extracellular apoptotic signals — death ligands — on the cell surface and bind to them to trigger apoptosis[5,6]. The prototypical death receptors are Fas/CD95 and tumour-necrosis factor receptor 1 (TNFR1); once bound to their ligand, these receptors sequester components of the cell-death pathway — such as inactive precursors of the caspase enzymes — within the cytoplasm, thus activating them[7]. Each of the other known death receptors functions through subtle permutations of this process (different ligands, adapters and points of entry into the caspase cascade). In this regard, little information exists for DR6, which has thus been considered 'orphan'.

Nikolaev *et al.*[4] show that, on withdrawal of NGF from their cultured neurons, N-APP activates DR6, which then triggers activation of caspase-3 in neuronal cell bodies. In the axons, however, caspase-6 — something of an orphan enzyme itself — is the primary responder to N-APP engagement of DR6.

The enigmatic caspase-6 is often classified as an effector caspase because it cleaves the nuclear lamin proteins during apoptosis. Nonetheless, its substrate preferences indicate that — similarly to caspases-8, -9 and -10 — it probably functions early in the apoptotic pathway, before 'death' signals reach the nucleus.

Strikingly, caspase-6 can itself liberate N-APP by cleaving APP in almost the same spot as the β-secretase[8] (Fig. 1). So, although Nikolaev *et al.*[4] provide evidence that β-secretase is the initial perpetrator of N-APP release from the cell surface, it is possible that the newly activated caspase-6 feeds back to liberate more N-APP, thus either amplifying the apoptotic process or spreading it to neighbouring cells. Such potential secondary effects are hard to ignore, particularly because they might be relevant to Alzheimer's disease.

But disease-associated effects of caspase-6 are not limited to Alzheimer's disease: this bad-boy caspase contributes to at least one other neurodegenerative disorder, Huntington's disease[9]. Whereas Alzheimer's disease affects neurons and synaptic junctions of the cerebral cortex, Huntington's disease is characterized by progressive and inexorable deterioration of neurons that project to the striatum region of the brain. Caspase-6-mediated breakdown of huntingtin, the protein that is mutated in Huntington's disease, is necessary for neuronal dysfunction and degeneration in this disorder. Whether the circuitry involved in APP cleavage, DR6 triggering and caspase activation have broad, overlapping mechanistic commonalities in the development of the nervous system, response to injury and disease-associated neurodegeneration is not known. But the links are intriguing and warrant further attention.

The molecular events that Nikolaev and colleagues describe might seem linear and binary (with loss of NGF resulting in APP cleavage to generate N-APP that binds to DR6 and activates caspases). But the reality is probably that there is a dynamic equilibrium, and that subtle perturbations to that fine balance can evoke either necessary responses, including culling of neurons or pruning of their axons, or inappropriate ones, such as neurodegeneration. APP, for example, is continually generated and processed, forming a fluctuating pool of amyloid-β peptides and N-APP. Not all amyloid-β peptides form plaques, nor does N-APP always kill neurons. But as we come to understand the pathways and interrelationships within these sophisticated systems better, so will we come to understand what goes wrong and why. ■

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1. Thinakaran, G. & Koo, E. H. *J. Biol. Chem.* **283,** 29615–29619 (2008).
2. Mattson, M. P. *Nature* **430,** 631–639 (2004).
3. Walsh, D. M. & Selkoe, D. J. *J. Neurochem.* **101,** 1172–1184 (2007).
4. Nikolaev, A., McLaughlin, T., O'Leary, D. D. M. & Tessier-Lavigne, M. *Nature* **457,** 981–989 (2009).
5. Pan, G. *et al. FEBS Lett.* **431,** 351–356 (1998).
6. Ashkenazi, A. & Dixit, V. M. *Curr. Opin. Cell Biol.* **11,** 255–260 (1999).
7. Kumar, S. *Cell Death Differ.* **14,** 32–43 (2007).
8. Gervais, F. G. *et al. Cell* **97,** 395–406 (1999).
9. Graham, R. K. *et al. Cell* **125,** 1179–1191 (2006).

MEDICAL IMAGING

MRI rides the wave

Paul Glover and Richard Bowtell

An innovative approach for exciting and detecting signals in magnetic resonance imaging not only improves image quality but also enables radical changes in scanner design by freeing up space around the patient.

Magnetic fields varying at radio frequency (RF) are fundamental to nuclear magnetic resonance (NMR) and the related technique of magnetic resonance imaging (MRI). In NMR, RF fields are used in conjunction with a strong, constant magnetic field to excite hydrogen nuclei in water into precession. The precessing nuclei in turn generate an RF magnetic-field oscillation — the NMR signal. In almost all MRI experiments, the RF field is generated by a coil of wire — the RF coil[1] — and the nuclear precession is detected by electromagnetic induction in a similar coil. But excitation and detection of the NMR signal require that the RF coils lie in close proximity to the human body because it is the short-range signals (the near fields) that are exploited in the interaction.

In a radical rethink of the experimental set-up used for MRI, Brunner *et al.*[2] (page 994 of this issue) now show that this conventional approach based on RF coils can be replaced by one that uses travelling radio waves in a long-range interaction with the sample, offering more-uniform coverage of larger samples. What's more, by freeing up space in the bore of the scanner, this innovative approach could make the scanning experience more comfortable for human patients.

In a scanner with magnetic-field strength of 1.5 tesla (T) — the workhorse of clinical MRI — the RF required to excite the NMR signal is 64 megahertz (MHz), which corresponds to a free-space wavelength of 4.7 metres. This wavelength is reduced to about 70 centimetres in the human body as a result of the electrical properties (the permittivity and conductivity) of tissue. The near-field approach works well for this frequency regime because it readily produces a spatially uniform RF magnetic field inside the body. This means that the signal excitation is homogeneous and, consequently, that magnetic resonance images show a uniform sensitivity to structure and pathology in different anatomical regions.

Magnetic resonance scanners operating at magnetic-field strengths higher than 1.5 T are increasingly being used because they provide higher sensitivity and spatial resolution, with 3 T (128 MHz) scanners becoming commonplace and scanners operating at 7 T (300 MHz) and above appearing in research environments. But at these operating fields the wavelength of the RF field is reduced and can become smaller than the structures of both the RF coil and the human body. As a result, standing waves formed by the RF coil give rise to significant spatial inhomogeneity of the RF amplitude, which degrades image quality at 3 T and can produce areas of total signal loss in images acquired at 7 T. Brunner *et al.*[2] show that these problems can be overcome by replacing the RF coils with a waveguide and a remote antenna. The new approach uses travelling waves for NMR signal excitation and detection, and its advantages result from the intrinsically lower spatial variation of RF amplitude in a propagating rather than standing wave pattern.

In their proof-of-principle experiments, Brunner *et al.* inserted a cylindrical waveguide into a 7 T human scanner and positioned an antenna at one of its ends (Fig. 1c on page 994). The waveguide diameter was just large enough to sustain a spatially uniform RF magnetic field at 300 MHz. A human patient sited inside the waveguide could thus be exposed to a homogeneous far-field wave pattern originating from the antenna. The same antenna was

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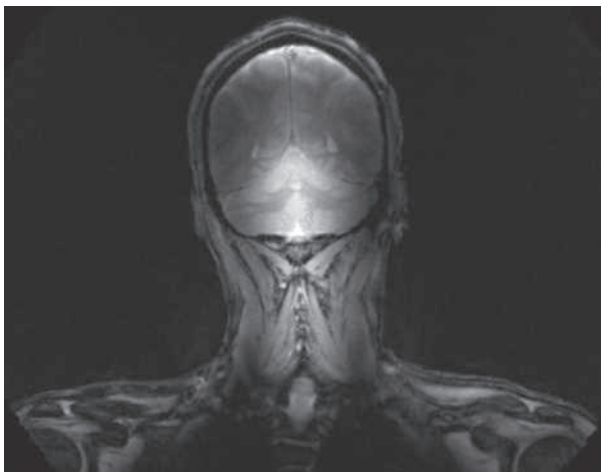

D. BRUNNER & K. PRUESSMANN

Figure 1 | Travelling-wave MRI. Magnetic resonance image of the head and shoulders of a human volunteer obtained by Brunner *et al.*[2] using their travelling-wave MRI technique at a magnetic-field strength of 7 tesla. It demonstrates an impressive extent of coverage for an image obtained at such a high field: most conventional 7-tesla scanners are used for imaging only the brain, but this image shows detailed structure in the brain stem, neck and shoulders.

used to pick up the RF signal generated by nuclei in the body. Brunner and colleagues used this arrangement to record spectra and images from large test samples and the lower leg of a human volunteer. Figure 1 shows an additional image of the head and shoulders. Comparison with images obtained using a conventional RF coil shows that the travelling-wave approach can produce a uniform excitation over a much larger volume (Fig. 4 on page 996).

Until now, methods for moderating the effect of RF inhomogeneity at high magnetic-field strengths have generally focused on using multiple RF coils in parallel[3] for signal excitation. Although this approach shows promise, it is complex and expensive because it requires duplication of costly RF amplifiers and other circuitry. The beauty of Brunner and colleagues' travelling-wave approach, in comparison, lies in its simple implementation and inherently lower cost. In addition, the authors' approach has the advantage of being immediately compatible with all standard MRI techniques.

Although the main motivation of Brunner and colleagues' work is to reduce RF inhomogeneity, their approach has the additional, significant advantage of freeing up space inside the bore of the scanner because it does not require close-fitting RF coils. This extra space is extremely valuable because the cost of the large, superconducting magnets needed for MRI increases rapidly with size. Removal of the RF coil thus opens up the possibility of redesigning the scanner's interior to make it more comfortable for patients and/or to reduce cost.

To reap the benefits of the travelling-wave approach, it is important to minimize the reflection and refraction of radio waves that can occur at boundaries between regions of different wave impedance, such as tissue and air. Brunner *et al.* demonstrate the problems that arise from these effects, but also introduce potential solutions, including the use of wave-impedance matching and absorbers. These involve positioning materials with appropriate electrical properties in the bore of the scanner near to the subject.

The use of waveguides comes with a limitation. These structures can only guide signals whose frequencies are above a certain value, the cut-off frequency, which depends on the diameter of the waveguide (the larger the diameter, the lower the cut-off). This places a lower limit on the size of waveguide that can be used for implementation of the travelling-wave approach. At 7 T, there is a fortuitous conjunction of the required NMR frequency and the frequency cut-off of a waveguide that easily accommodates the human body. Extension of the travelling-wave approach to more commonly available lower-field scanners will require the development of loading arrangements that can reduce the cut-off frequency to encompass lower NMR frequencies.

One potential disadvantage of using the travelling-wave approach for signal detection is that of increased noise pick-up compared with the conventional approach, because the antenna is sensitive to resistive noise sources, such as tissue, or wave absorbers, positioned anywhere in the far field. The high premium placed on the signal-to-noise ratio in MRI means that the optimal technique may involve using the travelling-wave approach for signal excitation and multiple conventional coils for signal detection[4].

Although Brunner and colleagues' work represents a unique application of the travelling-wave approach to NMR, there are strong analogies with methods used in electron spin resonance and optics. Transfer of ideas that have already been developed for these more mature areas of application should shape future exploitation of the travelling-wave approach in NMR and MRI, and ensure that its full benefits can be realized. ■

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1. Hayes, C. E., Edelstein, W. A., Schenck, J. F., Mueller, O. M. & Eash, M. *J. Magn. Reson.* **63,** 622–628 (1985).
2. Brunner, D. O., De Zanche, N., Fröhlich, J., Paska, J. & Pruessmann, K. P. *Nature* **457,** 994–998 (2009).
3. Katscher, U., Börnert, P., Leussler, C. & van den Brink, J. S. *Magn. Reson. Med.* **49,** 144–150 (2003).
4. Pruessmann, K. P., Weiger, M., Scheidegger, M. B. & Boesinger, P. *Magn. Reson. Med.* **42,** 952–962 (1999).

50 & 100 YEARS AGO

50 YEARS AGO

A brief review of the history of the calendar by Y. G. Perel suggests the urgent desirability of establishing a world calendar, such as was proposed by India in 1953 before the United Nations. According to this proposal, the year will be divided into four quarters of thirteen weeks each, with the first month of thirty-one days and the following two of thirty days each. An additional day (the day of peace and friendship) is added after December 30, and on leap years an additional day after June 30.

From *Nature* 21 February 1959.

100 YEARS AGO

In this day of encyclopaedias numerous and ponderous, one is often struck with the fact that in spite of the manifest care and conscientious thought bestowed by the responsible editors, the omissions and evidences of discontinuity of treatment, and lack of recognition of the prime purposes of the compilation, are as noteworthy as the imposing array of the results of our steadily advancing knowledge is startling ... As an illustration, take the word "research," or any of the associated terms — "discovery," "experiment," "investigation," and "observation." Turning to the index volumes of the ninth and tenth editions of the "Encyclopaedia Britannica," I find but two references in which the word "research" appears — one to the exploring vessel, the *Research*, and the other to "research degrees."

ALSO:

The *Petit Journal* recently asked its readers to select by their votes twelve great Frenchmen worthy of being included in the Pantheon. Pasteur's name appeared at the top of the poll with 315,203 votes, and was followed by that of Gambetta with 279,443 votes. We wonder whether a man of science would head the list if a similar plebiscite were taken by a popular daily paper in this country.

From *Nature* 18 February 1909.