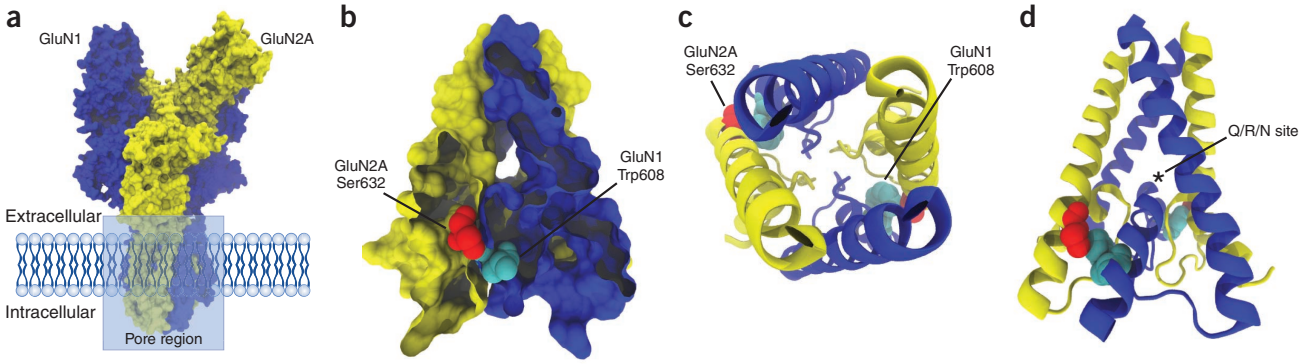

Figure 1 A model of the GluN1-GluN2A NMDA receptor. (**a**) Space-filling representation of a homology model of the tetrameric GluN1-GluN2A built from crystallographic data from ref. 12. (**b**) Cutaway view of the pore-forming region of the closed channel modeled by Retchless *et al.*[1]. GluN1 Trp608 is a residue identified by Retchless *et al.*[1] as coupling to the serine/leucine site in GluN2. (**c**,**d**) View from the extracellular face (**c**) or plane of the membrane (**d**) of the pore represented as a ribbon structure. The asterisk shows the apex of the M2 re-entrant loop (Q/R/N site)[2], which harbors residues that can influence ion permeation and block in several members of the glutamate receptor family. Images provided by G. Wells.

and Ca^{2+} permeability and Mg^{2+} block in NMDA receptors (see ref. 2).

Despite decades of work, an understanding of the physical nature of the pore that enables behaviors such as asymmetrical sublevel transitions and controls the physiologically important differences in Ca^{2+} permeability and Mg^{2+} block has remained elusive. These data represent an important advance in our understanding of the NMDA receptor pore. Furthermore, this finding provides a rare example in biology of convergence, where high-resolution data simplify a storyline rather than complicate it. That is, three different properties (Mg^{2+} affinity, Ca^{2+} permeability and conductance) all seem to reflect conformations of the pore controlled by the same structural determinant involving the M3 serine residue in GluN2A and GluN2B and the corresponding leucine residue in GluN2C and GluN2D. Prior to these findings, it seemed likely that each property would have a distinct set of control elements with only modest atomic overlap.

Furthermore, these data shed light on the mysterious nature of subconductance levels, a poorly understood feature of many channels. These findings also offer an experimental path forward, as future work focused on regions near the intracellular end of M3 and its configuration, as well as M3-M2 inter-subunit interactions, should provide further insight. Thus, after decades of describing how NMDA receptor subunits differ in three critical pore properties underlying important events such as neuronal development and memory formation, there finally appears to be light in the tunnel to guide future studies of how ions traverse this complicated molecular machine.

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COMPETING FINANCIAL INTERESTS

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1. Retchless, B.S., Gao, W. & Johnson, J.W. *Nat. Neurosci.* **15**, 406–413 (2012).
2. Traynelis, S.F. *et al. Pharmacol. Rev.* **62**, 405–496 (2010).
3. Cull-Candy, S.G. & Usowicz, M.M. *Nature* **325**, 525–528 (1987).
4. Jahr, C.E. & Stevens, C.F. *Nature* **325**, 522–525 (1987).
5. Howe, J.R., Cull-Candy, S.G. & Colquhoun, D. *J. Physiol. (Lond.)* **432**, 143–202 (1991).
6. Gibb, A.J. & Colquhoun, D. *J. Physiol. (Lond.)* **456**, 143–179 (1992).
7. Mayer, M.L., Westbrook, G.L. & Guthrie, P.B. *Nature* **309**, 261–263 (1984).
8. Nowak, L., Bregestovski, P., Ascher, P., Herbet, A. & Prochiantz, A. *Nature* **307**, 462–465 (1984).
9. Ogden, K.K. & Traynelis, S.F. *Trends Pharmacol. Sci.* **32**, 726–733 (2011).
10. Kuner, T. & Schoepfer, R. *J. Neurosci.* **16**, 3549–3558 (1996).
11. O'Leary, T. & Wyllie, D.J.A. *Biochem. Soc. Trans.* **37**, 1347–1354 (2009).
12. Sobolevsky, A.I., Rosconi, M.P. & Gouaux, E. *Nature* **462**, 745–756 (2009).
13. Schneggenburger, R. & Ascher, P. *Neuron* **18**, 167–177 (1997).
14. Burnashev, N. *et al. Science* **257**, 1415–1419 (1992).
15. Kashiwagi, K. *et al. Mol. Pharmacol.* **61**, 533–545 (2002).

Cilia: conductors' batons of neuronal maturation

Fadel Tissir & Andre M Goffinet

The primary cilium, a signal transduction organelle, is present on the cell bodies of adult-born dentate gyrus granule cells as they begin maturation. In its absence, their maturation and integration are impaired.

For two decades, we have known that adult neural stem cells (NSCs) retain the capacity to generate new neurons destined for the olfactory bulb and the dentate gyrus, a part of the hippocampal formation[1]. But generating new neurons is one thing. Bringing them to their right location and integrating them into functional, pre-existing networks is another. In this issue, Kumamoto *et al.*[2] contribute an exciting piece of evidence concerning the latter process, showing that primary cilia orchestrate morphological and physiological maturation of newly generated adult granular neurons in the dentate gyrus.

Primary cilia are cellular 'antennae' present in many cells, including neurons, that are endowed with receptors and signal transduction capabilities, notably, but not solely, for the sonic hedgehog (Shh) pathway. Primary cilia are present at the apical, ventricular surface of embryonic and adult NSCs, where they probably detect extracellular cues and transduce them into signals

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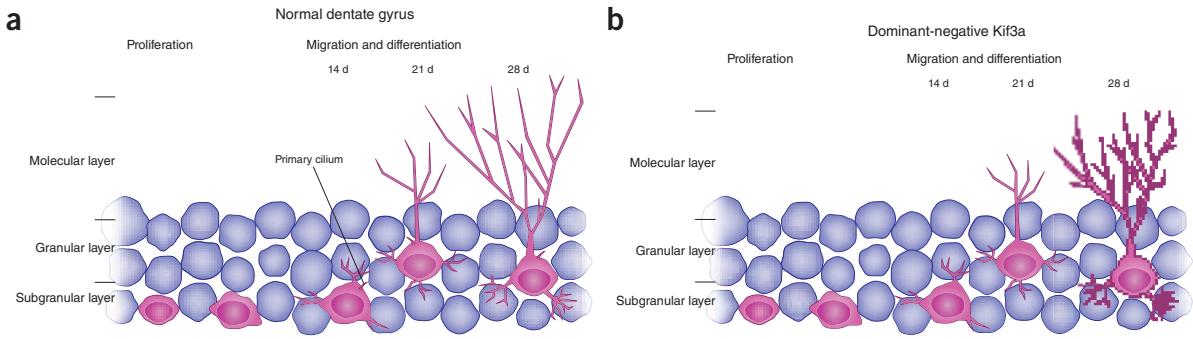

Figure 1 The primary cilium and granule cell migration. (**a**) New granule cells arise from mitosis in the subgranular layer of the adult dentate gyrus, migrate into the granular layer and send out dendritic processes to form functional connections in the molecular layer (reviewed in ref. 1). Cilia are detected on postmitotic granule cells from 14 d after the cells are born[2]. (**b**) Blocking ciliogenesis by downregulation of Kif3A impairs neuronal maturation, resulting in shorter dendrites.

that regulate NSC formation, self-renewal and differentiation[3,4].

Primary cilia are anchored to the mother centriole, the older centriole of the centrosome, which is a complex organelle made of two centrioles and associated pericentrosomal matrix that is strategically located adjacent to the Golgi and the proteasome-rich region at the center of the microtubule network. In NSCs, the centrosome is located in the subapical domain (on the side of the ventricle), whereas it is found in the opposite side of migrating and immature neurons, on the leading process and growing dendrite. Thus, a translocation of the centrosome occurs in postmitotic cells as soon as they leave the ventricular zones of progenitor proliferation.

In contrast with NSCs, in which the location and role of cilia are well established, the fate of the primary cilium in postmitotic neurons during migration and maturation is less clear. Recent work has shown that a cilium can be found in the basolateral aspect of early postmitotic neurons[5], and short, blunted cilia have occasionally been described in intracellular vacuoles in migrating cortical neurons (so-called vestigial cilia), hinting at a possible function of primary cilia in neuronal migration. However, displacement of the centrosome in the leading process of migratory neurons is an important element of migration, particularly of the progression of the nucleus (nucleokinesis), and rapid centrosome movements may preclude its acting as a docking station for ciliogenesis. Accordingly, a recent study of neocortical development did not detect cilia in migrating neurons, but instead found that they appear in end-migration neurons and that they grow in size during maturation and synaptogenesis[6].

Using local injection of retroviral vectors in the hilus of the dentate gyrus to label newly generated neurons, Kumamoto *et al.*[2] detected no cilia until 14 d after infection, the time at which immature neurons reach the end of their migration (**Fig. 1a**), confirming an earlier result[6]. To assess the incorporation of new dentate gyrus neurons in physiological networks, Kumamoto *et al.*[2] administered retroviral vectors to label newly generated dentate gyrus cells and injected an adeno-associated virus encoding channelrhodopsin2 in areas that provide excitatory glutamatergic input to the dentate gyrus, thereby allowing induction of depolarizing current in dentate gyrus targets following illumination with blue light. They then recorded electrical activity of labeled, newly generated, and unlabeled, pre-existing control dentate gyrus neurons using the whole-cell patch configuration (with GABAergic activity blocked). Robust glutamatergic synaptic activity could be induced in new dentate gyrus neurons 14–21 d after their generation, at the same time that they assemble cilia.

To assess a causal link between ciliogenesis and network activity, Kumamoto *et al.*[2] then prevented assembly of cilia by infection with a retrovirus expressing a dominant-negative form of the kinesin plus-ended microtubule motor protein Kif3A in a doxycycline-inducible manner. This procedure abolished cilia formation and reduced glutamatergic transmission from entorhinal projections to dentate gyrus granule cells. Furthermore, abrogating cilia formation resulted in blunted dendritic arborization, demonstrating that primary cilia function in synaptic maturation and dendritic deployment (**Fig. 1b**). Similar effects were obtained by short hairpin RNA–mediated knockdown of IFT88, which disrupts cilium assembly independently of Kif3A.

Finally, Kumamoto *et al.*[2] found that preventing ciliogenesis in dentate gyrus neurons results in hyperactivity of canonical Wnt signaling, a phenomenon that has been reported in other contexts[7,8]. The researchers proposed that increased sensitivity to Wnt is responsible for the abnormal maturation of newly formed dentate gyrus neurons.

Those impressive and elegant results open new vistas on the function of primary cilia during NSC proliferation as well as during maturation of adult-born neurons and their integration into physiological networks[1]. Kumamoto *et al.*'s[2] findings also raise new questions. Inasmuch as cilia are found in NSCs and again during neuronal maturation, the fate of the ciliary machinery in early postmitotic neurons remains to be investigated. For example, instead of growing *de novo* at the end of migration, could a small, preformed ciliary anlage be transported in vesicles along the moving centrosome? Another possibility, recently emphasized[9], is that specialized areas of plasma membrane adjacent to the centrosome could receive signals and transmit them to the centrosomal hub and then to the cytoskeleton, even in the absence of a full-blown cilium. Although none has been clearly identified, a role of primary cilia in neuronal migration is not excluded, particularly in the case of cells that need to travel over long distances, as in tangential migration of forebrain interneurons[10]. Finally, besides Wnt and Shh pathways, other signals are mediated or tuned by cilia in various cell types, probably including maturing neurons. It will be important to define and study these signaling pathways further.

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1. Suh, H., Deng, W. & Gage, F.H. *Annu. Rev. Cell Dev. Biol.* **25**, 253–275 (2009).
2. Kumamoto, N. *et al. Nat. Neurosci.* **15**, 399–405 (2012).
3. Han, Y.G. *et al. Nat. Neurosci.* **11**, 277–284 (2008).
4. Breunig, J.J. *et al. Proc. Natl. Acad. Sci. USA* **105**, 13127–13132 (2008).
5. Wilsch-Bräuninger, M., Peters, J., Paridaen, J.T. & Huttner, W.B. *Development* **139**, 95–105 (2012).
6. Arellano, J.I., Guadiana, S.M., Breunig, J.J., Rakic, P. & Sarkisian, M.R. *J. Comp. Neurol.* **520**, 848–873 (2011).
7. Lancaster, M.A., Schroth, J. & Gleeson, J.G. *Nat. Cell Biol.* **13**, 700–707 (2011).
8. Jonassen, J.A., San Agustin, J., Follit, J.A. & Pazour, G.J. *J. Cell Biol.* **183**, 377–384 (2008).
9. Baldari, C.T. & Rosenbaum, J. *Curr. Opin. Cell Biol.* **22**, 75–80 (2010).
10. Métin, C. *et al. Development* **134**, 2815–2827 (2007).