Chapter 26

Pharmacological Applications of fMRI

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Abstract

Increasing societal expectations for new drugs, lack of confidence in short-term endpoints related to long-term outcomes for chronic neurological and psychiatric diseases and rising costs of development in an increasing cost-constrained market all have created a sense of crisis in CNS drug development. New approaches are needed. For some time, the potential of clinical functional imaging for more confident progression from preclinical to clinical development stages has been recognized. Pharmacological functional MRI (fMRI), which refers specifically to applications of fMRI to questions in drug development, provides one set of these tools. With related structural MRI measures, relatively high resolution data concerning target, disease-relevant pathophysiology and effects of therapeutic interventions can be related to brain functional anatomy. In this chapter, current and potential applications of pharmacological fMRI for target validation, patient stratification and characterization of therapeutic molecule pharmacokinetics and pharmacodynamics are reviewed. Challenges to better realizing the promise of pharmacological fMRI will be discussed. The review concludes that there is a strong rationale for greater use of pharmacological fMRI particularly for early phase studies, but also outlines the need for preclinical and early clinical development to be more seamlessly integrated, for greater harmonization of clinical imaging methodologies and for sharing of data to facilitate these goals.

Key words Pharmacological fMRI, Target validation, Patient stratification, Pharmacokinetics, Pharmacodynamics

1 Introduction

Both the pharmaceutical industry and regulators are searching for better models and for new drug development, particularly for CNS drugs [1]. Public confidence in the industry has declined in the face of what is viewed as a lack of commitment to addressing major diseases with innovative drugs, while new drug costs continue to escalate. Industry sees the risks of drug development to be high particularly for chronic CNS diseases, for which there is a notable lack of consensus regarding underlying causes and mechanisms in the scientific community. CNS drug development appears uncertain, slow, and expensive.

Pharmacological fMRI provides a relatively direct measure of CNS functions. Noninvasive imaging methods also allow the same

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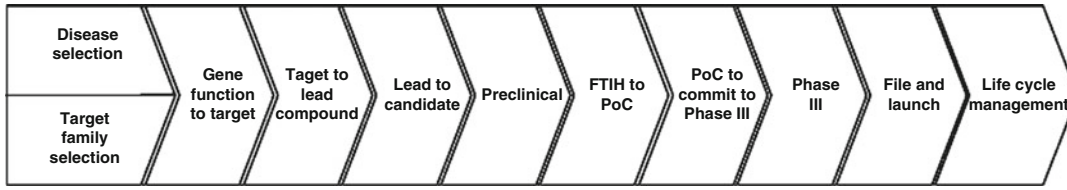

Fig. 1 The "critical path" for drug development. Pharmacological MRI has the potential to enhance the efficiency of early clinical development with better translation of biological concepts from preclinical to clinical studies, providing a new pharmacodynamic measure and enhancing potential in proof-of-mechanism studies (*FTIH* first time in human study, *PoC* proof of concept study)

endpoint measures to be used in preclinical as in clinical development. This facilitates interpretation of clinical imaging outcomes in terms of molecular and cellular changes found with invasive methods preclinically [2]. These and related considerations have embedded imaging in drug development already. Almost 30% of new molecular entities approved for neuropsychiatric indications by the Food and Drug Administration between 1995 and 2004 were developed with contributions from imaging [3]. A 2013 review identified 70 CNS drug trials registered on the registry website clinicaltrials.gov, that incorporated imaging endpoints [4]. In selected areas, such as multiple sclerosis drug development or recent trials of molecules for Alzheimer's disease, clinical imaging measures are used routinely for patient selection, for trials, or for response and safety monitoring. While most of these applications have relied on serial structural MRI, they have demonstrated the feasibility of implementing large scale, regulatory compliant clinical trials with imaging endpoints. They make the case for future use of pharmacological fMRI plausible.

Another factor that contributes to the plausibility of greater use of pharmacological fMRI in clinical drug development is the increasing premium being placed on integration of preclinical studies and early-phase development in an "experimental medicine" (sitting fluidly on the Phase I/IIa boundary) stage as part of confidence building and risk mitigation. Experimental medicine uses human experimentation to address mechanistic questions in ways that traditionally were reserved for preclinical studies. It is part of a biologically driven therapeutics development strategy involving hypothesis-led research that often is performed widely across levels of biological complexity (e.g., cells to the whole organism). A fundamental premise is that animals can be used to model biology, but cannot be expected to model human disease, which must be studied in the human. With this thinking, the classically unidirectional "critical path" from drug development (Fig. 1) is enabled by tools (e.g., from omics and imaging) to

become more powerfully bidirectional (e.g., from preclinical to clinical data and "back again").

2 Principles of Functional MRI (fMRI)

FMRI is based on indirect measures of neuronal response mediated through associated changes in blood flow. Increased neuronal activity is associated with a local hemodynamic response involving both increased blood flow and blood volume. This neurovascular coupling is related to the increased local energy consumption associated with neuronal activity, which generally is believed to reflect predominantly presynaptic activity [5–7]. The hemodynamic response has a magnitude and time course that depends on contributions from both inhibitory and excitatory inputs to the local field potential [8]. It therefore can be considered as a measure of local information input. While this may be correlated with local multiunit activity (neuronal spiking activity) under some conditions, such a relationship is not necessarily generalizable.

The neurovascular response is regulated by neuronal–glial interactions mediated by multiple signaling mechanisms. Pharmacological fMRI applications therefore need to take into account any potential impact of experimental molecules (or the disease of interest) on these coupling mechanisms. For example, the cerebrovascular effects of multiple neurotransmitter systems that may be the target for therapeutic molecules (e.g., glutamate, dopamine, norepinephrine, serotonin, acetylcholine, and prostaglandins) are well described [9]. Disorders of cerebrovascular regulation also are recognized in a number of disease states including not only primary cerebrovascular diseases such as stroke, but also, e.g., Alzheimer's disease [10–12].

The most commonly used fMRI methods rely on blood oxygen level-dependent (BOLD) imaging contrast [13, 14]. This contrast arises because the concentrations of deoxyhemoglobin, which is paramagnetic and thus locally modulates an applied static magnetic field, vary with local blood flow and oxygen consumption. In the MRI magnet, where a highly *homogeneous* (i.e., spatially invariant) magnetic field is generated, the paramagnetic deoxyhemoglobin generates small magnetic field *inhomogeneities* around blood vessels. Their magnitude increases with the amount of paramagnetic deoxyhemoglobin. These inhomogeneities reduce the MRI signal acquired with a gradient echo MRI acquisition sequence (echo planar imaging or EPI). Transient decreases in BOLD contrast associated with brain activity reflect neuronal activation because blood flow increases with greater neuronal activity to an extent that is larger than is needed simply for increased oxygen delivery with greater tissue demands. This reduces the local ratio of deoxy- to oxyhemoglobin in the blood

enough to be associated with an increase in the local EPI MRI signal. While this effect is small (0.5–5 % typically at 3 T), it can be measured reliably with signal averaging.

Alternative approaches to brain functional imaging rely on measures of brain blood flow. The advent of fMRI was heralded by changes in blood flow measured by tracking a bolus of intravenously injected exogenous contrast material [15]. Arterial spin labeling MRI (ASL) has been developed more recently as an alternative, noninvasive pharmacological fMRI approach that is based on measuring brain activity associated changes in blood flow by means of noninvasive magnetic "tagging" (with a radiofrequency pulse) of blood flowing into the brain. Methods have become increasingly standardized in recent years, are widely available on commercial clinical imaging systems and can have considerable precision [16].

Both approaches to pharmacological fMRI can be applied in two general ways. In "task based" pharmacological fMRI, constrained shifts in cognitive state are induced to explore the way in which physiological differences between the states are modulated by an associated intervention. A typical experiment would involve acquisition of a series of images over the course of a controlled, periodic variation in cognitive state (e.g., performing a working memory task relative to resting) with and without the putative modulatory intervention of interest. Regions of significant change in the difference in BOLD signal between the two cognitive states then are defined by statistical analysis of the time series data.

An alternative design relies on the modulation of brain spontaneous activity in the absence of specific stimuli, i.e., in the "resting state". This approach is based on the observation that correlated, local and long-distance temporally varying signals are found with fMRI just as was previously found in the EEG [17]. This oscillatory activity appears fundamental to brain functional organization. Far field activity in the gamma range (~30–80 Hz) may be particularly relevant for the BOLD signal responses found in resting-state fMRI [7, 18]. There are multiple ways of defining the long-distance oscillatory coupling in fMRI [19], as yet without great standardization. For both task- and resting-state fMRI applications, assessment of responses to interventions involves statistical contrasts of time-courses before and after the intervention [20].

Both BOLD and ASL-based fMRI signals are low and can be confounded by other contributions to the temporally varying brain signal from subject movement (even on the order of mm), cardiorespiratory variations, image acquisition artifacts, and even difference in imaging system performance over time [21]. Some artifacts (e.g., movement) are easier to recognize and can be "edited out" *post hoc* [22]. Controlling for potential systematic variation in the parameters (e.g., increased respiratory rate in anxious subjects with a brain disease relative to healthy control subjects) as best as is possible is particularly important [21]. The potential for these factors

to have an impact on outcomes emphasizes the importance of replications of results across laboratories and study populations, although this has rarely been achieved to date.

3 Target Validation

The traditional progression of drug development through target validation in preclinical models that express phenotypes plausibly related to the human disease is hugely challenged by most of the major diseases of the brain. Concepts for preclinical analogues of neuropsychiatric disorders with complex behavioral phenotypes (e.g., schizophrenia) and the validity of models for other major diseases including the chronic diseases of late life and those involving slow, progressive neurodegeneration are limited by differences in biological context and environment. New strategies for drug development are needed.

Preclinical models still provide powerful tools for detailed study of specific biological mechanisms believed to contribute to disease. With these models, pharmacological fMRI endpoints can be related to the underlying molecular changes in ways that both validate interpretation of the imaging endpoints and establish a framework in which they can be used to infer the dynamics of molecular pathogenic events. For example, the acute effects of NMDA receptor antagonism with ketamine were mapped in the rodent, demonstrating a pattern of cortico-limbic-thalamic activation and establishing a relationship between specific cognitive systems and the pharmacology [23]. Similar functional effects also were seen with other antagonists against the same target [24, 25], further confirming the specificity of the systems modulated. A framework for interpretation of these results was able to be provided by convergent studies using 2-deoxyglucose autoradiography [26] as an index of presynaptic activity, along with single unit electrophysiological recording and immediate early gene expression [27]. Analogous pharmacological fMRI experiments conducted in human studies provided mapped homologous systems in humans and to relate the pharmacology to the associated thought disorder and disturbance of consciousness in turn [28]. While indirect and insufficient alone, these clinical studies together provided important information supporting target validation of NMDA receptors for psychotic disorders; the "bi-directional" translational approach also supported the potential relevance of this preclinical pharmacology for understanding a form of human psychosis.

An exciting, emerging extension of this approach applies structural MRI and pharmacological fMRI measures together as *endophenotypes* in testing for heritable quantitative traits [29]. Consider, for example, a complex genetic disease such as schizophrenia, which shows a heritable phenotype with variable expression. Both structural

and functional differences can be defined relative to the healthy brain. The concept of the endophenotype is that their *forme fruste* are heritable and can be identified in people even without clinical expression of the disease or trait. To the extent that this is true, the imaging endpoints themselves can be used as outcome measures in searches for genetic or other factors that may contribute to the disease. An endophenotype-based target validation approach also may bias detection towards causative rather than simply (possibly incidental or nonspecific) associated features. Candidate genes *DISC1*, *GRM3*, and *COMT*, which are associated with altered hippocampal structure and function [30], glutamatergic fronto-hippocampal function [31], and prefrontal dopamine responsiveness [32], respectively, all have been related to imaging endophenotypes for schizophrenia in this way.

The concept of fMRI endophenotypes strengthens the rationale nosological reclassification of disease in terms of shared neurobiological system dysfunction. Applications of fMRI approaches that define neurobiological bases for general cognitive processes (such as, in the context of psychiatric disease, motivation, or reward) facilitate more holistic views of targets that may be relevant to more than one disease. For example, fMRI approaches have contributed to the current appreciation for neural mechanisms common to addictive behaviors across a wide range of substances abuse states. Studies of cue-elicited craving have defined similar activities of the mesolimbic reward circuit in addictions to nicotine [33], alcohol [34], gambling [35], amphetamine [36], cocaine [37] and opiates [38].

Combination of pharmacological fMRI with positron emission tomography (PET) receptor mapping can be used to relate systems-level dysfunction directly with the molecular targets of drug therapies in ways that enhance target validation for new pharmacological treatments faster and more cheaply than conventional clinical designs allow (see, e.g., [39]). In another example, a combined PET D3 receptor availability and resting-state pharmacological fMRI study provides a paradigmatic example of the way in which modulation of both target and system contributes to better defining fundamental mechanistic relationships between different symptoms [40]. First, D3 receptor availability was assessed in the ventral tegmentum/substantia nigra in healthy subjects using PET with the D3/D2 selective radioligand, [^{11}C](+)-4-propyl-9-hydroxynaphthoxazine ([^{11}C]PHNO). Differences in receptor expression and basal dopamine release determine binding of the [^{11}C]PHNO, which varied across subjects. A resting-state pharmacological fMRI study was conducted simultaneously. Parametric variation of the resting-state pharmacological fMRI functional connectivities with D3 receptor availability measured by PET showed that low midbrain D3 receptor availability (reflecting dopamine release) was associated with increased connectivity between orbitofrontal cortex (OFC) and brain networks implicated in cognitive control and salience processing. The results together further validated dopamine D3 receptor signaling as an important modulator

of systems underpinning human goal-directed behavior, while highlighting differentially modulated interactions between OFC and networks implicated in cognitive control and reward.

With confidence in the relationship between a pattern of brain functional network activation and behaviors of interest, the former can be used as a clinically relevant biomarker for target validation. One of the first demonstrations of this was with the modulation of hippocampal activation with a working memory fMRI task based on allelic differences in a *BDNF* gene polymorphism [41]. This provided early evidence in humans supporting target validation of the TrkB receptor agonism for the treatment of cognitive symptoms associated with synaptic plasticity [42]. A different example illustrating how such studies can be used for decision making in drug development was provided by an imaging experimental medicine study linking to a PET receptor occupancy of a highly specific μ-opioid antagonist, GSK1521498, to pharmacological fMRI modulation of brain activation associated with palatable taste stimuli [43]. This allowed a first demonstration that salience and reward systems relevant to food intake were modulated by the target, suggesting the potential of antagonists as appetite suppressants, an inference supported by a later, larger Phase IIa study with a direct behavioral endpoint [44].

4 Patient Stratification

A critical issue in early drug development is to establish an appropriate level of confidence in the potential of a new molecule to become a therapy. One way in which this can be done is by better controlling for the substantial variations in therapeutic responses between individuals in early-phase studies. As well demonstrated in oncology [45], stratification of patients based on specific disease characteristics can enable more powerful trial designs [46]. Consider, hypothetically, the difference in outcome of trials for a population in which a new molecule has a 50% treatment effect in 20% of patients (giving a 10% *net* treatment effect, i.e., unlikely to be detected) relative to that in a stratified population enriched so that 70% are responders (a net 35% treatment effect). By predicting potential responders, imaging also can suggest ways of best selecting optimal indications for new molecules. To the extent that the enrichment is successful and any new pharmacological activity being evaluated is detectable, clinical trials may demonstrate molecule effects with fewer subjects exposed. This can be of special value in early Phase II trials when safety data is limited and the focus is on internal decision making.

An early application of imaging based stratification is expected to be for enrichment of populations for clinical trials in diseases such as Alzheimer's disease for which there is considerable phenotypic overlap between different disorders manifesting in the same population (e.g., dementia and late-life depression). The posterior cingulate and

hippocampus show high functional connectivity in resting-state fMRI [47] and form the core of a so-called "default mode" network [48]. Decreases in default mode resting-state fMRI connectivity distinguish Alzheimer's patients from healthy subjects and can distinguish patients with mild cognitive impairment who undergo cognitive decline and conversion to Alzheimer's disease from those who remain stable over a medium term follow-up period [49, 50]. Distinct patterns of resting-state fMRI may distinguish patients with Parkinson's disease, for whom reduced resting state functional connectivity from the basal ganglia was reported [51]. Together, these findings suggest that resting-state fMRI (conducted in conjunction with other structural imaging measures), could be used to enrich trials for early disease modification of Alzheimer's disease.

Establishing fMRI measures for stratification of patients [52] also ultimately could aid in establishing prognosis and in patient management. Where alternative treatment approaches are available that have potentially significant individual variation in response across a population, selection of the optimal treatment for an individual patient could be assisted by fMRI (*personalized medicine*). For example, with depression, treatment responses are highly variable, e.g., only about 70% of patients respond well to a given antidepressant [53]. Higher BOLD signal in the amygdala with a simple task fMRI may be predictive of subsequent treatment response [54]. Multivariate fMRI responses that change with treatment in depression also have been proposed as candidate pharmacological fMRI markers, e.g., signal change in the ventromedial prefrontal and anterior cingulate cortices [55] or modulation of cortico-limbic functional connectivity [56].

In similar ways, there is a potential for integrated structural MRI and verbal task fMRI to distinguish people with prodromal schizophrenia from phenotypic mimics [57]. Network based analyses provide evidence for a continuous spectrum of psychosis from healthy variants to disabling expressions of schizophrenia [58]. Brain functional measures distinguishing abnormal network functions ultimately may provide more meaningful approaches to the classification of neuropsychiatric diseases for improved prognosis and for targeting of treatment [59–62], although establishing the robustness of classifiers in terms of longer term clinical outcome will demand standardization of methods and long-term, prospective studies.

Arguably fundamental changes in the understanding of chronic pain as a disease with individual differences in susceptibility have developed in recent years in part as a consequence of fMRI studies [63, 64]. Activity in the posterior insula with nociception provides a link between the subjectively "painful" experiences of pain empathy [65], hypnotically induced pain [66], and recalled pain experiences [67]. Inspired by studies showing a dopaminergic response with anticipation of benefit in Parkinson's disease, nigro-striatal pathways (as well as those associated with endogenous opioid

release) have been implicated in the placebo response in pain and depression [68]. Individual variation in pain vulnerability thus is associated with alterations in wide range brain networks concerned with reward, motivation/learning, and descending modulatory control [69]. Greater functional connectivity between the PFC and nucleus accumbens explains pain persistence, suggesting that the frontal-striatal connectivity mediates the transition from acute to chronic pain; cortical-striatal connectivity explains longer term outcomes of patients with sub-acute back pain [70].

Nonetheless, despite this promise, validation and development of these concepts as clinical tools or for confident use as an enrichment strategy or as a secondary outcome measure in later-phase clinical trials appears stalled by lack of standardization of evaluations and methods for quality control and analysis [4]. A focus on longer term, well powered clinical studies is needed to validate relationships between fMRI measures and disease pathology or long-term clinical outcomes. Confident demonstrations are needed to establish that fMRI or pharmacological fMRI reliably distinguish clinically meaningfully changes.

5 Pharmacodynamics

As the previous section highlighted, applications of pharmacological fMRI to the direct assessment of drug action are expanding. *Pharmacodynamic* data (e.g., testing whether a drug at the chosen dose has an effect on brain function) can be obtained from analysis of brain imaging changes induced by the administration of a drug. The similar intrinsic brain architecture across species can support translational proof of mechanism studies with comparisons of endpoints from preclinical and imaging-supported Phase I studies using similar methodologies [71]. Additional information can come from correlation of brain activity with behavioral effects of drug administration [72] (Fig. 2) or with characterization of the way in brain activity associated with a probe-task is modulated by a drug [73–75]. This information can inform clinical dose-ranging studies. As noted earlier, correlations between fMRI measures of brain functional system response and drug receptor or receptor occupancy measurements by PET are possible [39, 43, 76]. The last, more recent study [43], demonstrated additionally how integration of time-receptor occupancy data from PET with fMRI measures can differentiate the distinct pharmacologies of different antagonists.

In some situations, by providing a measure of *endophenotype* responses, pharmacological fMRI can define effects of treatment in populations too small for behavioral effects to be discerned or where usual clinical measures are simply insensitive to drug effects [77–79]. In the simplest application, modulation of brain activation in functional anatomically plausible regions after dosing with

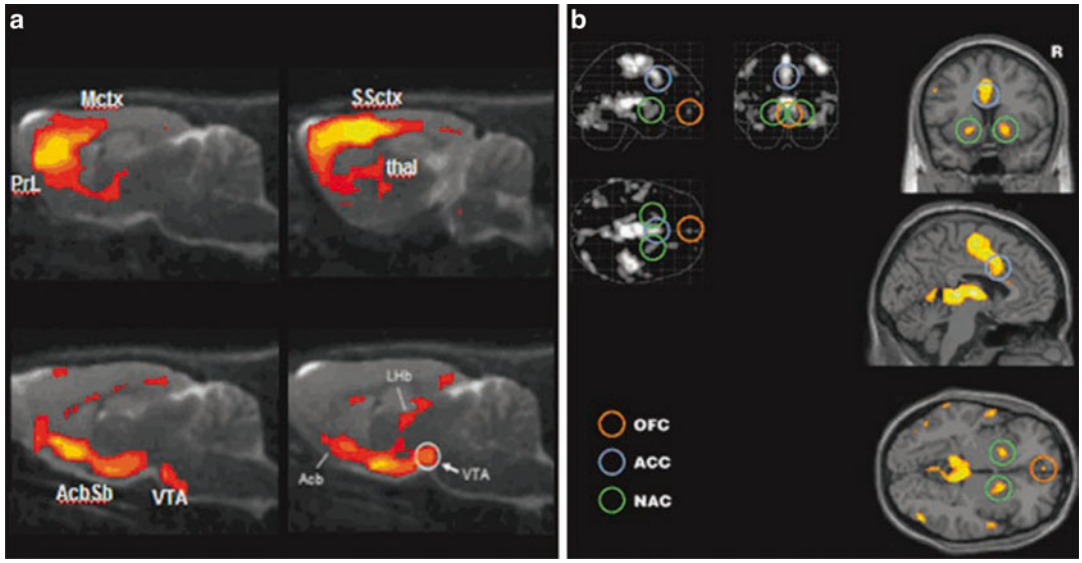

Fig. 2 Pharmacological fMRI can be performed in both animals and humans to assess correspondences in tests of mechanisms. (**a**) Pharmacological fMRI results with metamphetamine challenge of a rodent, identifying major regions in the monamine network as sites of direct or indirect action (*Mctx* motor cortex, *PrL* prelimbic medial prefrontal cortex, *thal* thalamus, *SSctx* somatosensory cortex, *AcbSh* shell of the nucleus accumbens, *VTA* ventral tegmental area) (Images courtesy of Dr. A. Bifone, GSK, Verona). (**b**) A similar pharmacological fMRI experiment with acute amphetamine infusion in human subjects performed using "mind racing" as a behavioral index of drug effects identified comparable elements of the core response network (*OFC* orbitofrontal cortex, *ACC* anterior cingulate cortex, *NAC* nucleus accumbens)

candidate molecule simply to provide supportive evidence for relevant direct CNS activity. A retrospective case study of NK-1 receptor antagonists for chronic pain proposed that early decisions based on fMRI measures could have anticipated the later failure of clinical trials [80]. However, a potential risk of such entirely pharmacological fMRI-derived pharmacodynamics markers is that they may not be specific for (or predictive of) clinically relevant changes.

One way of minimizing this risk is to frame the measures in terms of important disease symptoms based on the relationship between fMRI measures and individual symptoms. Mechanistic plausibility is suggested by the extent to which changes in the associated networks have been independently related to clinically meaningful symptoms. An illustration of this is provided by the way fMRI has been used to dissect the *subjective experience* of pain into anatomically distinct activities of different functional systems (including arousal and the somatosensory and limbic systems), the precise pattern for which may vary for an individual depending on context, mood, and cognitive state [64, 81].

As highlighted in the introduction to this review, imaging has the potential to bridge directly between preclinical and clinical studies [2]. While many behaviors cannot be translated across species, functional-anatomical correlations allow direct drug responses

elicited in the brain for translation of underlying neurobiology. For example, pharmacological fMRI experiments in which unstimulated brain responses to acute compound challenges can be used to define brain regions in which activity is modulated by the same compound in animals (Fig. 2). Preclinically, these observations can be linked to results from more invasive studies, e.g., direct measurements of neurotransmitter release that distinguish direct and indirect effects of the compound [82]. Similar observations of drug modulation of brain activity can be made in human volunteers, providing a way of confirming mechanism (Fig. 2) [72]. State-dependent modulation of these regions can further contribute to this [83]. By relating plasma concentrations to brain responses, similar approaches could be used to define dose, for example. fMRI can address the need for evaluation of receptor agonists, partial agonists, and inverse agonists, as well as antagonists. Even when a receptor targeted radioligand is available, PET methods generally will not be informative with the former classes of agents [84].

However, caution is needed in the confidence with which fMRI endpoints are interpreted. There are two distinct validation issues that must be addressed. First is the "proof of biology" based on demonstration that the biological change being measured is related to the relevant target engagement. Second is the "proof of concept" that the biological change has relevance for clinical outcome [9]. Relationships seen with the natural history of the disease should not be assumed to hold after therapeutic modulations [85]. Testing for any changes in this relationship with pharmacological modulation is important to ensure that the biomarker remains plausibly related to a clinically meaningful outcome.

In general, validation of a candidate biomarker's surrogacy involves the demonstration that it possesses the properties required for its use as a substitute for a true endpoint. A surrogate can be used at the individual subject level when there is a perfect association between the surrogate and the final endpoint after adjustment for treatment. This criterion essentially requires the surrogate variable to 'capture' any relationship between the treatment and the true endpoint, a notion that can be operationalized by requiring the true endpoint rate at any follow-up time to be independent of treatment, given the preceding history of the surrogate variable [86].

6 Current Limitations and Some Future Extensions of Pharmacological fMRI

Although there is real promise for pharmacological fMRI, there are major general challenges to meaningful, quantitative interpretations of measures that need to be considered in planning applications. A first challenge is to distinguish disease or pharmacodynamic effects on hemodynamic coupling from those on neuronal activity and metabolism [11]. Some limitations to interpretation of the BOLD response can be addressed with use of complementary forms of MRI

contrast. For example, direct measures of brain blood flow can be made using noninvasive "arterial spin labeling" MRI methods and the BOLD signal can be calibrated as a measure of local oxygen extraction for quantitative MRI [87]. However, even without this uncertainty, the relationship of blood flow changes to modulation of presynaptic activity can change with physiological (and, potentially, pharmacological) context. Even the relative direction of relative activation in disease states may be difficult to interpret precisely. For example, reduced activation may reflect brain functional impairment [88] or improved efficiency [89] in different contexts. Experimental designs need to recognize this uncertainty and incorporate elements that allow meaningfully specific interpretations, e.g., by studying dose–response relations, parametric activity relationships and behavioral correlates [90]. A more direct approach is to link pharmacological fMRI with electrophysiological measures [91].

General validation of methods to enable their wider use will depend on standardization across sites, reliability and repeatability, and the development of validated quantification methods, ideally largely automated to minimize needs for harmonization of user training. Practical considerations also need to be address to enable integrated use of the most accurate and efficient combination of markers and optimization of costs for the clinical trial environment [92]. Greater openness and sharing of data would be an important enabler of this. These steps, while still not yet part of routine practice in the academic laboratories in which advanced clinical imaging is most often performed, need not stifle innovation, which can progress in parallel, but is essential of translation of this promising method as a major tool for drug development is to be achieved.

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