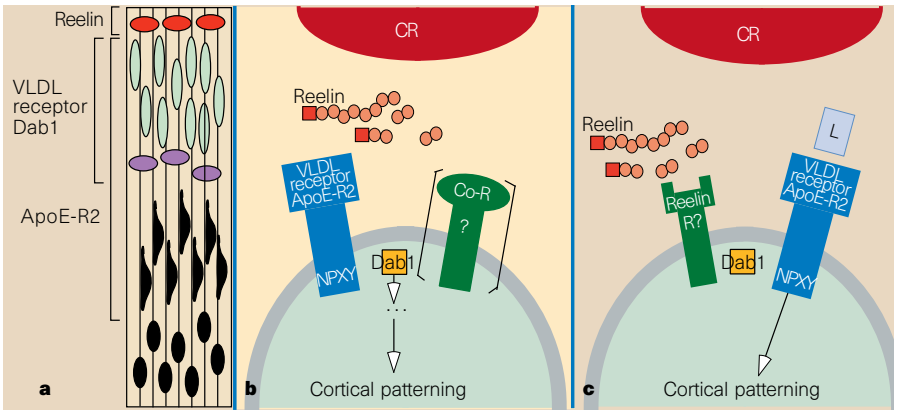


Figure 1 **Lipoprotein receptors and the Reelin signalling pathway.** a, **In the developing cortex, neuron precursors (black ovals) give rise to immature, elongated neurons that migrate (black) to settle in the cortical plate (green). This area is bordered externally by Cajal–Retzius cells (CR; red), which secrete Reelin, and internally by the subplate (pink). Patterning of the cortical plate depends not only on Reelin, but also on proteins expressed in the cortical-plate cells — Dab1 and, according to Trommsdorff *et al.*[2], the VLDL receptor and the ApoE-R2.** b, **The VLDL receptor and ApoE-R2 could react to the presence of Reelin or Reelin fragments by docking Dab1 through their NPXY cytoplasmic sequence. A co-receptor (Co-R) to Reelin could also be present.** c, **Reelin could act on an unidentified Reelin receptor and, via Dab1, recruit the VLDL receptor and ApoE-R2. Then, the VLDL receptor and ApoE-R2, together with an associated putative extracellular ligand (L), could direct cortical patterning.**

LDLR-related protein. Apparently, the other three members of this family do not share the effects of the VLDL receptor and ApoE-R2 on brain development.

The best-known ligand for the VLDL receptor and ApoE-R2 is apolipoprotein E (ApoE). Although this protein is synthesized in the brain — probably in glial cells — it is unlikely to be critical in the Reelin pathway, because mice that lack ApoE develop normally. As well as ApoE, lipoprotein receptors can bind thrombospondin-1, lipoprotein lipase, the serine protease urokinase-type plasminogen activator and probably others. The ligands implicated in patterning the embryonic brain have not, however, been defined thus far.

The fascinating finding that Reelin, Dab1 and the VLDL receptor/ApoE-R2 participate in the same genetic pathway fits nicely with previous observations. For instance, Dab1 interacts with the cytoplasmic tail of lipoprotein receptors and binds directly to the NPXY sequence, which has been implicated in lipoprotein-receptor-mediated cellular uptake[8,9]. The Dab1 protein also docks to the cytoplasmic signalling protein Ship, to some phosphatidyl inositols, as well as to the β-amyloid precursor protein and related proteins (ref. 9; R. Homayouni and T. Curran, personal communication). The β-amyloid precursor protein is cleaved to form the amyloid deposits in Alzheimer's disease. Moreover, the ApoE4 allele is associated with an increased predisposition to this disease. So, these observations might have pathophysiological implications.

Although several pieces of the puzzle are still missing, Trommsdorff and colleagues' data can be interpreted in at least two ways. The most parsimonious explanation (Fig. 1b) is that the VLDL receptor and ApoE-R2 are receptors to Reelin or fragments of this protein[10]. By docking Dab1, these receptors then modulate associated tyrosine kinase(s), and instruct the patterning of neurons at the end of migration. A variant of this explanation is that the VLDL receptor and ApoE-R2 could bring Dab1 to a Reelin co-receptor that has an associated tyrosine kinase activity. The main difficulty with this model is that, as far as we know, nobody has yet shown a physical association between the VLDL receptor/ApoE-R2 and Reelin or Reelin fragments.

A different view (Fig. 1c) is that the VLDL receptor/ApoE-R2 could act downstream of Reelin and Dab1. Lipoprotein receptors are involved in cellular uptake so they could, for example, modify membrane trafficking, thereby shaping the normal characteristics of postmigratory neurons. As yet, though, the putative Reelin receptor, its interaction with Dab1, and the ligand(s) for the lipoprotein receptor remain to be characterized. Whichever model (if either) is correct, both point to the necessity to identify and define putative Reelin receptors. This task will not be any the easier if the processing of Reelin into fragments, which has now been confirmed by several groups, is functionally important. □

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**Daedalus**

## Total digital recall

**How we store our memories is still a mystery. The secret seems to lie in the synapses where a dendrite from one brain cell touches the axon of another. But the information may be recorded physically, via the growth of new synapses; or chemically, via the synthesis of special encoding substances. These alter the chance that the synapse will convey a nervous impulse from one neuron to the other, or the chance that the receiving neuron will fire under this stimulation.**

**To settle the matter by experimenting on living brains is daunting, and maybe unethical as well. So Daedalus plans to study the information content of dead ones. Already organizations exist which will freeze your corpse in liquid nitrogen, and store it until science is sufficiently advanced to thaw you out and restore you to life. If you cannot afford a whole-body cryogenic crypt, you can merely have your head stored instead. In due course, science will then have to give you a new body. Alternatively, says Daedalus, it might be possible to read all the information in your dead and frozen brain. The totality of your experience would thus be captured for posterity — a rather second-class form of immortality, but better than nothing.**

**DREADCO physiologists are now working out how to do it. They propose sectioning the frozen brain into micron-thin slices with a cryogenic microtome. Each slice will be scanned by electron microscope, and recorded as a digitized image. The resulting 100,000 images will be stored in a terabyte memory, and used to reconstruct the complete synaptic 'wiring diagram' of the brain. Its chemical map will be harder to recover. Each slice will have to be treated with fluorescent immunoassay reagents binding to the crucial encoding substances, so as to record their distribution in the slice.**

**Daedalus cheerfully admits that the resulting vast mass of data will be utterly incomprehensible. But, as with the steadily growing incomprehensible data of the human-genome project, we must hope that one day it will all make sense. In due course science will advance enough to interpret your stored brain map — when your heroic sacrifice will finally bear fruit. Every detail of your life will be recovered, as a fascinating historical record. Secrets you took to the grave will be revealed at last. And if the data can by then be inserted back into a living brain, you might live again as a parasitic consciousness within the mind of someone else.**

**David Jones**