NEUROLOGICAL DISORDERS

Convulsions at the fringes

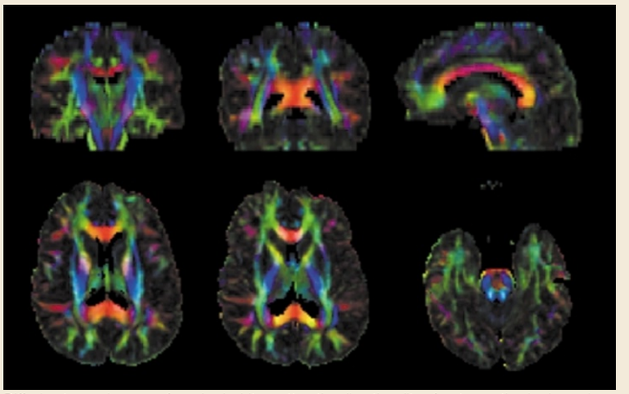
The high incidence of epilepsy in humans places this disorder among the most common neurological conditions. So, it's not surprising that many different causes underlie the onset of seizures. Epilepsy is sometimes related to developmental abnormalities or brain injury. Other forms of epilepsy have a more subtle genesis and can be traced to genetic defects. Mutations in single genes can lead to abnormal neuronal firing and the development of convulsions. So far, the culprits in every case of non-symptomatic monogenic epilepsy have been mutations in ion channel genes. Now, Skradski *et al.* report an exception to this rule: the identification of *Mass1* (monogenic audiogenic seizure susceptible 1), a gene that encodes a protein with no homology to any known ion channel, which, when mutated, leads to the appearance of audiogenic seizures in mice.

Skradski *et al.* studied a strain of mouse susceptible to audiogenic seizures that has been known for 50 years — the *Frings* mouse. The phenotype of *Frings* mice had been traced to a single gene on chromosome 13 — *Mass1* — and the authors used positional cloning techniques to identify and characterize this locus in detail. They found that *Mass1* encodes a protein predicted to have multiple transmembrane domains, but no significant similarity to any ion channel or to other proteins. Only two motifs from Mass1 shared homology with other molecules — a sequence present in several sodium/calcium exchangers and a multicopper oxidase consensus site. Although both motifs provide some clues as to the nature of Mass1, its actual function will require the biochemical analysis of the protein, a task that promises to be daunting, as the *Mass1* transcript seems to be expressed at very low levels.

The authors also analysed different strains of mice and identified several polymorphisms in *Mass1* that

AGING

Staying in touch



Diffusion tensor images of cerebral white matter; the directionality of water motion is shown in red (left/right), blue (dorsal/ventral) and green (anterior/posterior). Courtesy of Tom Barrick, MARIARC, University of Liverpool, UK.

A gradual decline in our cognitive abilities is one of the less welcome aspects of normal aging. Our 'executive skills' — high-level cognitive functions that allow us to perform complex goal-directed tasks — are often preferentially affected, but despite the fact that such age-related deficits in cognition are well documented, the underlying structural and functional brain changes remain largely unknown. By using the recently developed method of diffusion tensor magnetic resonance imaging, O'Sullivan *et al.* provide the first direct *in vivo* evidence that aging might be associated with the structural 'disconnection' of regions of the neocortex involved in cognitive processing.

In cerebral white matter, axonal membranes and myelin restrict the motion of water, such that it tends to move in the direction of fibre tracts. In diffusion tensor imaging, this directionality of movement can be quantified by fractional anisotropy (FA), which varies from zero (isotropic; equal diffusion in all directions) to 1 (unidirectional diffusion). A directionally averaged measure of diffusion — mean diffusivity — can also be obtained. If the integrity of a white matter tract is disrupted — for example, if the tract becomes demyelinated or less tightly packed — FA will decrease, whereas diffusivity will increase.

O'Sullivan *et al.* used these measures to examine the status of white matter in the brains of healthy volunteers. They showed that white matter FA declines with age, whereas mean diffusivity increases, consistent with an age-related deterioration of white matter tracts. When the sampled volume was divided into anterior, middle and posterior regions, they found that anterior white matter was disrupted most, whereas posterior areas were affected least; moreover, the integrity of anterior white matter seemed to decline more rapidly with age than that of more posterior regions. These data point to a selective disruption of frontal connections with advancing age, consistent with a progressive loss of executive skills, which are served by frontal cortical areas.

To test whether a disruption of cortical connections could account for a decline in cognitive ability, O'Sullivan *et al.* examined the relationship between measures of water diffusion and the scores of volunteers in tests of executive function and verbal fluency. They found that performance in an executive test correlated with mean diffusivity in anterior regions, whereas verbal fluency scores, which would be expected to depend on connections between temporal and frontal regions, correlated with the FA of

could account in principle for the epilepsy observed in the *Frings* mutants. However, they found a strong correlation between a deletion at the carboxy-terminal tail of the protein and the presence of audiogenic seizures, pointing to this mutation as the best candidate to explain the phenotype.

It will now be interesting to investigate the effect of mutations in the human orthologue of *Mass1*. Intriguingly, the human gene is located in the vicinity of two noteworthy loci: *FEB4*, which has been mapped in people with febrile convulsions, and *USH2C*, which has been mapped in patients with Usher syndrome 2C (a condition characterized by deafness and retinitis pigmentosa).

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Skradski, S. L. *et al.* A novel gene causing a mendelian audiogenic mouse epilepsy. *Neuron* **31**, 537–544 (2001)
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middle white matter. So, the structural findings in this study agree with what is known about the functional anatomy of executive and verbal tasks.

O'Sullivan *et al.* present compelling evidence that age-related cognitive decline, and executive dysfunction in particular, could involve the disconnection of components of neurocognitive networks. Diffusion tensor imaging provides a means of characterizing further the structural correlates of aging, a quest that could ultimately lead to a means of preserving our cortical connections, and the cognitive functions that they serve, into old age.

Rebecca Craven

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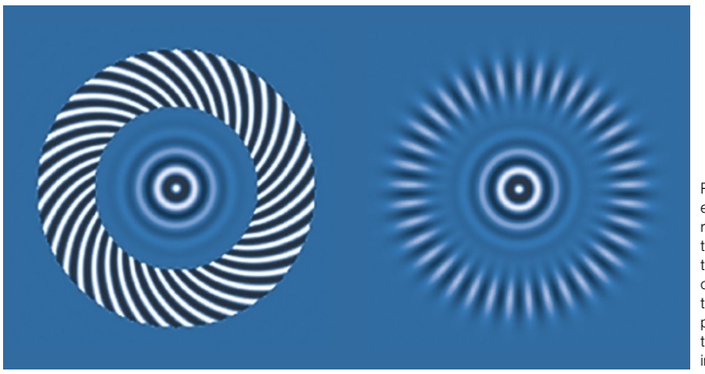

Readers capable of free fusion can experience the waves of binocular rivalry for themselves by fusing the two images above and fixating on the central spot. The spiral stimulus on the left and the radial stimulus on the right will each become perceptually dominant in turn, with the dominance typically progressing in waves around the circle.

PERCEPTION

On the crest of a wave

Under normal circumstances, our two eyes see the same visual scene. The inputs from both eyes are combined in the visual system to generate stable binocular single vision. Under experimental conditions, if the two eyes are presented with different images, one might expect to perceive a combination of the two. But in fact, people perceive only one or the other image, and their perception can switch unpredictably between the images. This phenomenon, known as binocular rivalry, raises many interesting questions about the nature of conscious perception.

Anecdotal reports of the subjective experience of binocular rivalry have described how, rather than one image being suddenly replaced by the other, the transition seems to sweep across the visual field in a wave. Wilson *et al.* have used specific stimuli to quantify this effect and to gain insight into the nature of binocular rivalry.

They used simple annular stimuli to study waves of binocular dominance. The stimuli that were presented to the two eyes were the same shape, but differed in contour orientation. In the example shown, one annulus contains a radial grating whereas the other contains a spiral pattern. When individuals view both stimuli, one with each eye, waves of dominance are seen to sweep around the annulus. You can see this for yourself if you can free-fuse the images shown above.

In the study, people were asked to indicate, by pressing a key, when the spiral stimulus was completely dominant. A brief change in contrast at one point in the radial stimulus would then trigger that stimulus to become dominant, and people would see waves of dominance travelling around the annulus in both directions from the starting point.

By releasing the key, people indicated when the dominance wave reached a target location, allowing the researchers to measure the speed of propagation of the waves. Dominance waves for the radial grating propagated around the circle at about 3.6 degrees per second. But when an annular stimulus containing a pattern of concentric circles was used instead of the radial grating, propagation was much faster, averaging 9.6 degrees per second. This increase in speed supports the idea that dominance waves show 'colinear facilitation' — preferential excitatory connections in visual cortex between cells with similar preferred orientations (colinear receptive fields mean that dominance waves can spread faster along a continuous contour than around the radial grating).

When the stimuli were made larger, propagation times increased, as expected if dominance waves were propagating across the retinotopic map in primary visual cortex. The authors calculated that the speed of propagation would correspond to a relatively constant average speed of around 2.24 cm per second across this cortical map. They also found that dominance waves that would have to cross the corpus callosum between the hemispheres travelled more slowly than those that remained within one hemisphere. Finally, Wilson *et al.* show that their results can be simulated by a simple two-layer neural model of cortical function.

These new results add weight to the theory that at least some of the neural operations involved in binocular rivalry occur early in the visual system, in an area of cortex that is topographically mapped. Many questions remain about the nature and site of rivalry, but work such as this is bringing us increasingly close to the answers. Similar studies might also give us more insight into cortical dynamics and excitability.

Rachel Jones

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WEB SITE
Blake's lab (including more examples of binocular rivalry waves) http://www.psy.vanderbilt.edu/faculty/blake/rivalry/BR.html