You've stared the dazzling brain images on PowerPoints, papers, and websites. But what do these pictures mean? What do they represent? And what's the connection between the giant donut magnet and the images you see?

The goal of this review is to conceptually overview how neuroimaging—specifically magnetic resonance imaging—works and what it sets out to accomplish.

**THE PROTON WHISPERER**

You are an intricately organized pile of protons. Protons are everywhere in your body: carbohydrates, lipids, proteins, membranes and, of course, water. Like all matter, protons are constantly in motion—spinning and vibrating around their bonds at a particular speed, known as a Larmor frequency.

While the proton cycles around its bond, it emits a tiny electromagnetic signal, like an individual proton's voice. This simple observation led to one of the most important developments of the 20th century: magnetic resonance imaging, or MRI.

Unfortunately, no one has developed a recording device sensitive enough to catch an individual proton's voice. The best we can do is listen to millions of protons simultaneously, which sounds like a bunch of noise because each proton is whispering at a slightly different cycle.

The genius of MRI—what won Paul Lauterbur (1) and Peter Mansfield the 2003 Nobel Prize—is to eke out a useful signal from the mess of protons in your body. By finding a clever way to make the protons spin faster and in synchrony, the protons give off a large enough radio signal to be detected.

A thought experiment can help explain how this works: imagine Yankee Stadium, just before the Yankees play the Texas Rangers. You’re standing on the pitcher’s mound with a huge megaphone, and tell everyone in the stadium to start repeating “Neuroimaging rocks.” All of a sudden, all 50,000 fans begin—at slightly different times—whispering the phrase.

The buzz of the crowd is impressive but, try as you will, you can’t make out what everyone is saying and you certainly can’t make out any one individual’s voice.

Then you have an idea, you call everyone quiet and, with your arms held high, tell everyone that when you drop your arms, they should whisper “Neuroimaging rocks” just once.

At the drop of your arms, the chorus “Neuroimaging rocks” crashes through the stadium.

Then you notice something else: sections of the bleachers with more people are a bit louder than those with less people. You also notice something else a bit funny: sections full of fast-talking Yankee fans finish saying “Neuroimaging rocks” before sections with the Rangers fans, who in no hurry drawl out “Neuroimaging rocks.” So you realize that just by careful listening, you can figure out how many and which type of fans are seated where!

By analogy, this is the foundation for MRI.

With each proton spinning on their own cycle, it’s impossible to tell what the protons are “saying” as a group. But, inside a strong enough magnet—one 60,000 times the magnetic field of the earth—the protons speed up and begin to align their spin, as if they are starting their sentences all at the same time.

But they’re not spinning at precisely the same time so, similar to your dropping your arms at Yankee stadium, you zap all the protons with a one radiofrequency pulse, and, in response, they give off a synchronized burst of energy.

Whamo—this signal is strong enough for you to detect!

Because there are more protons in some tissue than in others, the signal is a bit stronger by comparison. And because different protons are bound to different molecules, the protons give off their burst of energy faster or slower depending on how strongly they are bound.

By dividing the brain into small cubes (called a voxel, or volume-pixel), you create useful divisions of protons, similar to sections of the bleachers.

Voxels have an extremely useful property: just like louder bleacher sections must have more fans, voxels with a stronger signal must have more protons. So you end up with a measure of protons per volume, or a measure of proton density.

And, just like different fans finish saying “Neuroimaging rocks” at different speeds, protons in different tissues give off their burst of energy faster or slower than others. This difference in speed allows you to tell what tissue is present in a particular voxel based on how quickly you detect their energy.

**STRUCTURAL MRI**

Structural MRI uses the MRI magnet and a radiofrequency pulse to get the protons to give up information about how many there are and what type of molecule they’re attached
to. By gathering this information for each voxel in the brain, you can create a 3-dimensional image that shows the brain's main tissue types.

All structural MRI analyses of the brain are simply various ways of counting how many voxels are white matter, gray matter, or cerebrospinal fluid. Such analyses can determine things like the volume of a brain structure, the thickness or curvature of the cerebral cortex, even the tissue density of a particular region.

Application of these methods can be used to ask useful questions like: how does the size of the amygdala differ in people who are depressed? You could perform such an analysis by counting how many voxels are in the amygdala in patients and controls.

Another question could be whether brain anatomy changes as a result of schizophrenia. You could scan the brains of people with schizophrenia at the onset of their symptoms and then again a few years later and compare the scans.

In 2003, Ho et al (2) performed just such a longitudinal study. They obtained high-resolution structural MRI scans of 73 patients with schizophrenia and 23 controls. By comparing how the brain changes over time in patients compared to controls, Ho reported that patients with schizophrenia were more likely to have enlarged ventricles and decreased frontal lobe white matter and grey matter volume. They further correlated these changes in patients to specific functional impairments.

Ho et al. (2003) was one of the first reports to show that despite treatment with antipsychotic drugs, schizophrenia was a progressive disease with anatomical abnormalities confined to specific brain regions, providing a physical basis for behavioral symptoms.

FUNCTIONAL MRI

In combination with studies of brain structure, we can also study where and how much the brain is working by measuring the blood oxygen-level dependent (BOLD) signal.

Using our analogy of fans in Yankee stadium, imagine that in some sections of the stadium, there are groups of fans that will switch sides depending on the score: if the Yankees are winning, they will act like fast-talking New Yorkers; if the Rangers are winning, expect a southern drawl.

If you go down to the pitcher’s mound at the end of each inning, raise your hands, and record how quickly each bleacher section says “Neuroimaging rocks!”, you could use this to figure out how each team is performing. If the Yankees are winning, you would expect sections that once sounded like Rangers fans to sound like fast-talking Yankees; vice versa if the Rangers pull it off (which doesn’t often happen).

Blood oxygen-level dependent (BOLD) MRI is based on the observation that deoxyhemoglobin is magnetic while oxyhemoglobin is not. Like the fans in Yankee stadium, you can tell where and how much oxyhemoglobin loses an oxygen and becomes deoxyhemoglobin (or “switches sides” in the analogy) based on the effect magnetic deoxyhemoglobin has on neighboring protons. The signal difference can be detected by MRI and is computed as the ration of oxy- to deoxyhemoglobin.

Clever scientists manipulate this ratio and use it to map where particular cognitive functions occur in the brain. They begin with a task condition, which changes the metabolic demands of the brain in a predictable way. This task is often an activity, like the Wisconsin Card Sorting Task, wherein a participant has to learn how to match a series of cards with shapes on them. Because this task increases the metabolic demands of specific brain areas, you can determine where these areas are located by detecting where the ratio of oxy to deoxy-hemoglobin changes during the task as contrasted to a rest condition. This is known as a functional BOLD contrast. (3)

BOLD functional MRI has helped us understand emotional function in patients with schizophrenia. One highly-cited study was performed by Gur et al. (4) at the University of Pennsylvania.

Impaired emotional functioning had long been considered a fundamental aspect of schizophrenia. Studies of animal and human emotion networks had been performed for decades, implicating limbic networks including the amygdala and hypothalamus and cortical networks including the orbitofrontal, dorsolateral prefrontal and temporal cortex. But within these wider networks, people were still unsure whether and which specific components were affected in schizophrenia.

To study the brains of patients with schizophrenia, the group asked participants to view faces that were happy, sad, angry, fearful, or disgusted and decide whether the face had a positive or negative emotion. Gur, et al. hypothesized that because schizophrenia is related to impaired emotion processing, patients with schizophrenia would show less brain activity in regions that subserve emotional processing.

Patients with schizophrenia showed reduced brain activity in the left amygdala and bilateral hippocampus during the face task. By limiting the regions of abnormal change to the amygdala and hippocampus, subsequent studies focused on these areas have further teased apart why these regions dysfunction.
REFERENCES


ADDITIONAL READING


'Physiology-minded readers might like to know that there is another layer to the oxy-deoxyhemoglobin ratio. The brain responds to local brain activity in two ways: 1) oxyhemoglobin “switches sides” to deoxyhemoglobin as oxygen leaves the blood to fuel the metabolic demand of nearby cells; and 2) local blood vessels dilate in response to the brain’s oxygen need, bringing relatively more oxyhemoglobin to protect against an oxygen deficit until the oxygen demand of the cells are met. So while brain activity converts oxy- to deoxyhemoglobin, because blood vessels simultaneously dilate, the overall ratio actually shifts towards oxyhemoglobin. This shift in the oxy- to deoxyhemoglobin ratio is the foundation for BOLD functional MRI.

In terms of the analogy, imagine that while you’re tracking the game, you notice something odd: whenever the Rangers momentarily pull ahead, sections where Yankee and Ranger fans are switching sides seem to get a bit louder. You’re kind of puzzled by this and, after some looking around, discover that whenever the Rangers look to have an edge, the owner of Yankee stadium busses in more Yankee fans, hoping the additional fans will sway the game! This is comparable to the way blood vessels dilate and “bus in” more oxyhemoglobin, thus shifting the oxy- to deoxyhemoglobin ratio towards oxyhemoglobin.