Advanced magnetic resonance imaging of the brain

MRI is now the method of choice for neuro- and spinal imaging.

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Ernesta Meintjes has been involved in various studies involving neuroimaging of children with fetal alcohol spectrum disorder. Through collaboration with Massachusetts General Hospital, she and her team have developed navigated MR sequences that implement real-time motion correction and, for spectroscopy, shim correction. These methods are currently being employed to study the effects of different ARV treatment arms on brain development in children with HIV. They have also developed a control system to update the slice position in real time during free breathing cardiac MRI.

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Since the development of magnetic resonance imaging by Paul Lauterbur and Peter Mansfield using a back projection technique in 1973, MRI technology has improved at an unparalleled rate and, due to its exquisite soft-tissue contrast, has become the method of choice for neuro- and spinal imaging. Today a three-dimensional image of the entire brain can be acquired at a 1x1x1 mm^3 spatial resolution in just 5 minutes. The true power of MRI, however, lies in its flexibility and the fact that the contrast of images can be manipulated by changing machine parameters in a way that exploits the different magnetic properties of different tissues. Another advantage of MRI over other modalities is the fact that there is no ionising radiation. This makes MRI uniquely suited to research applications where subjects require repeated imaging and to the study of children.

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This paper aims to present an overview of two advanced neuroimaging methods: functional MRI (fMRI) and diffusion tensor imaging (DTI). These techniques are increasingly used in routine clinical practice and each provides specific information that is not available using standard imaging methods.

Functional MRI (fMRI)

Functional brain imaging refers to the family of techniques that aim to measure the physiological changes that accompany brain activity. These techniques are not concerned with the behaviours of single neurons, but with the activities of large populations of neurons and rely on the fact that single neurons do not work independently but function in large aggregates, so that, despite the small size of neurons, useful information concerning brain function can still be obtained using methods that have an in-plane spatial resolution of 3 mm or greater. These methods measure dynamic brain changes that have a time course similar to brain sensory, motor or cognitive activities, and include methods such as electroencephalography (EEG), positron emission tomography (PET), fMRI, and near-infrared spectroscopy (NIRS).

Electrophysiological methods, such as EEG and magneto encephalography (MEG), are based on the direct mapping of transient brain electrical (or the associated magnetic) dipoles generated by neuronal depolarisation and as such define the underlying cortical neuronal events in real time. As a result, these methods have high temporal resolution of the order of 10 - 100 ms, but provide relatively poor spatial resolution (many mms to cms).

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In contrast, fMRI and PET provide information on the changes in blood flow that accompany neuronal activation with relatively high spatial resolution (1 - 10 mm), but with a temporal resolution limited by the rate of the much slower haemodynamic changes that accompany neuronal depolarisation.

Optical imaging methods (NIRS) also measure changes in cortical blood flow, but have poorer spatial resolution due to light scattering by the skull, unless the cortical surface is exposed. Optical imaging methods are also limited to the cortical surface, whereas PET and fMRI methods allow mapping of neuronal activation deep in the brain.

Principles of fMRI

The contrast in fMRI is a consequence of the higher ratio of *oxy- to deoxyhaemoglobin* that accompanies neuronal activation in local draining venules and veins and is known as the blood oxygenation level dependent (BOLD) signal. Oxyhaemoglobin is diamagnetic, while deoxyhaemoglobin is paramagnetic; these different magnetic properties give rise to contrast in magnetic resonance images. Coupling of the haemodynamic changes to neuronal activation is still poorly understood due to an incomplete appreciation for the mechanisms responsible for regulation of local cerebral blood flow. It is generally assumed that increased neuronal activity leads to an increase in energy metabolism and oxygen consumption, which triggers an increased flow of oxyhaemoglobin to active sites.

In its simplest form, fMRI requires rapid repeated scanning of the brain while a subject performs a task of some kind. In clinical scanners, one can typically acquire 20 - 34 slices every 2 seconds.

Since fMRI measures a change in MRI signal, the task requires alternating activation and 'rest' states. 'Rest' states should be as similar as possible to the active states, to exclude cognitive processes not related to the task/domain under investigation. Furthermore, since the BOLD signal change is of the order of about 1%, each state should be repeated a number of times to improve the power of the experiment. The two most common task designs are block - and slow event-related designs.

Block design tasks consist of alternating periods of activation and 'rest'. This design assumes that the MRI signal will reach a steady state if a subject performs a task continually for a period of time. Block durations are typically of the order of 20 - 40 seconds, and are repeated as often as possible without making a single run too long. Since subjects have to remain absolutely motionless during a run, 5 - 8 minutes are recommended. It is generally better to repeat a shorter task more often than to make a task too long.

Event-related designs measure the change in MRI signal following a brief presentation of a stimulus. In order to allow time for recovery of the MRI signal following a stimulus, inter-stimulus intervals are typically of the order of 12 seconds. Jittered and rapid event-related designs have become more popular as they improve the specificity of the signal.

Fig. 1 shows a simple block design finger tapping task, where subjects are instructed to either tap the fingers of their left hand against their left thumb, the fingers of their right hand against their right thumb, or rest. The duration of each block is 20 seconds and each block is repeated 5 times. Fig. 2 shows a volume comprising 34 slices acquired at 1 time point. Such a volume is acquired every 2 seconds throughout the 5 minutes of the experiment, resulting in a total of 150 volumes. Another interpretation is that, for every voxel in the brain, the MRI signal is measured at 150 time points over the duration of the task, resulting in a time course plot for every voxel in the brain (Fig. 3).

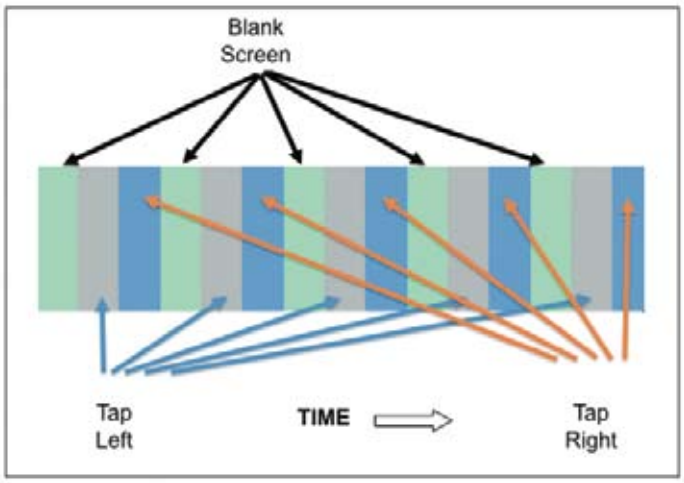

Fig. 1. Schematic showing the timing and design of a simple block design finger tapping task with alternating periods of rest, left hand finger tapping, and right hand finger tapping. Each block is 20 seconds and is repeated 5 times, total task duration 5 minutes.

The analysis of the fMRI data involves finding voxels where the MRI signal correlates with the task. This is generally done using a general linear model approach. Fig. 4 shows a brain activation map where

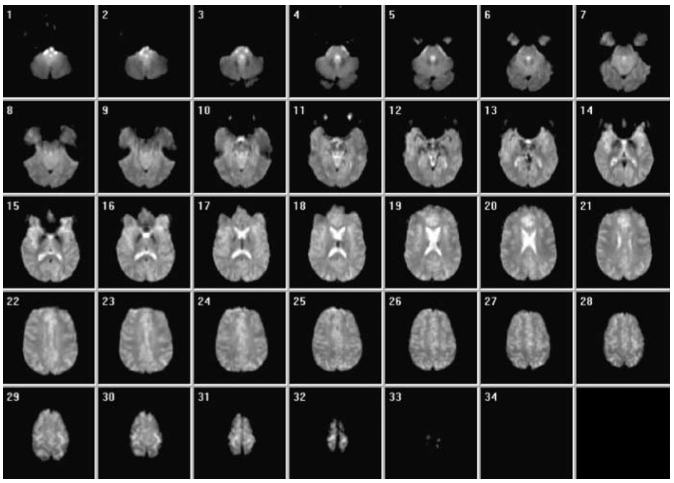

Fig. 2. Image volume comprising 34 slices acquired at a single time point.

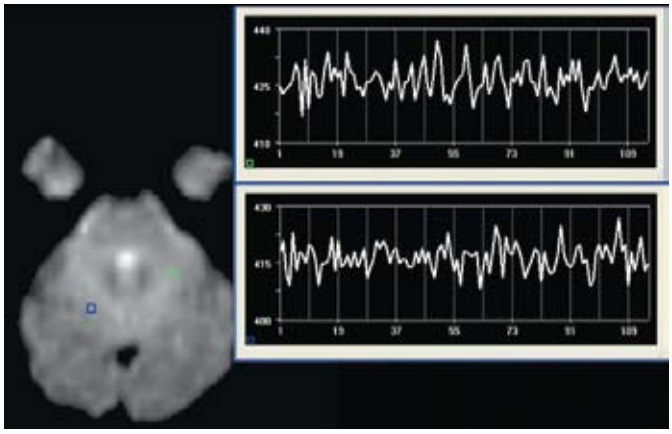

Fig. 3. Plots showing how the MRI signal changes during the fMRI scan for two voxels in a single slice. This is termed the time course data. Time course data throughout the duration of the fMRI task are available for every voxel in the brain.

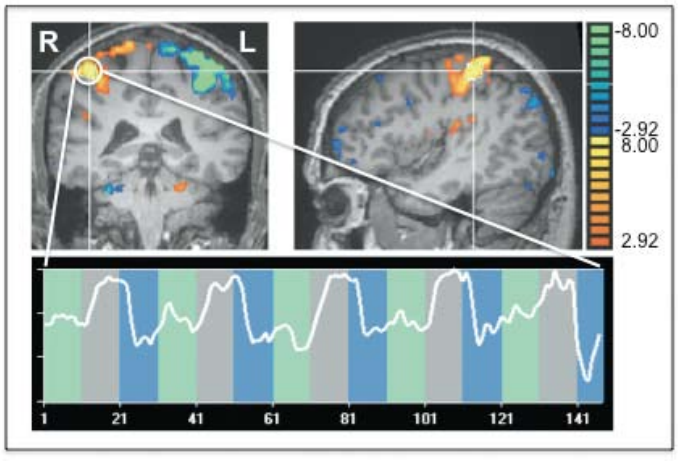

Fig. 4. BOLD activation map showing greater activity in right motor cortex and less in left motor cortex during left finger tapping compared with right finger tapping. The average time course of the MRI signal is shown for the selected voxels in the right motor cortex.

orange regions have greater activity during left hand finger tapping compared to right hand finger tapping, and vice versa for blue regions. The time course plot shows the average MRI signal for the selected voxels and clearly demonstrates increased signal during periods of left hand finger tapping.

Diffusion tensor imaging (DTI)

DTI is an extension of the widely used diffusion weighted imaging (DWI) technique and allows for the visualisation and characterisation of white matter tracts of the brain *in vivo*.[3] Essentially, DWI uses the application of a diffusion gradient to make the MRI signal sensitive to the amount of diffusion that occurs parallel to the direction of the diffusion gradient. DWI is routinely used in stroke imaging, but is also increasingly used in the investigation of other brain diseases, such as multiple sclerosis, trauma, brain tumours, and hypertensive encephalopathy.[1]

Principles of DTI

DTI exploits the fact that diffusion is anisotropic (greater in one direction than in other directions) in white matter axons, while it is isotropic (equal in all directions) in cerebrospinal fluid (CSF) and grey matter. By repeating DWI with the diffusion gradient applied in 6 or more different directions, the diffusion tensor, a measure that captures the combined diffusivity in the different directions, can be computed at each voxel.

Two commonly reported measures of diffusion are the mean diffusivity and anisotropy. The mean diffusivity (MD) is a measure of the magnitude of diffusion. Fractional anisotropy (FA) indicates how directional the diffusion is in a particular voxel. Low FA indicates that diffusion is isotropic. In contrast, high FA indicates highly directional diffusion, such as is found in white matter tracts. The principal diffusion direction can be colour-coded, resulting in colour-coded maps or directionally encoded FA maps (Fig. 5).

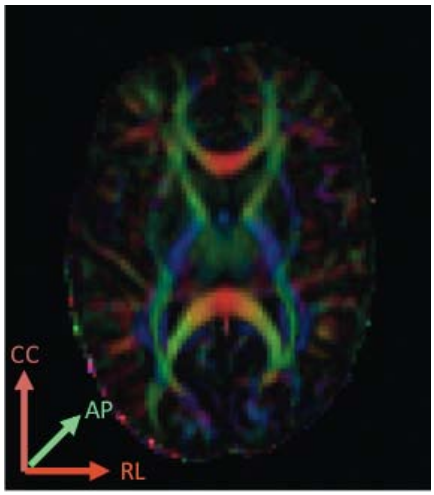

Fig. 5. Principal diffusion directions are displayed on a colour-coded FA map.

Fibre tract reconstruction, or tractography, creates continuous 3-dimensional tracts by sequentially piecing together estimates of fibre orientation from the direction of diffusion within individual volume units (Fig. 6).

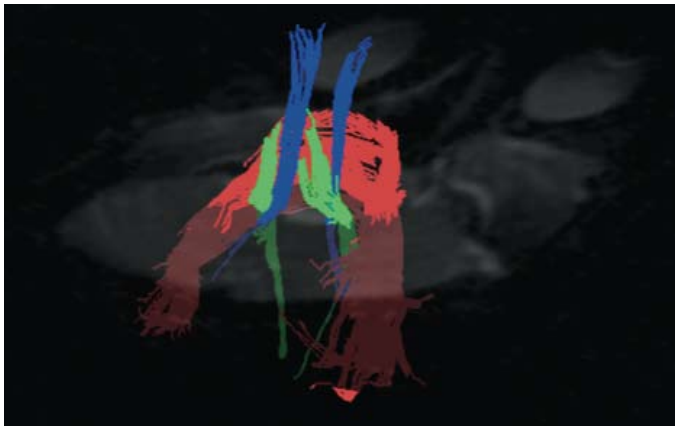

Fig. 6. Tractography of the cerebellar peduncles (red = middle peduncle; green = inferior peduncle; blue = superior peduncle).

Alone DTI is, however, fairly nonspecific. For example, demyelination might cause the radial diffusivity (perpendicular to tracts) to increase with minimal influence on the axial diffusivity (parallel to tracts). Increased tissue water in oedema will increase the MD, whereas cell proliferation in neoplasia may decrease the MD. Conversely, in complex diseases like multiple sclerosis (MS), brain regions may experience an unpredictable combination of demyelination, axon loss, gliosis, and inflammation, which could result in competing influences on the diffusion tensor.[2]

Conclusion

During the past decade, both fMRI and DTI have made a transition from being purely research imaging techniques to being viable clinical tools.[4-6] fMRI is primarily used for presurgical planning in patients with brain tumours and other resectable brain lesions. It is also increasingly used in paediatric neurology for understanding not only normal development in healthy children, but abnormal development, as seen in children with epilepsy, attention-deficit/hyperactivity disorder, and autism.[7]

The largest clinical application of DWI is the diagnosis and characterisation of acute ischaemic lesions in the CNS. FA appears to increase in acute lesions and decrease below baseline levels in the chronic phase. Another large clinical application of DTI is in the characterisation of white matter in patients with brain tumours. Much of this work focuses on using DTI maps and tractography, in combination with fMRI, to help localise WM fibre tracts that are important for critical functions such as motion, language and vision in pre-surgical planning to minimise injury to these critical tracts during surgery.

In addition to studies of neuroanatomy, fibre connectivity, and brain development, DTI has also gained popularity for the investigation of brain pathologies, such as cerebral ischaemia, trauma, MS, presumed AD and cognitive impairment, epilepsy, brain tumours and metabolic disorders.

References available at www.cmej.org.za

In a nutshell

- Functional MRI (fMRI) measures the changes in blood flow that accompany brain activity.
- The blood oxygenation level dependent (BOLD) signal arises from the higher ratio of oxy- to deoxyhaemoglobin that accompanies neuronal activation.
- FMRI rapidly acquires low-resolution images of the entire brain roughly every 2 seconds while a subject performs a task.
- Tasks can be either block design or event-related design with durations of the order of 5 - 8 minutes.
- Diffusion tensor imaging (DTI) allows for the visualisation and characterisation of white matter tracts of the brain.
- DTI utilises the fact that diffusion is anisotropic in white matter axons, while it is isotropic in cerebrospinal fluid (CSF) and grey matter.
- Mean diffusivity (MD) is a measure of the magnitude of diffusion.
- Fractional anisotropy (FA) indicates the degree/extent to which the diffusion is anisotropic, i.e. directional.
- Radial diffusivity (perpendicular to tracts) appears to be modulated by myelin in white matter, whereas axial diffusivity (parallel to tracts) is more specific to axonal degeneration.