BRAIN BYTES

Psychopharmacological MRI

Introduction

Understanding the neural substrates underlying psychopharmacological modification of neurotransmitter systems is a cornerstone of neuroscience research and critical in the development of suitable drug therapies for neuropsychiatric disorders. Magnetic resonance imaging (MRI) may be used as a non-invasive technique for the *in vivo* investigation of the effects of psychoactive substances on human brain functioning. The application of microangiographic techniques to pharmacology, termed pharmacological MRI (phMRI) may be used to demonstrate the regions of the brain that respond to a wide range of different psychotropics. This exciting application of MRI holds the promise of providing quantitative biomarkers of psychotropic drug effects, aiding in establishing optimised dosing, identifying patients likely to respond to psychopharmacotherapy and being a valuable tool in the development of novel psychoactive drugs.

Methodological principles

The basic techniques commonly used in phMRI are the so-called blood-oxygen-level-dependent functional MRI (BOLD-fMRI) (1) and arterial spin labeling (ASL) (2). Both methods provide an indirect neuroimaging measurement of brain activity based on its coupling to brain haemodynamics. Using drugs in combination with MRI-based microangiographic measurements it is possible to investigate the effect of the drug itself in the brain (challenge phMRI) or to examine how the drug manipulates neural processing (modulation phMRI).

Using the BOLD-fMRI-based technique one can measure a relative change in MRI signal intensity in the brain during the performance of a task and/or a psychopharmacological challenge. The measured signal intensity change is based on a combination of changes in the oxygenation state of haemoglobin and haemodynamic changes that are induced by a task or a drug challenge. The mechanism of the origin of the BOLD-fMRI-signal is still not fully understood, and the exact relationship between the measured BOLD-signal changes and actual neural activity is still being vigorously debated. In practice, this means that BOLD-fMRI results have to be interpreted strictly in relation to the events occurring during the imaging procedure and it is difficult to generalise results over subjects and sessions using this method. Effort is being made, though, to develop ways to 'calibrate' the BOLD-signal to facilitate quantification of the output (3), so as to enable better interpretation of results and comparison between subjects and over time.

By using an ASL-based technique, it is possible to obtain an objective measure of the neurovascular changes that are induced by a drug and/or a task. The technique is a more 'pure' microangiographic method than the BOLD-approach, and generates results that are reproducible between subjects and also over time as it quantifies cerebral blood flow changes. As the ASL technique is a relatively recent development in MRI, it is still not routinely implemented on commercial scanners, therefore limiting its use to dedicated research settings.

Since cerebral blood flow change is an epiphenomenon rather than a direct measure of brain activity, it is of utmost importance to record and correct for confounding physiological parameters such as heart rate, blood pressure and respiration when collecting neuroimaging data, as they may all be substantially influenced by psychotropics. The inclusion of control tasks to identify the effect of systemic changes of vascular tone is always warranted (4).

The analysis of phMRI data is basically done using the same principles as for other dynamic neuroimaging methods like fMRI and positron emission tomography (PET). A more novel and exciting way to look at the data is through the use of connectivity analysis (5), which offers insight into how psychotropics can modify interactions between different brain structures.

Use of phMRI in neuropsychiatric research

The principal advantage of phMRI in drug research is the non-invasiveness of the technique, which allows for longitudinal and larger scale studies than by using emission tomography (ET) methods, whose use is considerably limited by their radioactive burden. The method also boasts unparalleled spatio-temporal resolution, better availability and lower costs compared to ET. phMRI studies modifying all major neurotransmitter systems have been successfully conducted (6), providing proof of the methodological concept, valuable insight in the physiological and neurocognitive effects of psychotropic drugs and inspiration for performing further studies.

The most attractive quality of phMRI is that it can provide mechanistic measures regarding the effect of psychoactive drugs. Psychiatric signs and symptoms and their response to psychopharmacotherapy are inherently difficult to objectively define and evaluate using behavioural assays

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only. It has been argued that phMRI may even be more sensitive and objective than the behavioural assay it reports (7).

Conclusions

The list of useful applications of phMRI is limited only by the imagination of scientists willing to explore this exciting new technology. It is still an emerging field, and clearly much work is needed to establish the validity and reliability of the methods and exactly how to interpret results. The recent great interest from pharmaceutical corporations in applying phMRI indicates that the role of the technique is likely to expand greatly in the future, and that granting may be generous for those mastering its application. The method bears the promise of substantially decreasing costs and risks of psychotropic agent development by increasing the ability to make focused rational choices that aid decision-making and in this way speed the discovery of safe and effective treatments for neuropsychiatric illnesses.

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