Functional Magnetic Resonance: Constructing the Data?

OLGA CHELNOKOVA
University of Oslo

Although fMRI imaging is a powerful technique for studying brain functioning, it presents certain challenges for the researchers at different stages starting from image acquisition and up to statistical analysis of the data. FMRI images are not photographic pictures of brain structures. Rather, they are representations of the spatial distribution of and temporal changes in some physical characteristics of the scanned tissue, which in turn are considered to correlate with brain function. Many parameters for obtaining an fMRI image, such as the contrast, pulse sequence, slice timing, region of interest, threshold, and others, are chosen and set by the researchers according to what they are looking for and interested in. Thus, the information about the studied brain function that is obtained with the use of fMRI technique can be viewed as constructed data. Taking this notion into account is important for understanding the quality, meaning, and significance of fMRI results.

"Verum esse ipsum factum." (Giambattista Vico)
"The true is precisely what is made."

Functional magnetic resonance is an established method within cognitive neuroscience and psychology. In the last 10-15 years, the number of fMRI studies published in scientific journals has grown exponentially. The knowledge obtained in those studies has greatly impacted our understanding of the human brain and nervous system. According to the perspective of constructivist epistemology, the scientific knowledge, like any other kind of knowledge, is constructed and not discovered from the world in its pure form (Von Glaserfeld, 1995). According to constructivist epistemology, the only kind of reality that is accessible to humans is the reality represented by human thought. Thus, any kind of knowledge that humans poses cannot be obtained from reality itself, but instead is constructed. For several reasons, fMRI data is, in this sense, a very good example of the knowledge, constructed by the researchers. Firstly, unlike data collection methods that provide a direct measure of the variable in question (for example, single-unit recordings from a neuron), fMRI is *not* a direct measure of neuronal activity. This means that although fMRI data enables researches to make inferences about neuronal activation in the brain, it is change in the level of oxygenated hemoglobin and not neuronal activity per se that is detected and measured by fMRI. Secondly, throughout all the steps of data acquisition, preprocessing, and analysis data is extracted according to what researchers are *looking for* in a certain study. It is crucial that both rationales are understood and taken into account by both the general public and the scientific community, as the former should not perceive fMRI data as precise photographs that tell us what exactly is happening in the human brain, while the latter should produce reliable and valid fMRI results and critically address the conclusions based on potentially questionable assumptions and research paradigms.

HOW DOES fMRI WORK?

fMRI Physics

Functional magnetic resonance enables researchers and medical specialists to receive images of brain activity at high spatial resolution and measure changes in brain activation over time. An important issue to understand about fMRI is that magnetic resonance images are not photographs of the scanned objects, but rather representations of the spatial distribution of some physical characteristics of the scanned tissue that relate to the properties of atomic nuclei of the tissue. Atomic nuclei with a magnetic moment and angular momentum are referred to as spins in physics and are known to precess in a magnetic field. In a strong magnetic field, each spin adopts a state, which is either parallel to the magnetic field – the so-called low-energy state, or anti-parallel to the magnetic field – the high-energy state. The process of excitation causes spins in high-energy state to return to the low-energy level and emit electromagnetic energy. This energy can be received and measured, and the strength of this signal over time provides us with the information about the properties of the tissue.

Depending on the purpose of the study, it is important to know what imaging technique to use in order to get the images that will actually show what the researcher is looking for. Since MRI images depict certain physical properties of scanned objects, one needs to know which physical properties to be looking at for the particular kind of research that he or she is doing, as well as how to set the scanner so that the acquired images will be sensitive to a particular physical property.

In order to create images sensitive to a particular physical property, it is necessary to choose the right imaging contrast (the signal difference between any two types of tissue) and pulse sequence. Each contrast has associated pulse sequences that describe series of magnetic field gradient changes and radiofrequency pulses used for MR signal collection. The basis of the blood-oxygen-level dependent (BOLD) fMRI forms the T_2^* contrast, since T_2^*-weighted images are sensitive to the amount of deoxygenated hemoglobin in the blood. While for anatomical images contrast is more important than the speed of acquisition, the situation is different for function imaging, as there the speed of image acquisition cannot be slower than the speed of physical changes that are being measured. For this reason pulse sequences that make it possible to acquire a large number of images in a relatively short period of time are required for fMRI imaging. Echo-planar imaging (EPI) is a fast sequence commonly used for fMRI.

Neurobiological Basis of fMRI

Understanding the physics of fMRI signal generation and image acquisition is important for working with this technique. However, it doesn't explain what and how fMRI measurements can tells us about brain activity. FMRI technique does not directly measure or provide images of neuronal activity of the brain. Instead, it measures the physiological activity that is correlated with neuronal activity. More specifically, the main idea behind using fMRI for

neuroscience and psychology research purposes is that changes within the vascular system of the brain reflect changes in brain activity.

For the normal activity of the human brain, large amounts of energy are required. Little energy is stored in the brain, and for this reason it needs to be supplied by the blood. The main source of energy for the brain is adenosine triphosphate (ATP), which is generated from glucose through a chemical process consisting of several steps, one type of which requires the presence of oxygen at a certain stage. Two main components of neuronal activity – depolarization of the postsynaptic membrane and generation of action potential – themselves do not require the usage of an external source of energy. However, after the neuron has been active, additional energy supply is necessary for restoring the membrane potential. Glucose and oxygen that are required for energy generation are delivered to the brain cells through the vascular system.

Increased neural activity is supported by increased blood flow: oxygenated hemoglobin is supported to the brain by the vascular system, and oxygen is extracted from it in the capillaries. An important factor for BOLD-fMRI is this change in the level of oxygenated hemoglobin. The reason for it is that the magnetic properties of a hemoglobin molecule differ depending on whether oxygen is bound to it or not, so that magnetic susceptibility of fully deoxygenated blood is significantly greater than that of fully deoxygenated blood.
The presence of deoxygenated hemoglobin in the blood decreases MR signal. However, MR signal still increases during neuronal activity. A solution for this mismatch, as described by Huettel et al. (2004), is that more oxygen is supplied to an active brain region than is consumed. Thus, BOLD contrast results from displacement of deoxygenated hemoglobin that has been suppressing MR signal by the greater amounts of oxygenated blood that makes MR signal stronger.

OBTAINING fMRI DATA

Data Preprocessing

In addition to the signal data itself, raw fMRI images also contain non-task-related information, or noise. According to Kybic et al. (2000), task induced signal changes account for 5-10% of the mean signal intensity. In order to increase the ration between the intensity of the signal associated with the brain function and variability in the data due to all sources of noise (functional signal-to-noise ratio), after the reconstruction of fMRI images, the received data must first undergo the preprocessing procedures before it can be statistically analyzed.

Since each slice is acquired at a different point in time, and the collection of the signal occurs gradually in time, while the hemodynamic changes happen as a single response in a certain brain area, the resulting slice-timing differences should be corrected. This can be done either by using the predicted hemodynamic response, created by convolving the predicted neural activity curve with calculated hemodynamic response function, or by temporal interpolation, when the information from nearby time points is used to estimate the amplitude of MR signal.

In EPI images, local field inhomogenities cause significant geometrical distortions, which if uncorrected, can make the further processing of the data meaningless. The process of correction these geometrical distortions in EPI images is referred to as unwarping, and consists of registering an EPI image with a corresponding undistorted anatomical MRI image (Kybic et al., 2000). To correct for geometrical distortions of fMRI images caused by field inhomogenities, field maps – images of the intensity of the magnetic field across space – can also be obtained and used after the image reconstruction phase.

No matter how well the head of the subject is fixated inside the scanner, head motion still occurs, and even the smallest movement can have a very strong negative effect on the data. That is why the images should be adjusted so that the brain is in the same position in all of the images. For motion correction, acquired images are spatially realigned or coregistered to a single reference volume (for example, one of the first acquired images). Then spatial interpolation is used in order to estimate the values that would have been received if there had been no motion and thus to correct for the differences that occurred due to the motion of the subject's head.

When processing fMRI data, it is important to know how the obtained data corresponds to the neuroanatomy of the brain. Functional MRI data is itself of rather low resolution and anatomical contrast, and thus is not good enough for providing researches with sufficient anatomical information. For this reason, functional data is mapped onto high-resolution and contrast structural images of the brain (that can be obtained in the prior to the functional scanning) in the process called functional structural co-registration.

When the data obtained from several subjects is to be analyzed, there occurs the problem of comparing the data, as there is a big variation in brain size, shape, and orientation among different people. In order to make a meaningful inter-subject comparison, the data from each subject should be transformed so that it is the same in shape and size as the data from all other subjects in a process known as normalization. Each individual data is fit through certain algorithms into a common stereotaxic space. The two main stereotaxic spaces used for normalization of fMRI data are Talairach and MNI (Huettel et al., 2004).

Statistical Analysis of fMRI Data

Since fMRI data contains a small proportion of signal compared to the ratio of the noise, statistical analysis of the preprocessed data is required for receiving reliable results and detecting which voxels are actually active. Two sets of hypotheses are formulated: one of whether the data fits a certain experimental prediction, and a null hypothesis based on random chance. Most of the tests used for testing the hypotheses are variants of general liner model (Huettel et al., 2004). For testing the statistical significance of the results a threshold alpha is being set to a certain level. However, since the number of compared voxels is extremely high, using a widely accepted in psychological research threshold of 0,05 for testing the significance of the comparisons can result in receiving a number of positive results by mere chance (false positive results). For avoiding this problem of multiple comparisons, uncorrected p-threshold can be divided by the number of analyzed

voxels before thresholding. This is known as Bonferroni correction. Although it successfully helps to eliminate the problem of multiple comparisons, Bonferroni correction is very strict, so that a number of true activations may not pass the thresholding level. An alternative to Bonferroni is Random Field Theory, which accounts for the rate of the false positive results in the data based upon how smooth the data is. Another possible solution to control for multiple comparison problem is choosing the region of interest (ROI), setting a certain region for further statistical analysis reduces the number of voxels that will be compared.

There are two most commonly used options for setting the threshold for the analyzed data. The first option is controlling for Family-Wise Error Rate (FWE) and False Discovery Rate (FDR). Results obtained with the use of FWE thresholding are highly significant, while FDR-thresholded analysis is more sensitive to active voxels (Logan & Rowe, 2004).

DISCUSSION

As a method of brain research, fMRI imaging provides researchers with many advantages and possibilities. It is a noninvasive method that makes it possible to acquire both functional and structural images of different contrasts sensitive to the differences in tissue characteristics. Compared to other techniques used to study brain function, fMRI has higher spatial resolution than EEG, scalp ERPs, and PET. However, its ability to distinguish changes across time (temporal resolution) is lower than that of scalp ERPs and in many instances of EEG as well. An important fact that should be taken into consideration when discussing temporal resolution of fMRI is that fMRI measures changes in blood oxygenation over a period of a few seconds to a few tens of seconds (Huettel et al., 2004), while neuronal activity itself occurs much more rapidly. Thus not only is not fMRI a direct measure of neuronal activity, but it also takes measurements of the correlate of neuronal activity with a certain delay from the activity itself.

These issues taken together point out in a quite literal sense to the constructivist perspective on scientific knowledge and show that fMRI data is not a direct measurement of brain activity as some objective physical property, but rather a certain construct – a measurement of a property that is considered by the scientists to correlate to the actual functioning of the brain. However, taking into account already available to the researches preprocessing and analyzing methods to assure high accuracy and reliability of fMRI data, as well as the work being done to improve and refine fMRI methodology, the issue of fMRI data being constructed through those processing steps rather than discovered in its pure form can be considered more of a philosophical rather than methodological question. The aspects concerning the validity of fMRI research more important to address when evaluating fMRI as a research method, as well as for interpreting fMRI data.

An important issue for discussing the validity of a scientific method is understanding the nature of the data that is obtained with the use of this method. With regards to fMRI, it is important to point out to the fact that the generally accepted model that would fully explain the exact link between glucose and oxygen consumption, and the blood flow is yet absent. In addition to that, it has long been unclear with what exactly in the activity of neurons the blood-flow changes correlate: with changes in local field potentials or with spiking activity –

that is, with the input to or with the output from the neurons. Recent literature reviews indicate that local field potentials are the most likely candidates to correlate with changes in the blood flow; however they agree with the notion that the full understanding of the relationship between functional imaging signals and the underlying cellular events is yet to be obtained (Raichle & Mintun, 2006).

Taking into account the fact that fMRI is not a direct measure of neuronal activity, some aspects of fMRI data interpretation can create challenges for the researchers. One potentially tempting assumption to make is that of the linear relationship between the fMRI signal and the underlying neural activity. Indeed, it might seem to be quite logical that the increased duration of the stimulus would result in the increase of the BOLD response, because of the increase in the neural activation. Results of some studies, however, show that their data do not fit into this simple linear model. In their study of the fMRI response of the human auditory cortex to trains of tones, Robson et al. (1998) found out that for short stimuli the relationship between the stimulus duration and the fMRI response is nonlinear. Researchers consider adaptation to be the most likely candidate for explaining their data. However, whether this adaptation occurs due to the nature of neural response per se, or due to certain features of haemodynamic response (or combination of both) is not clear and is hard to determine with the use of fMRI technique alone.

A potential pitfall of any brain imaging research that some fMRI studies, unfortunately, do not manage to avoid, is the assumption of pure insertion. The assumption of pure insertion underlies widely used experimental design paradigms for fMRI studies in which brain activation during the performance of one task is subtracted from that of another task. Pure insertion requires that one cognitive component does not affect the effect produced by another cognitive component. According to the logic of pure insertion, if activation in a certain brain area is observed during the performance of two different tasks, subtracting one pattern of activity from the other one can tells us about some central aspect of both tasks that activates the brain area in question. This, however, appears not to be always true in relation to brain activity. As argued by Friston et al. (1996), it can very likely be an interaction of several cognitive processes and not a "center aspect" of both that accounts for activation of a certain brain region by multiple tasks. Thus, adopting an experimental design that would rely on the assumption of pure insertion may result in misinterpretation and misrepresentation of the role of particular brain regions in performing certain cognitive functions.

Although fMRI has many advantages as a brain imaging technique, it also has certain limitations to what it can actually tell about brain activity. As argued by Page (2006), based on fMRI brain activation maps, we cannot always tell whether the activated areas are functional, modulated, or activated but nonfunctional. Put more plainly, by mere observing activations in certain brain areas in response to the stimuli we cannot tell how the information is being processed in those areas, whether the cognitive function that is crucial for processing that type of stimuli is localized in those brain areas, or whether their activity interacts with the activity in other parts of the brain to perform the task in question. While fMRI technique has been shown to work well for localizing brain areas specialized for processing specific types of information (as an example, see the study by Kanwisher et al.

(1997) on fusiform face area), based solemnly on fMRI data one cannot determine whether a certain area is sufficient for processing this type of information. Carefully planned and well controlled experimental design can help answer these questions to some extent, but there might also be a limitation to what can be inferred about a certain cognitive function based on the imaging data. Finally, since the problem of field inhomogenities and susceptibility artifacts presents serious challenges for fMRI imaging, some regions of the brain, such as amygdala region, are more vulnerable to signal dropouts and distortions than other regions. Although attempts to create more effective localizer paradigms are being made (Morawetz et al., 2008), in some cases detecting no signal from certain areas may not necessarily mean that there was no activation in that area, and the outcome of a study in this case depends on the interpretation of the negative results by the researchers.

The most important objective of fMRI research (as well as other functional imaging techniques) is to understand the observed brain physiology in a way that would meaningfully relate to the underlying cognitive processes. Although obtained not through a direct measurement of brain activity, fMRI data should still be able to tell us reliable and valid information about how the brain performs cognitive functions and not present us with a construct based on conclusions and assumptions that can be questionable. This can be achieved (and is achieved in many well-conducted imaging studies) not only by proper adherence to all the necessary steps of data collection and analysis, but also by making sure that the question being asked in the experiment is correctly posed, the experiment itself is designed to reveal what is being studied, the study is valid, and the interpretation of the data is correct and does not go beyond the limits of what the data can actually show.

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AUTHOR BIOGRAPHY

Olga Chelnokova is currently a master level student at the Department of Psychology, University of Oslo. Her current research topics are facial recognition, synaesthesia, and pain and pleasure interactions. Email olgach@student.sv.uio.no.