really fit into the model of familial AD, and one even tends to forget about them by stating that "all familial AD associated mutations increase Aβ42 generation".

The new Arctic mutation is a striking example of this paradox. Surprisingly, plasma samples from carriers of the Artic mutation displayed reduced levels of Aβ40 and Aβ42. The same was found in conditioned media derived from cells transfected with the corresponding βAPP cDNA[2]. The finding was further substantiated by demonstrating that cells transfected with the Italian and Dutch mutation also showed reduced secretion of Aβ40 and Aβ42 (ref. 2).

Therefore, all three mutations at codon 693 result in a pathogenic phenotype opposite to what would have been predicted. At first glance, these findings are incompatible with models of AD pathogenesis in which increased Aβ42 production or ratio is the common denominator. However, AD pathology is ultimately linked with the assembly and extracellular accumulation of fibrillar Aβ.

One of the intermediates in the pathway of Aβ fibril formation, the structural component of all amyloid plaques, is the protofibril. Protofibrils, originally identified by Teplow[10] and Lansbury[11], are short, flexible assemblies ~5 nm in diameter and rarely exceeding 200 nm in length. They are not only important intermediates in amyloid fiber formation, but also cause selective neuronal cell death[12,13].

Nilsberth *et al.*[2] investigated how the Arctic amino acid substitution affected protofibril formation *in vitro*. Whereas no apparent difference was found between the overall fibrilization rates of wild-type and Arctic Aβ, the mutant peptide produced protofibrils at a much higher rate and in larger quantities. The Arctic mutation thus increases the quantity of an Aβ assembly that not only has potent intrinsic neurotoxic activity, but also converts into fibrils, neurotoxic moieties in their own right.

Taking this into consideration, the Artic mutation can indeed fit into the unifying hypothesis, as one can state that all familial AD mutations facilitate Aβ assembly (be it into protofibrils, fibrils or other toxic moieties). One could speculate that selective increases in the levels of protofibrils may be a common cause for the early onset of AD pathology in all the familial cases. This would be in line with the recent finding that very similar protofibrils are formed by α-synuclein, the protein found within the major lesions of Parkinson's disease[14]. Moreover, rare mutations causing early-onset Parkinson's diseases also accelerate protofibril formation[14], although it has not yet been shown that they can cause selective neuronal cell death.

Unifying assembly mechanisms may be a common phenomenon of neurodegenerative disorders associated with the deposition of amyloidogenic peptides, a hypothesis strongly supported by the findings of Nilsberth *et al.*[2]. A popular theory within the field has been that amyloid plaques are the toxic unit directly associated with neurodegeneration. However, it became clear that the density of amyloid plaques does not necessarily correlate with the dementia and neuronal cell loss. The level of protofibrils may finally fulfill this critical correlation.

Protofibrils may also represent an ideal target for anti-amyloidogenic drugs. However, one still needs to prove that protofibril formation is critically required for disease-specific pathology in the human brain—a very difficult task which probably needs several additional years of intensive research. In the end, drugs against protofibrils may provide an important therapeutic alternative to the secretase inhibitors and vaccination approaches that are already under investigation.

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Neuronal migration and the evolution of the human brain

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A new study demonstrating a pathway for neuronal migration in humans, but not in monkeys, suggests that migration has a key role in the evolution of the brain, as well as its development.

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Neurons are natural migrants; most, if not all, of the neurons in the mammalian nervous system migrate from their places of birth to their locations of function. In the brain, neurons usually originate in the ventricular zone, where their precursor cells proliferate. They can then migrate radially to other layers in the brain, or tangentially (in a direction parallel to the surface of the brain) to other regions of the brain[1–3]. Radial migration is dependent on radially aligned glial fibers, whereas tangential migration is independent of glial cells and perhaps relies on contacts with other neurons. Although radial migration was the focus of research in the 1970s and 1980s, tangential migration was suggested in the 1960s and, through work in the 1990s, has now been established as a major mode of neuronal migration. Neuronal migration is a crucial step in neural development, as defects in neuronal migration cause multiple human diseases.

Similar to other fields of experimental biology, our knowledge of neuronal migration is based primarily on experiments with brains of laboratory animals.

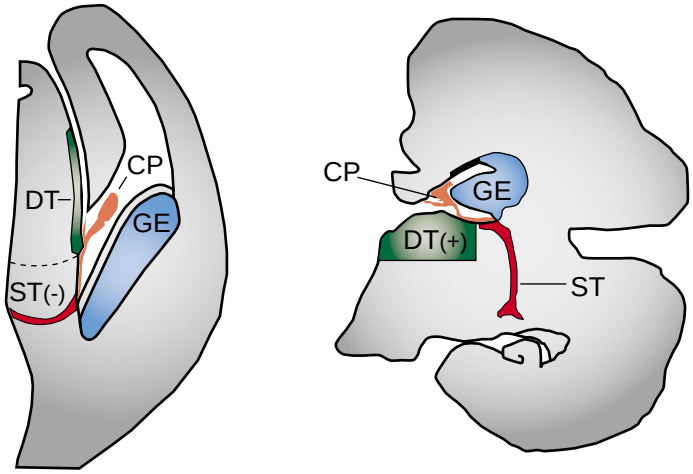

Fig. 1. Guidance activities involved in the GE–DT pathway. Schematic coronal sections of mouse and human brains at the level of the thalamus. +, attractive activity for cells from the GE; –, repulsive activity. GE, ganglionic eminence; DT, dorsal thalamus; ST, subthalamus; CP, choroid plexus.

Because developmental mechanisms are widely conserved across species ranging from flies and worms to humans, there has not been much effort devoted to experimental studies of neuronal migration in the human brain. However, a series of studies carried out by Pasko Rakic and colleagues, culminating in the paper published in this issue, show that certain important questions about the human brain can only be addressed by studying live tissue from the human brain (in this case, human brain slices from aborted fetuses)[4]. This study extends earlier suggestions, based on histological analysis of fixed human brains, that neuronal precursor cells migrate from a structure in the telencephalon, the ganglionic eminence (GE), to the thalamus in the diencephalon[5]. By comparing neuronal migration in humans with those in mice and monkeys, Rakic and colleagues demonstrate that the human brain may possess migratory pathways that do not exist in other mammals, or perhaps even in other primates.

Human thalamic nuclei connected to the frontal cortex are larger than those in other primates[6]. For example, the pulvinar nucleus in the dorsal thalamus (DT) is larger in primates than in other mammals and, among primates, is larger in humans than in chimpanzees and macaque monkeys. In previous work, Rakic and Sidman asked whether the larger pulvinar nucleus results from increased cell proliferation in the ventricular zone of the diencephalon. They found that there are two phases of pulvinar development in humans[5]. Whereas the early phase correlates with cell proliferation in the diencephalon, the late phase does not; cell proliferation in the diencephalon was not detected from the eighteenth to the thirty-fourth week of gestation, which is the major period of human pulvinar growth. This suggests that cells contributing to the late phase of pulvinar growth are not likely to be derived from the ventricular zone of the diencephalon[5]. During the late phase, the ganglionic eminence (GE), contains proliferative cells, and streams of cells extend from the GE to the thalamus. Cells in these streams are bipolar in the tangential direction, which suggests that they are migrating. Rakic and Sidman thus proposed that cells from the GE migrate through these streams to the thalamus in the human brain[5]. The positioning of the streams, their transient nature, and the direction of the leading and trailing processes of cells in the streams are consistent with the possibility that these streams were migratory pathways. However, there was no direct evidence that cells actually migrate from the GE to the thalamus.

In similar studies, Ogren and Rakic found in macaque monkeys that only the early phase of pulvinar development occurs, and that the pulvinar nucleus does not receive contributions of neurons from the telencephalon[7]. These findings led to the suggestion that neuronal migration from the GE to the pulvinar nucleus might be unique to humans[7].

In the work reported in this issue, Letinic and Rakic report the first direct evidence that neurons indeed migrate from the GE to the DT in human brain slices[4]. They placed the lipophilic dye DiI in the GE and found labeled cells in the DT, including the pulvinar and mediodorsal nuclei[4]. These neurons seem to be migrating in a fashion similar to other types of tangential migration described in the olfactory system[8], as they seem to be independent of glial fibers, but instead rely on contacts with other neurons. Furthermore, the migrating neurons contain GABA, the major inhibitory neurotransmitter in the brain. Taken together with earlier studies of GABAergic neuronal migration from the GE to the neocortex[9,10], the new results in human tissue indicate that the GE contributes to GABAergic neurons in multiple regions of the brain.

Using similar techniques, Letinic and Rakic did not detect cell migration from the GE to the DT in the monkey or the mouse brains[4]. Because earlier work on human brains[5] was done at times and under conditions different from the work on the mouse or the monkey brains[7], the present study provides the strongest evidence that the GE to DT migratory pathway is apparent only in the human brain.

Previous studies in rodents showed that regions surrounding the migrating neurons in the GE can influence migration[10]. To address the question of what contributes to the difference in neuronal migration between human and mouse brains, Letinic and Rakic isolated explants of human and mouse GE and co-cultured them with either the DT or the subthalamus (ST), which is part of the path from the GE to the DT[4]. Human GE cells were attracted by human DT, whereas mouse GE cells were neither attracted nor repelled by the mouse DT (**Fig. 1**). ST was repulsive in the mouse explants, but neither repulsive nor attractive in the human explants. The repulsive and attractive activities are contact-independent, indicating that they are diffusible guidance cues. These results suggest that guidance cues in the DT and the ST could explain the presence of the GE to DT pathway in the human, and its absence in the mouse.

The Letinic and Rakic paper thus provides not only direct evidence for a new migratory pathway in the human brain, but also suggests possible cellular mechanisms that may underlie the differential migration of GE cells in humans and other species. It also raises a number of questions. For example, is the species difference in GE to DT migration due solely to changes in the positioning of the guidance cues, or to changes in cellular responsiveness in the GE cells? It will be interesting to see results from cross-species co-cultures of the GE with the DT and the ST, which may provide

a more definite answer to the question of whether changes in GE responsiveness are involved in the species differences in GE to DT migration. It will also be interesting to characterize the molecular identities of the repulsive and attractive guidance cues in the ST and the DT. Two secreted proteins, Slit and netrin, can repel rodent GE neurons[11,12]. Their patterns of expression remain to be characterized in monkey and human brains, as well as in relevant regions of the mouse thalamus. Because a guidance cue can act as both a repellent and an attractant[13], it is also possible that the same cues may function differently in the GE to DT pathway of different species.

One of the most interesting suggestions from the work of Rakic and colleagues is that new neuronal migration pathways may be involved in brain evolution. During the evolution of the mammalian brain, regions connected to each other anatomically and functionally are thought to co-evolve[14], but mechanisms for co-evolution are not known. Results from Rakic and colleagues suggest a novel and specific mechanism for co-evolution of brain structures. Thus, the GE to DT pathway may enable the co-evolution of the frontal cortex and the thalamic nuclei that are connected to it. There are perhaps multiple migration pathways from the GE to thalamic regions[15], and it will be interesting to know whether all of those pathways correlate with the evolution of the neocortex and the thalamus.

Evidence obtained so far indicates that the evolution of a new migratory pathway could, in principle, contribute to the presence of more neurons in the human thalamus. The significance of these pathways *in vivo* could be tested if these pathways could be experimentally manipulated in slices of mouse, monkey and human brains after the identification of distinct guidance cues. Perhaps studies of human patients with genetic defects disrupting a specific migratory pathway(s) may help answer the question of whether a migratory pathway leads to the evolution of a larger thalamus in humans.

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Virtual neurology

Robert Rafal

Using transcranial magnetic stimulation to induce a 'virtual lesion' in the parietal lobe, a new study reveals the mechanisms of hemispatial neglect, a neurological disorder of attention.

Patients with unilateral brain lesions, especially those involving the temporoparietal cortex, are often inattentive to objects and events contralateral to the lesion. This syndrome, known as hemispatial neglect, seems to involve a deficit in the orienting of attention rather than perceptual processing, as failure to detect contralesional stimuli is more likely when an ipsilesional object is competing for attention. This can be demonstrated by testing for a sign called visual extinction: the patient may be able to detect and report an object in the contralesional field when it is presented alone, but fails to do so when there is a competing item in the ipsilesional field that must also be 'reported'; that is, the object is extinguished from awareness by the competing stimulus.

One classic theory of neglect and extinction posits mutual inhibition between the hemispheres such that when systems for orienting attention in one hemisphere are damaged, homologous regions in the opposite hemisphere are disinhibited[1]. The presentation of a competing stimulus, which activates the disinhibited intact hemisphere, then further inhibits the lesioned hemisphere, causing extinction. A key feature of the hemispheric rivalry account is that it predicts better-than-normal performance in the field ipsilateral to the brain lesion.

In this issue, Hilgetag *et al.*[2] adapt the technique of repetitive transcranial magnetic stimulation (TMS) to temporarily inactivate parietal cortex in normal volunteers and produce a model of hemispatial neglect (**Fig. 1**), allowing them to test the hemispheric rivalry account of visual attention. Subjects were stimulated for 10 minutes with 1 Hz TMS at a point that was subsequently demonstrated, using structural MRI, to overlie the intraparietal sulcus. After TMS was terminated, the authors measured subjects' ability to detect visual stimuli presented in the field contralateral to TMS, in the ipsilateral field or simultaneously in both fields. Compared to before TMS, detection of contralateral stimuli presented alone was reduced, contralateral detection was further reduced by a competing ipsilateral stimulus (visual extinction), and detection of ipsilateral stimuli presented alone was facilitated—consistent with disinhibition of the unstimulated hemisphere as predicted by the hemispheric rivalry hypothesis.

Several previous observations are also consistent with the hemispheric rivalry account. In neurological neglect patients, not only is detection of contralesional stimuli impaired, but detection of ipsilesional stimuli is enhanced[3,4]. The rivalry account also predicts that a second lesion in the

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