

Comparison of [^{15}O] H_2O Positron Emission Tomography and Functional Magnetic Resonance Imaging in Activation Studies

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Abstract

[^{15}O] H_2O positron emission tomography (PET) has long been out of use in activation studies on the brain. Indeed, it is true that blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) has better spatial resolution and temporal resolution than PET, as well as no radiation exposure. However, PET and fMRI differ in their scope. Compared to fMRI, [^{15}O] H_2O PET offers advantages such as being quantifiable, less deteriorated by movement, and allowing for longitudinal studies. This article aimed to reassess the merits of PET in this context.

Keywords: Arterial spin labeling, blood oxygen level dependent, cerebral blood flow, magnetic resonance imaging, positron emission tomography

Introduction

Broadly categorized, there are two methods of studying the functions of the brain. One is an activation study, and the other is a lesion study. An activation study observes how the brain acts when it is performing a function, and includes methods such as single-unit recording (electrophysiology), event-related potential (ERP) using electroencephalogram (EEG), magnetoencephalogram (MEG), near-infrared spectroscopy (NIRS), and optical imaging [Figure 1]. On the other hand, a lesion study inhibits the function

of a part of the brain, and looks at whether that area of the brain is indispensable for performing a particular task. Examples of lesion studies include the injection of ibotenic acid or muscimol in animal subjects, and the amytal test (Wada test)^[1] in human subjects. Both types of studies play a crucial role in the study of brain function, as an activation study shows that an area of the brain relates to the task, while a lesion study shows that it is indispensable. Activation studies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are essential for use in human subjects.

Let us assume that you wish to commence a new activation study on the brain. Which is more appropriate: fMRI or PET? Even those who routinely use fMRI may find cause to read dated articles involving PET. One

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must know the strengths and limitations of both PET and fMRI in order to understand one's own research and the research of the past. [¹⁵O] H₂O PET has already fallen into disuse, which many may think is simply because fMRI was superior to PET. Certainly, fMRI has many superior points, but it would be untrue to say that PET does not have its strengths. Here, we compare fMRI and water PET, and attempt to investigate and re-examine the advantages of PET.

Relationship Between CBF and PET/ FMRI

Since the end of the 19th century, it has been known that localized increase in blood flow in the brain is related to the functions of the brain.^[2] Regrettably, we do not yet fully understand the coupling mechanism between the brain's functions and its blood flow, but it has been postulated that astrocytes play a role in regulation.^[3] fMRI and [¹⁵O] H₂O PET (or, water PET) are also closely related to the coupling between blood flow and the brain's functions. However, the manner in which they are related differs between the two methods.

Regional cerebral blood flow (rCBF) directly reflects the activity of the brain, and water PET investigates the functions of the brain by measuring rCBF. It compares the distribution of blood flow in the brain when activated by some task with baseline activity, and thus investigates the areas of the brain related to that task. This type of study was most popular in the 1980s and 1990s. It is also known that regional cerebral glucose metabolism (rCMR_{glc}) directly reflects activity of the brain, but is rarely used in activation studies as time is required for [¹⁸F] fluorodeoxyglucose to accumulate in the brain.

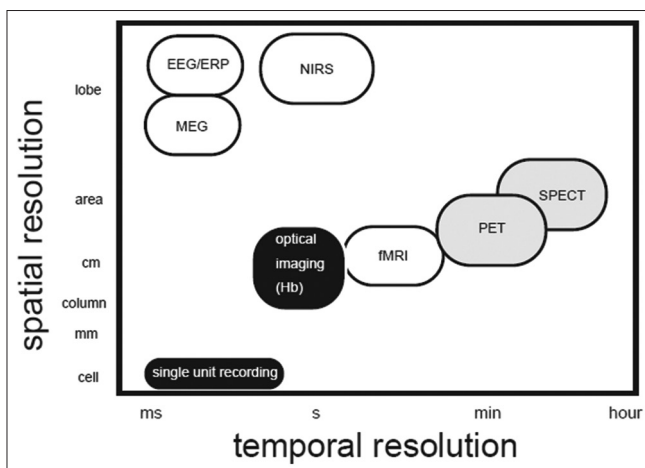


Figure 1: Comparison of the spatial resolution and temporal resolution of various methods used in neuroscience.

The color shows invasiveness; those with low invasiveness are white, and those with high invasiveness are black (including experiments on animal subjects). PET has been colored light gray as there is some radiation exposure

Compared to rCBF, regional cerebral oxygen metabolism (rCMR_{O₂}) does not increase as much as rCBF. Exercise and visual stimulation leads to an rCBF increase of as much as 50%, but rCMR_{O₂} increases by only 5%.^[4] As a result, the relative concentration of oxygen in the tissue increases only by a small amount. Blood oxygen level dependent (BOLD) fMRI^[5] looks at impact on T₂^{*} of minor disturbances in the magnetic field caused by changes in the ratio of deoxyhemoglobin (paramagnetic) to oxyhemoglobin (diamagnetic).

Comparison of FMRI and PET

The spatial resolution and temporal resolution of fMRI surpasses that of PET, and it is widely known that there is also no radiation exposure [Table 1]. In fact, for a single scan, PET has a better signal-to-noise ratio (SNR) than fMRI. However, overall fMRI provides a clearer image as fMRI can be repeated multiple times due to its lack of radiation exposure. Indeed, this perhaps provides ample reason for the decline in PET use and the rise in fMRI use.

Water PET requires a cyclotron, limiting the number of facilities where it can be conducted. In contrast, MRI can be conducted relatively easily at many facilities. Because of existence of some information only accessible through PET such as neurotransmitter imaging, those in the field of nuclear medicine have not chosen water PET over fMRI in recent times.

The development of event-related fMRI^[6] has significantly increased the convenience of fMRI. Owing to the limits of its temporal resolution, PET was only able to complete "boxcar type" studies, which repeat "on" imaging, when the task is being performed, and "off" imaging, when the task is not being performed. Initially, fMRI followed PET in this regard, but the emergence of event related fMRI led to a dramatic increase in the freedom of study design. Although the temporal resolution of fMRI is better than PET, it was not fully utilized until the emergence of event-related fMRI.

Strengths in areas of imaging also differ between PET and fMRI. PET has the advantage that the attenuation

Table 1: Comparison of water PET and fMRI

	Water PET	BOLD	ASL
Spatial resolution	6 mm	4 mm	
Temporal resolution	min	1 s	several seconds
Radiation exposure	1.6 mSv	none	none
Signal	50%	several %	poor
Measurement	rCBF	oxy Hb/deoxy Hb	rCBF
Suited to	brain surface	central brain	central brain
Ability to quantitate	excellent	none	practicable

The figures differ depending on the device, imaging method, and other factors, thus generalized representative values are shown. PET: Positron emission tomography; BOLD: Blood oxygen level dependent; ASL: Arterial spin labeling; rCBF: Regional cerebral blood flow, Hb: Hemoglobin

of annihilation radiation is less for the surface than central tissues of the brain, while MRI has the relative disadvantage that parts in contact with the air produce a large susceptibility artifact.

Perfusion MRI

Perfusion MRI by arterial spin labeling (ASL)^[7,8] is a technology that has been around for many years, but it has finally come into practical use in recent years, following the application of high magnetic fields and technical innovation. Thus, we are including perfusion MRI in this comparison.

Certainly, it appears image quality has significantly improved compared with before. However, it has yet to reach the level of image quality with PET. In particular, the longitudinal relaxation time (T_1) is quite short at about 2 s, so the signal from tracer labeled in the carotid artery becomes severely weakened by the time they reach the top of the brain. Artifacts produced during such transit time can become a major contributor to image ambiguity. In addition, it is thought that the susceptibility artifact for parts in contact with the air for perfusion MRI is still large in its current form. Though perfusion MRI is reliably able to measure CBF, like PET, various causes of artifacts remain and thus is thought to still be in a developmental stage.

On the other hand, the reliability of MR perfusion and CT perfusion is an issue due to the need for the use of a contrast agent. Contrast agents cannot pass through the blood brain barrier (BBB), hindering perfusion of the tissue. In this respect, contrast agents differ completely from diffusible tracers such as $[^{15}\text{O}] \text{H}_2\text{O}$. The CBF is sought from the cerebral blood volume (CBV) and mean transit time (MTT), according to the central volume principle.^[9]

$$\text{CBF} = \text{CBV}/\text{MTT} \quad (1)$$

The deconvolution method is used to work out the MTT,^[10] but the CBF image relies in large part on the deconvolution algorithm, so its reliability is low.^[11] In organs other than the brain (such as cardiac muscle) the contrast agent leaks from capillaries perfuses the tissue, thus by determining the rate constant, we are able to determine blood flow.^[12]

Possibility of the Active use of $[^{15}\text{O}] \text{H}_2\text{O}$ PET

Water PET is on the brink of falling into disuse but, can it survive? Here, we present a number of possibilities for its use in modern research.

- Certainly, BOLD signals become stronger relative to the size of nerve activity. However, blood oxygen levels and disturbances in a magnetic field are not strictly proportional. The same can be said of the relationship between magnetic field disturbance and MR signals. In addition, in recent years statistical analysis, such as statistical parametric mapping (SPM), has gained favor. In theory, t -value should increase in response to an increased BOLD signal. However, the t -value will vary depending on the section of the brain despite a constant BOLD signal. That is to say, these values do not directly correlate with signals from the brain. In contrast, the amount of blood flow in a section of the brain is a clear organic signal making PET preferable for obtaining quantitative results
- fMRI requires one to measure the difference between an activated state and baseline. As this comparison must take place in a single scan, fMRI is impracticable for longitudinal studies, such as comparison of brain activity in a single patient before and after the treatment. With PET, images of changes in blood flow or regional cerebral glucose metabolism at different points in time can be compared. However, this is also now possible with perfusion MRI. Thus, if perfusion MRI technology continues to advance, it may supersede PET
- PET and fMRI are both vulnerable to movement, but fMRI is more critically so. In both cases, large movements have an impact because they cause a difference with the transmission scan (PET) or shimming (MRI), but for small movements, correction with software is possible, and this type of compensation for movement is necessary. With PET images, neighboring pixels also represent blood flow and usually represent similar values, and as a result the impact of movement is relatively small. On the other hand, a BOLD signal is represented as several % of the T_2^* image, so even a movement with a voxel size of some $1/20^{\text{th}}$ can result in a critical error.^[13,14] In particular, care is required because false positives can occur easily in activation imaging in areas such as the border between gray and white matter. As a result, it is thought that PET is preferable in cases where movement, such as mastication, is unavoidable.^[15] As with water PET, the eventual image that emerges from perfusion MRI is of CBF. ASL involves a process that takes an image and calculates the difference with an image that has a different spin, and hence, is susceptible to corruption due to movement
- PET has the advantage that the attenuation of annihilation radiation is less for the surface than central parts, while MRI has the relative disadvantage that parts in contact with the air have a large susceptibility artifact. For example, various studies with single photon emission computed tomography (SPECT)

show an increase in blood flow in the frontal lobe on administration of donepezil hydrochloride;^[16-18] however, perfusion MRI (ASL) does not appear to be able to distinguish this^[19]

- BOLD signals are relatively weak and thus the action, thought, or experience being studied must be repeated multiple times to statistically analyze and extricate the signal from the noise. Therefore, rare phenomena that cannot be reliably replicated numerous times may be best captured by PET, which has a good SNR for a single trial. It should be noted however that the temporal resolution of PET is lower than BOLD fMRI, hence, such singular events would need to cause sustained activations of brain areas
- Loud sounds are unavoidable in MRI while PET is a comparatively quiet process.

Since fMRI has become popular, it appears that the majority of activation studies utilizing water PET involve movement.

Conclusion

The three different brain function imaging techniques of water PET, fMRI (BOLD), and ASL were compared. Through this comparison we hope to have illustrated, that while MRI has a number of advantages over PET, PET has its own practical applications.

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Conflicts of interest

The authors declare no conflicts of interest.

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