

Seeing How We Think About Words Using BOLD Contrast fMR Imaging

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Abstract

This review examines how blood oxygen level-dependent functional magnetic resonance imaging (fMRI) may be harnessed to study the brain when it engages in language processing tasks. This method makes clinical and scientific contributions to understanding language function. Issues such as the lateralisation of language function, brain plasticity in health, ageing and neurological disease, and as well as how 2 different languages are processed, may all be evaluated by fMRI.

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Introduction

Functional brain imaging refers to a set of non-invasive imaging techniques that are used to infer linkages between brain structure and function. In this review, blood flow functional magnetic resonance imaging (fMRI) is specifically discussed.

In the 19th century, Angelo Mosso made a serendipitous set of observations on a monk with a frontal skull defect that constituted the first experiments of task-related changes in brain blood flow.¹ Seeking to uncover how pulsation changes in this frontal dural defect correlated with cardiovascular changes, Mosso found that an increase in the pulsation occurred when the monk began to anticipate having to say his prayers, leading him to document similar changes occurring while the monk performed mental arithmetic.

Many years passed before imaging the living brain in active thought became practically possible through the advent of single photon emission computed topography and positron emission tomography (PET). These techniques require the use of radioactive tracers. The former has limited spatial resolution and PET is available in only a few centres around the world. So it was not until the advent of magnetic resonance (MR) imaging techniques to map blood flow that mapping functional areas within the living brain became a tool accessible to more scientists and physicians. As radioactive tracers are not used in MR

imaging, more information per subject can be obtained and over several sessions, if necessary. Besides pooled data from multiple subjects, it was possible to gather data from individual subjects.

The Basis of fMRI

Task-dependent increments in neuronal firing occur in specific areas of the brain. This increase in neuronal firing is an energy-dependent process, requiring glucose and oxygen. As such, there is a localised increase in blood flow to meet these demands. It turns out that oxyhaemoglobin and deoxyhaemoglobin have slightly different magnetic susceptibility (a tendency to distort a magnetic field). Voxels, where increased blood flow occurs, contain relatively less deoxyhaemoglobin and these voxels are associated with higher MR imaging signal. This blood oxygen level-dependent (BOLD) signal is harnessed to produce maps showing areas where task-related changes in blood flow occur (Fig. 1). In practice, many images are collected, some during the “task” condition and some during the “control” condition. This is time consuming but necessary, because although local blood-flow change is in the order of 30% to 50%,^{2,3} the BOLD signal change of interest is only in the order of 0.5% to 2%. Data processing methods, which are beyond the scope of this review, are necessary to generate activation maps arising from functional brain imaging evaluations.

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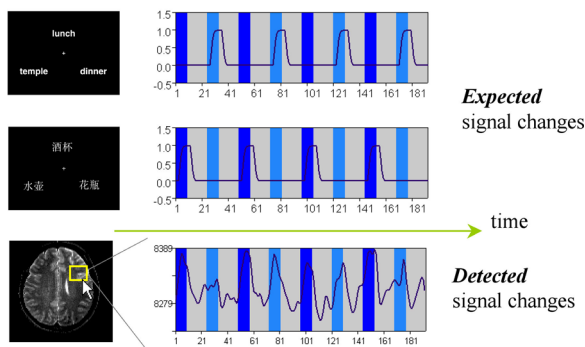


Fig. 1. Word stimuli requiring a decision on which of the 2 lower items are more closely related to the uppermost word in meaning are shown. The lighter and darker bars indicate when “blocks” of these stimuli are presented and when there is an expected signal change. When the detected MR signal change matches the expected changes, a voxel is flagged as being “active”.

What Does Functional Brain Imaging Tell Us?

Until recently, most of what we know about brain function has been garnered through lesion or electrical stimulation studies based on individuals with neurologic disease. In these individuals, there is a possibility that the underlying disease modulates brain function. As such, functional imaging of the brain is helpful because it provides an ethical means to study brain function in healthy persons.

Functional imaging provides information that either supports or refutes observations made using clinical and neuro-psychological methods. Specifically, by being able to observe the whole brain in vivo while it processes tasks, we can differentiate areas that are participatory from those that are essential to the performance of a particular cognitive task. This differentiation is important because results of contemporary functional brain imaging studies have revealed that the roles of different brain areas are more complex than previously envisaged.

Of interest to the medical community is the opportunity to study brain plasticity, for example, how in blind individuals the occipital cortex is activated when one reads Braille,⁴ and how brain activation changes following aphasia.^{5,6} Such information provides us with a set of expectations concerning the limits of cortical plasticity. Documenting the changes in brain activation that follow injury or disease could provide an objective tool with which to correlate behavioural changes with neural changes. This, in turn, could be used as a marker to track the benefit, or lack thereof, of therapeutic intervention.

What Has Brain Imaging Revealed about Language Processing in Normal Individuals?

The reading of whole words and sentences, listening to words and sentences, and component processes of reading,

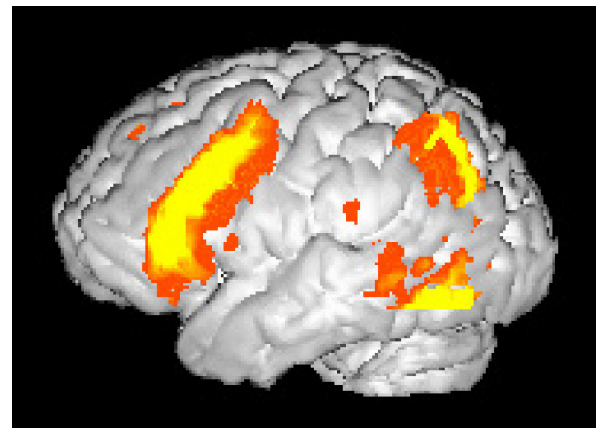


Fig. 2. Left hemisphere areas are activated when healthy volunteers performed a task requiring judgement of word meaning. The activated areas were projected onto the cortical surface. Data was pooled across 16 healthy right-handed volunteers. A corrected threshold of $P < 0.001$ was used.

including orthography (processing script), phonology (processing the sound of words) and semantics (accessing the meaning of words), have been studied using fMRI (see Price⁷ for a review). Phonologic processing of written words takes place in the left posterior pre-frontal region, whereas semantic processing has been documented at a location somewhat more anterior and inferior in the pre-frontal regions, as well as in the anterior and posterior temporal region and inferior temporal regions (corresponding to the basal temporal language area). Some studies suggest that the angular gyrus is engaged in semantic processing during sentence reading and the slow reading of words.⁷

Listening to any sound activates both superior temporal cortices, the left more than the right in most right-handed people.⁸ Specifically, when we listen to speech-like sounds there is a posterior-anterior flow in information processing, such that the more posterior parts of the dominant superior temporal sulcus are activated when processing speech-like sounds, but more anterior regions are activated only when the sounds have intelligible content.⁹

Compared to what we know from clinical studies, the left pre-frontal cortex has perhaps received disproportionate attention in the imaging literature because it is a readily activated brain region and plays several roles in phonologic and semantic processing, in addition to playing an important part in working memory, encoding and retrieval of memories.¹⁰ The ready activation of the pre-frontal cortex with tasks involving words has provided the basis for studying language lateralisation for clinical applications.

Lateralisation of Language Function

Lateralisation of language function for surgical decision-making has traditionally been performed using intra-carotid

amobarbital testing. However, in recent years, fMRI-based lateralisation of language function has been shown to produce results in good agreement with those obtained with intra-carotid amobarbital testing¹¹⁻¹⁵ and electrical stimulation.^{13,16} Most fMRI-based studies determined language lateralisation on the basis of frontal cortical activation.

A vast majority (94%) of right-handed individuals in a large fMRI-based series¹⁷ demonstrated left cerebral hemisphere dominance for language. Right hemisphere dominant language in right-handers is rare and has, to date, been reported in 5 out of 50 neurologically normal sinistrals¹⁸ and in 3 out of 50 epileptic patients.¹⁷ In a recent study, 1% to 2% of right-handed individuals were found to have right hemisphere language. While these individuals were functionally intact, neuro-psychological tests in the 3 individuals reported suggest that when right hemisphere dominant function (encoding of unfamiliar faces) is less than completely reversed (that is, found in the left hemisphere), verbal intelligence quotient scores may be rendered slightly inferior to performance (non-verbal) intelligence quotient scores.¹⁹

Earlier functional neuroimaging studies reported more left lateralised frontal lobe activation in men than in women performing a visual phonological task²⁰ and a semantic processing task.²¹ However, subsequent imaging studies have not replicated sex differences in cerebral lateralisation for language.^{22,23}

How Does the Brain Process 2 Languages?

Over 4 decades ago, Penfield and Roberts suggested that a common cortical substrate was involved in the processing of a person's native and second languages.²⁴ This view had both proponents²⁵ and opponents²⁶ amongst those studying bilingual aphasia. Early studies using PET²⁷ and fMRI²⁸ demonstrated intra-hemispheric differences in the processing of native and second languages. These studies were of an exploratory nature and did not control for second language proficiency. Subsequent studies involving English and Chinese,^{29,30} French and English,^{31,32} and Spanish and English^{33,34} have shown that macroscopically congruent areas are activated when fluent bilinguals perform a variety of word processing tasks.

Early studies showing across language intra-hemispheric differences in activation involved sentence level processing.^{27,28} Processing at this level is demanding and reveal proficiency related differences in activation. However, when language proficiency was balanced across the tested languages and when the task was not excessively demanding, considerable spatial overlap of activation between languages occurs.^{35,36}

Some reconciliation with earlier literature emerged when the role of relative language proficiency in modulating brain activation was studied. It was found that processing in the less proficient language leads to greater activation in the left and, to a lesser extent, right pre-frontal areas.³⁷ Greater activation for a hard task in the less proficient language has also been documented using the auditory route of presentation of stimuli.³⁶

How Plastic is the Brain in Second Language Learning?

The notion of critical or sensitive periods for language development has been proposed³⁸ and there is an intuitive appeal to the idea, given that most adult learners of a second language do so with considerable effort. Kim et al³⁹ found that, in the left frontal language areas, the centre of mass of activation for first and second languages is different in individuals who acquire a second language later in life, after the age of 12, but not for those who do so before that age. We did not replicate this finding when we studied cued word generation in fluent "late onset" Chinese-English bilinguals.²⁹ Instead, a striking congruence in activation across languages was observed, similar to what was observed of "early onset" bilinguals (those who mastered both languages before the age of 5). The fact that some individuals can acquire near native fluency in new languages later in life suggests that a rigid notion of sensitive periods may reflect less of a universal principle than a constraint that can be overcome with practice, given the appropriate neural machinery.

Linguistic Experience and Brain Activation

The processing of speech-like sounds occurs in a manner that is either dependent or independent of linguistic experience. In comparing activation resulting from the processing of electronically degraded speech to that elicited by normal English speech,⁹ it was found that the left superior temporal sulcus was activated by sounds containing phonetic information; however, only the anterior temporal region responded to speech that was intelligible. This suggests the importance of prior linguistic experience in processing speech-like sounds.

Regularity in spelling to sound rules differs across languages. Italian has a shallow orthography and English, a deep one. When native English readers were compared to native Italian readers, a difference in the topography of brain activation in relation to reading non-words (or plausible pseudo-words) emerged, whereby there was greater activation in the left inferior frontal and middle temporal areas only for English readers reading non-words⁴⁰ only. This, again, illustrates the effect of prior linguistic experience on cortical activation.

Age-related Changes in Ability to Remember Words

Compared to the young, cortical activation is less selectively lateralised in the elderly (above 65 years old). This is true for the healthy aged, but the effects are even more pronounced in those with mild cognitive impairment (a prelude to Alzheimer's disease). When given a list of words to memorise, the healthy elderly activated the pre-frontal regions less than young, healthy volunteers. The age-related differences in activation during encoding were partially compensated by having the aged volunteer involuntarily remember presented words while performing a task requiring judgement of word meaning (such as whether the word represents an abstract concept or a concrete item).⁴¹ Of interest is the fact that while test scores in neuro-psychological tests were reasonably comparable between the elderly and young adult populations in that study, recognition memory performance was less accurate and might be related to the lack of selectivity of lateralisation of brain activation. This lack of selectivity of activation has 2 postulated mechanisms: the failure to select the most appropriate brain region to perform the processing task and a compensatory mechanism for the loss of cognitive capacity. Whether or not lack of selective lateralisation of cortical recruitment can be reversed with therapeutic intervention, or whether it can be delayed by dietary/lifestyle interventions, remains to be seen.

Compensation Takes Place in Aphasics

When structures in the left hemisphere that have a role to play in language processing are damaged in stroke, activation in both the perilesional areas in the left hemisphere and homotopic (mirror location) contralateral right hemisphere has been documented using fMRI.^{5,6,42,43} Although there exists the possibility that right hemisphere activation is merely an extension of existing activation from a person who has bilateral cortical representation for language, there has been at least 1 case where the pre-existing left hemisphere language was documented pre-ictally.⁵ There is a consensus that homotopic right hemisphere activation may be a compensatory feature, but that recovery from aphasia better correlates with the extent of left hemisphere perilesional recovery of activation.^{5,6,43}

Summary

Functional brain imaging using BOLD fMRI and involving language processes will continue to provide valuable insights into how the brain is organised in health, and how circuitry may be modified with learning and illness. In the future, it is hoped that the method will be harnessed to provide objective measures that can be used to evaluate the effectiveness of specific interventions for brain-injured or cognitively impaired individuals.

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