Pharmacological MRI: a biomarker in CNS drug discovery and development?

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Today, in the pursuit of new objectives in medical research, innovative concepts and methods are increasingly coming into use. Some of them, applied to the development of CNS-active drugs, are becoming part of our current knowledge. These new concepts, methods and applications are sometimes merged, giving rise to new entities, and whereas specialists are well acquainted with these entities, many potentially interested researchers remain largely unaware of their full potential and limitations. Pharmacological magnetic resonance imaging (phMRI) as a possible biomarker in CNS drug discovery and development is a case in point.

In this editorial, we invite interested readers to focus on some of the concepts related to the use of MRI in drug development. We are certainly not setting out to provide an exhaustive analysis or overview of this issue, which remains very much open to methodological debate, or to provide definitive answers. Our aim, rather, is to offer a few reflections, to arouse curiosity, and to direct the reader towards some key studies and reviews.

What is pharmacological MRI?

The concept of phMRI first entered the arena nearly ten years ago. In 1998, Bryant and Jackson stated that “… functional magnetic resonance imaging can provide insight into the functional connectivity of the human brain in both health and disease, including the effects of aging and drugs on brain function”. According to these authors, neuroimaging measurement can either be direct (involving techniques using specific radio-ligands) or indirect (based on consideration of the neurophysiological consequences of pharmacological interventions). And in both approaches, combination with sensorimotor or cognitive activation makes it possible to examine interactions between the targeted receptor functions and sensorimotor or cognitive processes (1). These considerations summarize neatly what phMRI is all about.

The technique of fMRI, which is based on the blood oxygen level-dependent (BOLD) effect, yields functional activation maps with high temporal and spatial resolution during perceptual, cognitive and emotional tasks. phMRI-BOLD studies investigate cerebral activity following acute drug administration (single challenge) and CNS adaptation to long-term medication. Their results provide insight into brain physiology and neuropharmacological mechanisms which, in turn, is useful in preclinical pharmacological studies, responder analyses, and the investigation of pathogenetic mod-
Several imaging methods, including emission tomography, allow us to assess the pharmacodynamics of drugs in vivo. Positron emission tomography (PET) and single photon emission tomography (SPECT) remain unique in pharmacokinetic studies in that they allow investigators to assess the kinetics of uptake and clearance of ligands and drugs in the brain and blood vessels.

Taking a more positive view of the future of phMRI, Iannetti and Wise (5) recently looked at how this methodology may be improved. They recalled the well-known fact that BOLD fMRI does not measure neural activity directly, but instead relies on a cascade of physiological events that link neural activity to the generation of the MRI signal. In spite of this, to date, most studies have interpreted changes in BOLD fMRI as “brain activation”, ignoring the potential confounding effects of possible drug- or disease-induced modulation of events downstream of the neural activity. These authors reiterate that these influences must be identified, characterized and possibly corrected if meaningful information on brain activity is to be extracted from patient and pharmacological BOLD fMRI studies, and suggest a series of measures to improve their interpretability. Listed in order of their potential to provide meaningful information and their current practical feasibility, the following improvements are advocated: the inclusion of one or more control tasks, and the recording of physiological parameters during scanning and subsequent correction of possible between-group differences are absolutely essential; other, highly recommended improvements include the assessment of baseline brain perfusion, and of vascular reactivity, the inclusion of stimulus-related perfusion fMRI, and the recording of electrophysiological responses to the stimulus of interest. Finally, it would be desirable to include simultaneous EEG-fMRI, cerebral blood volume and rate of metabolic oxygen consumption measurements and, when relevant, animal studies investigating signaling between neural cells and blood vessels.

Furthermore – and this is an aspect whose importance is often underestimated – BOLD-fMRI results have to be interpreted strictly in relation to the task carried out during the imaging procedure: whenever a neural substrate is described as “activated”, or two populations are described as differing in their activation patterns, it must be appreciated that this activation, or these differences, emerged in a task-specific context (6).

**phMRI in CNS drug development: a biomarker?**

The term biomarker (biological marker), now part of biomedical terminology, has various definitions, including the one proposed by Frank and Hargreaves: “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (7). These authors also report a classification system for biomarkers created by the ‘Biomarkers and Surrogate Endpoint Working Group’ under the auspices of the Office of the Director of the National Institutes of Health. This system recognizes important differences among biomarkers. Type 0 biomarkers are markers of the natural history of a disease and correlate longitudinally with known clinical indices, such as symptoms over the full range of disease states. Type I markers capture the effects of an intervention in accordance with the mechanism of action of the drug, even though this mechanism may not be associated with clinical outcome. Type II markers are considered surrogate endpoints, or biomarkers intended to substitute for clinical endpoints. “A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that [through its changes] is expected to predict clinical benefit, harm, or lack of benefit or harm”. Definitions were proposed to distinguish clearly between biomarkers and clinical endpoints, the latter defined as characteristics or variables that reflect “how a patient feels or functions, or how long a patient survives”. Similarly, the US FDA states that “a surrogate endpoint, or ‘marker’, is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy”.

All this suggests that there is a need to define biomarkers, i.e. measurable target variables, in relation to the aims of phMRI studies as well. Borsook et al. (8) describe a number of potential applications of phMRI across different stages of the drug development process, such as target validation, assessment of off-target CNS effects and therapeutic window, early proof of CNS activity, early support for concept, optimized dosing, responder identification, patient stratification, as well as several further uses for phMRI after a drug has been approved (for example in the assessment of novel indications and expanded use), or even after it has failed to obtain approval (uses other than those originally envisaged).

**Concluding remarks**

Several imaging methods, including emission tomography, allow us to assess the pharmacodynamics of drugs in vivo. Positron emission tomography (PET) and single photon emission tomography (SPECT) remain unique in pharmacokinetic studies in that they allow investigators to assess the kinetics of uptake and clearance of ligands and drugs in the brain and blood vessels.
the living body. However, emission tomography techniques are limited considerably by their radioactive burden. BOLD-fMRI also has some limitations including the small signal-to-noise ratio (the signal represents 0.3-3.0% of the total "measured output" from the MRI scanner). Thus, the BOLD-fMRI signal, resulting from many different processes, is less specific than PET measures. However, BOLD-fMRI does offer several advantages: it is non-invasive, mainly inexpensive, and almost universally available; furthermore, it does not require the injection of radioactive tracers, and is thus repeatable in the same subject.

It is likely that interest in pHMRI will continue to grow. However, to be fully exploited the approach may need to be integrated with a flow of pharmacological tests during the process of drug discovery and development, and possibly with other companion methods including emission tomography.

References