molecule) β-catenin shows a tremendous increase in cortical size[14]. Adherens junction defects caused by cortex-specific Cdc42 deficiency also resulted in progenitor fate changes, increasing a population of intermediate progenitors that are more neurogenic than RGC and not attached to the ventricular surface[15]. The study by Rasin *et al.* now further underscores the importance of the neuroepithelium architecture for the generation and organization of the diverse neuron populations that make up the adult cerebral cortex.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

1. Noctor, S.C., Flint, A.C., Weissman, T.A., Dammerman, R.S. & Kriegstein, A.R. *Nature* **409**, 714–720 (2001).
2. Rasin, M.-R. *et al. Nat. Neurosci.* **10**, 819–827 (2007).
3. Li, H.S. *et al. Neuron* **40**, 1105–1118 (2003).
4. Petersen, P.H., Zou, K., Hwang, J.K., Jan, Y.N. & Zhong, W. *Nature* **419**, 929–934 (2002).
5. Petersen, P.H., Zou, K., Krauss, S. & Zhong, W. *Nat. Neurosci.* **7**, 803–811 (2004).
6. Wodarz, A. *Curr. Opin. Cell Biol.* **17**, 475–481 (2005).
7. Kuo, C.T. *et al. Cell* **127**, 1253–1264 (2006).
8. Zhong, W., Feder, J.N., Jiang, M.M., Jan, L.Y. & Jan, Y.N. *Neuron* **17**, 43–53 (1996).
9. Smith, C.A. *et al. EMBO J.* **26**, 468–480 (2007).
10. Wakamatsu, Y., Maynard, T.M., Jones, S.U. & Weston, J.A. *Neuron* **23**, 71–81 (1999).
11. Zhou, Y. *et al. Cell* **129**, 163–178 (2007).
12. Berdnik, D., Torok, T., Gonzalez-Gaitan, M. & Knoblich, J.A. *Dev. Cell* **3**, 221–231 (2002).
13. Lien, W.H., Klezovitch, O., Fernandez, T.E., Delrow, J. & Vasioukhin, V. *Science* **311**, 1609–1612 (2006).
14. Chenn, A. & Walsh, C.A. *Science* **297**, 365–369 (2002).
15. Cappello, S. *et al. Nat. Neurosci.* **9**, 1099–1107 (2006).