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What is the value of human FMRI in CNS drug development?

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Functional neuroimaging has the potential to improve the decision-making process in the development of new drugs. With the high cost of failure of compounds in later stages of development, there is a need to establish, early in man, reliable measures of drug activity and efficacy in the brain. Functional magnetic resonance imaging (FMRI) is a tool for serially examining normal and pathological brain function at the systems level. FMRI is helping us to understand therapeutic mechanisms and can provide clinically relevant markers of disease responses to drugs. An analysis of the value of FMRI to aid decision-making requires an appreciation of the techniques and their validation, a task that has begun and which necessitates an investment of its own.

Introduction

There is a discrepancy between the high spending levels in drug discovery and development and the comparatively small number of effective compounds for CNS disorders reaching the market [1,2]. There is a well-recognized need to cut down attrition rates in the clinical stages of drug development. The earlier in the process this is achieved, the greater the potential resource savings and overall greater therapeutic success across a portfolio. This is especially important given the trend towards personalized medicines and the threat therefore posed to the blockbuster[a] [3,4]. Although stratification of patients is likely to bring improved treatment efficacy, the increasingly smaller target groups bring smaller financial returns. Drug development costs, however, remain essentially similar. Research tools are needed to improve our understanding of CNS disease mechanisms and their modification in treatment and to improve the efficiency of decision-making in early clinical phases, reducing the likelihood of costly failure in phase III.

Although pharmacological functional magnetic resonance imaging (FMRI) is not the only available technique, it is emerging as a candidate for improving the efficiency of the drug discovery and development process, particularly in human studies. The cost of FMRI examination is not trivial; therefore, the widespread adoption of FMRI in drug development will require it to demonstrate penetration of a compound into the brain (central penetration) or clinically relevant markers of disease or treatment-based recovery or safety with a substantially greater sensitivity than currently available readouts, which might be cheaper. Where these improvements are demonstrated, a reduced number of patients can be studied. Careful assessment of the performance of FMRI in this process is still required to establish the real benefits that might accrue across the lifecycle of development of a novel or newly indicated compound. The assessment of FMRI as a tool has begun with some substantial investments from the pharmaceutical industry (http://cic.gsk.co.uk/), including public–private academic collaborations, in-house imaging facilities and the establishment of imaging consortia [5].

What is FMRI?

FMRI is rarely out of the news, being applied to fields of research as diverse as neuromarketing (http://news.bbc.co.uk/1/hi/sci/tech/8569087.stm) and persistent vegetative state (http://news.bbc.co.uk/1/hi/health/8497148.stm). The technique has spread to the point at which many universities have now invested in their own imaging facilities as brain research tools. FMRI can be performed in humans on most newer MRI systems, although

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[a] A blockbuster medicine is defined as being one that achieves annual revenues of more than US$ 1 billion at a global level.

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benefits are seen at higher field strengths (e.g. 3 T), with generally improved sensitivity to detect changes in brain activity.

FMRI encompasses a collection of evolving non-invasive MRI techniques sensitized to the haemodynamic state of the brain that are used to infer changes in neural activity through changes in blood oxygenation, blood flow and cerebral blood volume (Fig. 1). FMRI provides a systems-level view of brain function in humans and animals.

BOLD FMRI

Blood-oxygenation-level-dependent (BOLD) FMRI (Fig. 1) is by far the most commonly implemented method [6,7] for pharmacological and non-pharmacological studies because it provides the best functional image contrast-to-noise ratio. A rapid imaging technique known as echo-planar imaging provides whole-brain measurements with a resolution of typically 3 mm × 3 mm × 3 mm every 3 s. Localized BOLD image contrast arises from the exquisite capability of the brain to control blood flow on a small spatial scale. Increased neural activity results in a local vasodilatation, in which the fractional increase in cerebral blood flow (CBF) is a factor of two, or more, larger than the fractional increase in metabolic oxygen consumption [8–10]. The quantity of deoxyhaemoglobin on the venous side of the local vasculature decreases. Deoxyhaemoglobin, being paramagnetic, distorts the magnetic field from the MRI scanner in and around the blood vessels (capillaries, venules and veins), reducing the coherence and hence the net intensity of the NMR signal from hydrogen nuclei in that area. A reduction of these distortions with increased blood flow increases the signal intensity: the basis of the BOLD effect. The degree of BOLD signal change, or BOLD response, is small, typically 1% of the image intensity in response to a change in neural activity. This varies widely depending on the magnetic field strength, the brain region and underlying physiology or pathology (local blood volume and vascular responsiveness), and the type of stimulation task given to the subject (long blocks or short events).

Perfusion FMRI

Regional CBF measurement with dynamic imaging of bolus contrast agents has been performed for some time [11]. With recent improvements in scanner software and hardware, however, non-invasive (without exogenous contrast) measurements of CBF can be made in a few minutes (Fig. 1), using techniques known generically as arterial spin labelling (ASL) [12]. Blood on its way to the brain is 'tagged' using a radiofrequency excitation pulse. It flows into the brain and water is exchanged with the tissue; the tracer is delivered. The magnetization state of the tissue water is then interrogated with an imaging read-out. The procedure is repeated without tagging the inflowing blood to form a control image, and the difference in regional signal intensity between tag and control image is proportional to CBF [13]. Assumptions are normally made about the transit time for the blood, providing a convenient measure of CBF in ml/100 g tissue/min. These assumptions, however, must be examined where pathology might intervene (e.g. the increase of arterial transit time in stroke or where a pharmacological agent substantially increases the CBF). The functional contrast-to-noise ratio is normally lower for ASL CBF measures than for BOLD FMRI, but CBF offers the advantage of being a physical quantity and less susceptible to physiological alterations, which can modulate BOLD contrast [14,15] and confound its interpretation.

ASL CBF measures provide similar information to gold standard of oxygen-15 PET [16] but without the need for a radioactive tracer. ASL MRI, therefore, is more appropriate for human studies, especially where repeat scanning is beneficial, such as in cross-over studies. To date, ASL CBF measures have been applied in preclinical pharmacological studies [17,18] but are only just making their way into human pharmacological investigations [19–22] (Fig. 1). More widely, the potential of ASL perfusion measures in studying longer term changes in brain activity is now being recognized [23] and will undoubtedly become more important in investigating regional pharmacological activity in the brain. The sensitivity of BOLD FMRI is poor when the changes in brain activity of interest occur over a timescale longer than a couple of minutes because BOLD signal is subject to slow signal drifts. ASL perfusion is less sensitive to such noise and so is more appropriate for measuring haemodynamic changes over the timescale of minutes to days to months [24,25]. ASL perfusion measures, therefore, have the potential to measure long-term changes in local CBF such as those arising from chronic oral dosing.

Brain activity

BOLD contrast probably reflects most closely the input and intracortical synaptic processing of a brain area, rather than its spiking output [26]. This is important to consider when interpreting the pharmacological interventions in FMRI studies. An observed site of altered BOLD or blood flow response might be distant from the binding site. Logothetis [27] has reviewed the limitations of the interpretation of FMRI signal.

The dynamic nature of the BOLD signal has led to two principal manipulations of interest in pharmacological studies. The first is the classical FMRI approach of modulating the response to brief stimuli using a pharmacological agent. There are many examples of this; for example, the use of pain signals to demonstrate the time course of pharmacodynamics of an analgesic in the brain [28]. The second is the newer field of resting-state FMRI [29]. In BOLD and ASL signals, the brain exhibits long-range temporal correlations in the absence of an explicit task being performed by the volunteer (e.g. left and right motor cortices) [30]. On the basis of what we know about regional specialization of function, the areas in which BOLD signals co-vary in time seem to be robustly organized into plausible functional networks (e.g. visual, sensory motor [31] and one termed the 'default mode', which seems to be more active in the absence of a cognitively engaging task [32]). The strength of the temporal covariation is commonly interpreted, perhaps somewhat hopefully, as indicating the strength of functional connectivity. This has opened the way for pharmacological modulation of this property and the interpretation of drug effects on the communication between brain regions [33].

There are many pitfalls in the evaluation of FMRI data [15]. The application of what are normally arbitrary statistical thresholds – although important for rigour – arguably places too much importance on the apparent presence or absence of 'activity', which could lead to over interpretation when using results for decision-making in the development pipeline. In addition, in a pharmacological study, the molecular interactions of the compound might intervene in the signal transduction process, disrupting our ability to interpret

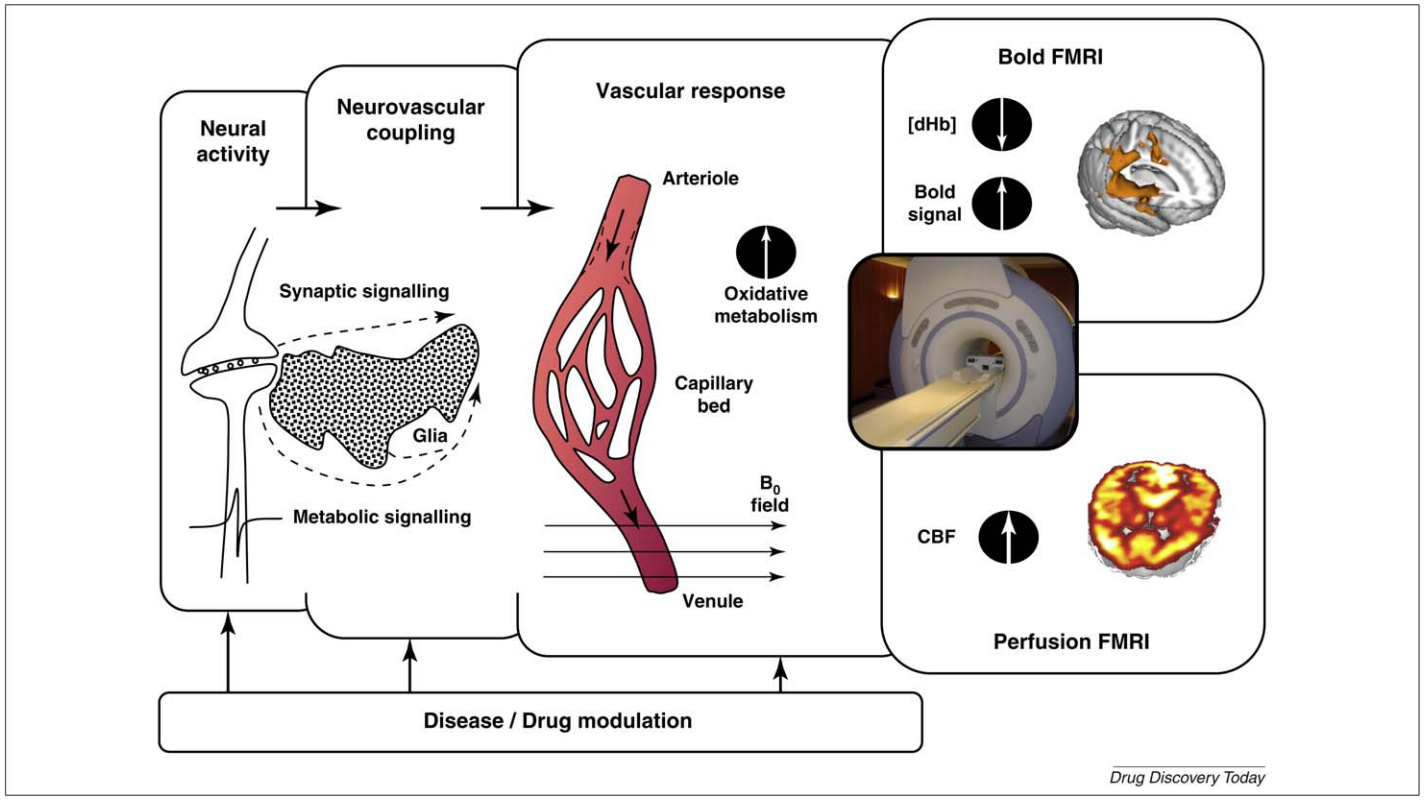

FIGURE 1

Steps in the generation of the BOLD FMRI signal. Alterations in neural activity demand more blood flow, resulting in a net decrease in venous deoxyhaemoglobin and an increase in MRI signal: blood-oxygenation-level dependent (BOLD). The cerebral blood flow (CBF) increase can also be detected directly and non-invasively using arterial spin labelling FMRI. A drug might influence the neural activity, signalling to the blood vessels or the vascular responsiveness of the brain region under examination.

BOLD signal changes as being a faithful representation of neural activity. This can occur through drug-induced changes in neurovascular coupling, vascular reactivity and/or dynamic alterations in the basal physiological (oxygenation) state at the global or local level. We and other groups are developing strategies to improve the specificity of FMRI in measuring drug-induced changes in neural activity. Such strategies need to be tested for each class of compounds under investigation. They include quantification of drug-induced changes in regional vascular reactivity [34], cerebral perfusion [35], altered components of physiological noise [36], metabolic oxygen consumption [20] and concurrent measurements of electrophysiological (electroencephalographic, or EEG) activity to compare with the haemodynamic (FMRI) response [37]. Simultaneous EEG-FMRI is particularly appropriate for examining coupling relationships between fast (millisecond-timescale) synaptic currents, measured at the scalp, and the highly spatially resolved (millimetre-scale) vascular BOLD FMRI response. The marriage of EEG and FMRI might provide more sensitive and specific markers of drug effects on receptor groups by supporting changes seen in FMRI as originating from alterations in synaptic currents.

Uses of FMRI

To make efficient and realistic use of FMRI in drug development, it is important to understand what it can and cannot offer. It would be unfortunate for the opportunity to exploit the true value of the technique to be missed through disillusionment arising from the dashing of false hopes. FMRI is likely to have a well-focussed and important role at specific stages of drug discovery and development (Fig. 2).

Early stages

Before the introduction of a drug, FMRI can improve our understanding of the normal function in animals and man of the network of brain regions (or circuits) believed to be related to the disease impairment. In pain, for example, FMRI has shed much light on the cortical and subcortical networks engaged in pain processing [38], providing the foundations for new neuroanatomical and hence neuropsychological hypotheses for treatment interventions. In a similar manner, the characteristics of disease models can inform us about potential disease processes and suggest relevant imaging markers for them (e.g. sensitization in neuropathic pain [39]). In the preclinical stages, FMRI can be combined with more invasive measures to aid in target selection, providing some early indication of a relevant pharmacodynamic effect and, by extension, lead optimization.

By virtue of the haemodynamic origin of the FMRI signal and the brain-network-based information that it reveals, FMRI is probably a closer reflection of behaviour and the associated interacting streams of information processing than it is the receptor distribution associated with a specific target. FMRI is likely to be sensitive to changes in brain activity downstream of the direct site of action, engaging multiple neurotransmitter systems, as well as potentially at that site, where it might be associated with a metabolic demand of binding. Although this property of FMRI signals results in

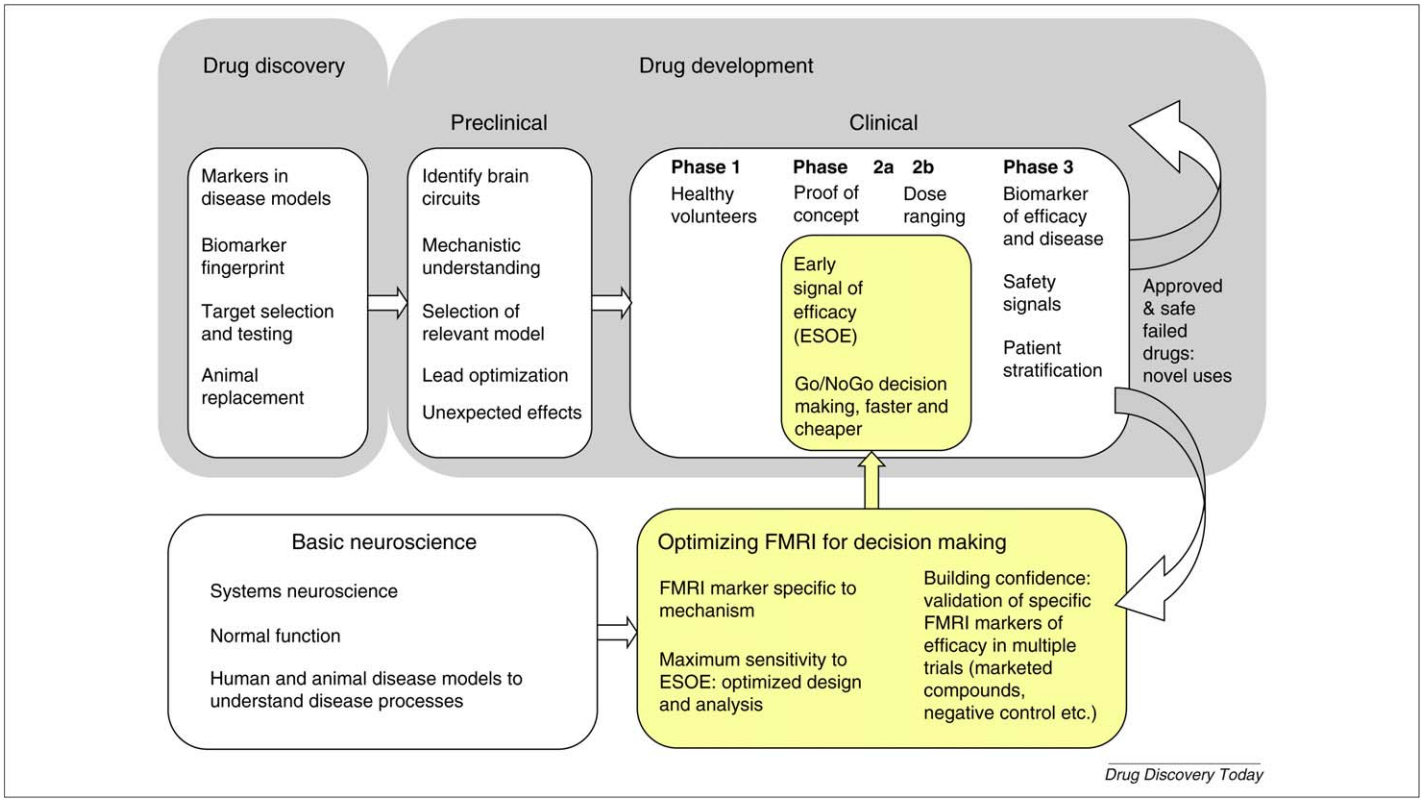

FIGURE 2

The roles for FMRI in the drug development process. The highlighted area indicates the role of FMRI early in the process in man to produce signals of efficacy and central penetration. One key aim of the use of FMRI is to assist in go–no-go decision-making.

reduced specificity to different target receptors, it does provide a translational systems-based tool to compare the effects of a drug on both animal and human. Translation from animals to man can provide reassurance of drug activity on the desired system and might promote replacement of animals with early studies in small cohorts of human volunteers. Conversely and more innovatively, translation from man back to animals could offer imaging measurements with which to refine the relevance of the animal model to the human condition and its treatment [40]. In preclinical models, FMRI also has the potential to indicate unexpected effects on brain systems, in drugs targeted centrally or indeed at the periphery, with a potential future treatment role or safety implication.

One of the key challenges in the early stages of drug development is to demonstrate some action of the compound in the CNS or central penetration and central activity. Although PET offers a direct approach to examining receptor binding, PET ligands might not be available for the compound in question. The haemodynamic nature of FMRI techniques means they cannot unequivocally distinguish between central action and the central consequences of a peripheral action of a compound; however, they might provide some additional confidence in making this distinction when combined with information from other sources (e.g. behavioural studies). ASL perfusion measurements, we believe, are likely to become more important in early studies in man in establishing central penetration (crossing the blood–brain barrier). Where a drug alters neural activity as a consequence of receptor binding or other activity, vascular tone, or metabolic activity, this is likely to result in a modulation of CBF. Blood flow is coupled to neural and metabolic activity. Therefore, the demonstration of a local change in CBF in response to a single dose of a compound in a functionally plausible network of brain areas at the most basic level would indicate a probable central drug effect, whether that be vascular, neuronal or metabolic, and provide some guidance on the choice of dose.

Clinical biomarkers

FMRI would be most useful as a sensitive indicator of pharmacological responses to a therapeutic intervention [1,41,42]. To have the greatest value in decision-making in the drug development process, FMRI needs to index changes in clinically relevant patterns of brain activity that can be mechanistically related to the disease process or treatment effect. At that stage, FMRI would be able to validate novel drug targets and predict drug responses, with a concomitant important contribution to gaining regulatory approval. Despite certain applications making good progress in the pharmacological FMRI field, such as psychiatry [43] and pain [44], FMRI has not yet yielded extensively validated biomarkers with a predictive value demonstrated in novel compounds. Most research effort has focussed on investigations with well-characterized licensed compounds. The lack of work in evaluating novel compounds is partly a question of time and the recency of the technique. We draw an analogy between the role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in cancer trials and the role of FMRI in drug discovery. DCE-MRI has become a well-used marker in the cancer field for examining angiogenesis. It is used in early clinical trials of anti-angiogenic compounds, in which it provides evidence of efficacy and dose-dependent responses to treatment [45]. FMRI, with further validation of its role, might prove equally useful in clinical trials in neurology and psychiatry.

An FMRI biomarker might predict clinical benefit or harm and could be in the form of a fingerprint of altered brain activity in response to the therapy [40,46], taking advantage of newer multivariate classification analysis techniques [47] rather than the more traditional univariate image voxel-wise or region-of-interest based analysis [48]. FMRI biomarkers and surrogate endpoints are in the process of being validated by academic and industrial centres. They will need to be validated for each indication and class of compounds to build up experience in interpreting each fingerprint, probably in a multivariate analysis of image data incorporating many brain regions. FMRI is likely to be particularly important in objectively quantifying subjective reports provided by patients with the potential for reducing variability in the data [49]. This is likely to be particularly important in psychopharmacology for psychiatric and certain neurological conditions because of the qualitative nature of self-reports and the potentially poor animal models for these human diseases. FMRI has the advantage of being non-invasive, permitting safe repeat scanning and facilitating cross-over studies with an appropriate washout period, within-subject dose–response investigations and comparisons of different agents. It also offers the possibility of long-term follow-up for treatment markers and safety signals in the late stages of development and post-marketing, particularly when combined with structural MRI markers such as regional atrophy. With a trend towards smaller target patient groups for any given compound, FMRI could also play an important part in stratifying patients to enter developmental trials to maximize the observed beneficial effects. Such an approach could conceivably continue into clinical practice.

The value of FMRI in decision-making

It is clear from the above that FMRI has the potential to be applied at various stages of drug development, but is the information it provides valuable and is the value sufficient to justify the additional costs of performing an FMRI study? One way to address this question is to develop a decision-analysis valuation framework [50], such as in the following example based on the development of a novel drug for treating neuropathic pain.

Because the purpose of the analysis is to quantify the benefit of the incremental cost of the FMRI study, the first step is to set out the development path that would be followed in the absence of an FMRI option. This will form the base case against which a decision to invest in FMRI will be assessed. Typically, the development path consists of a conventional phase I program, followed by a phase IIa 'proof-of concept' study in a highly selected population of pain patients. If this is successful, it will be followed by phase IIb studies to test a wider range of doses and a more broadly defined patient population. If these studies are successful, they will be followed by phase III confirmatory studies, registration and marketing. The evaluation of the base case is performed through a decision tree describing the cost, timing and probability of success of each phase, resulting in a range of commercial value that can be achieved if the drug successfully reaches the market (Fig. 3). Metrics can then be derived from the analysis representing the

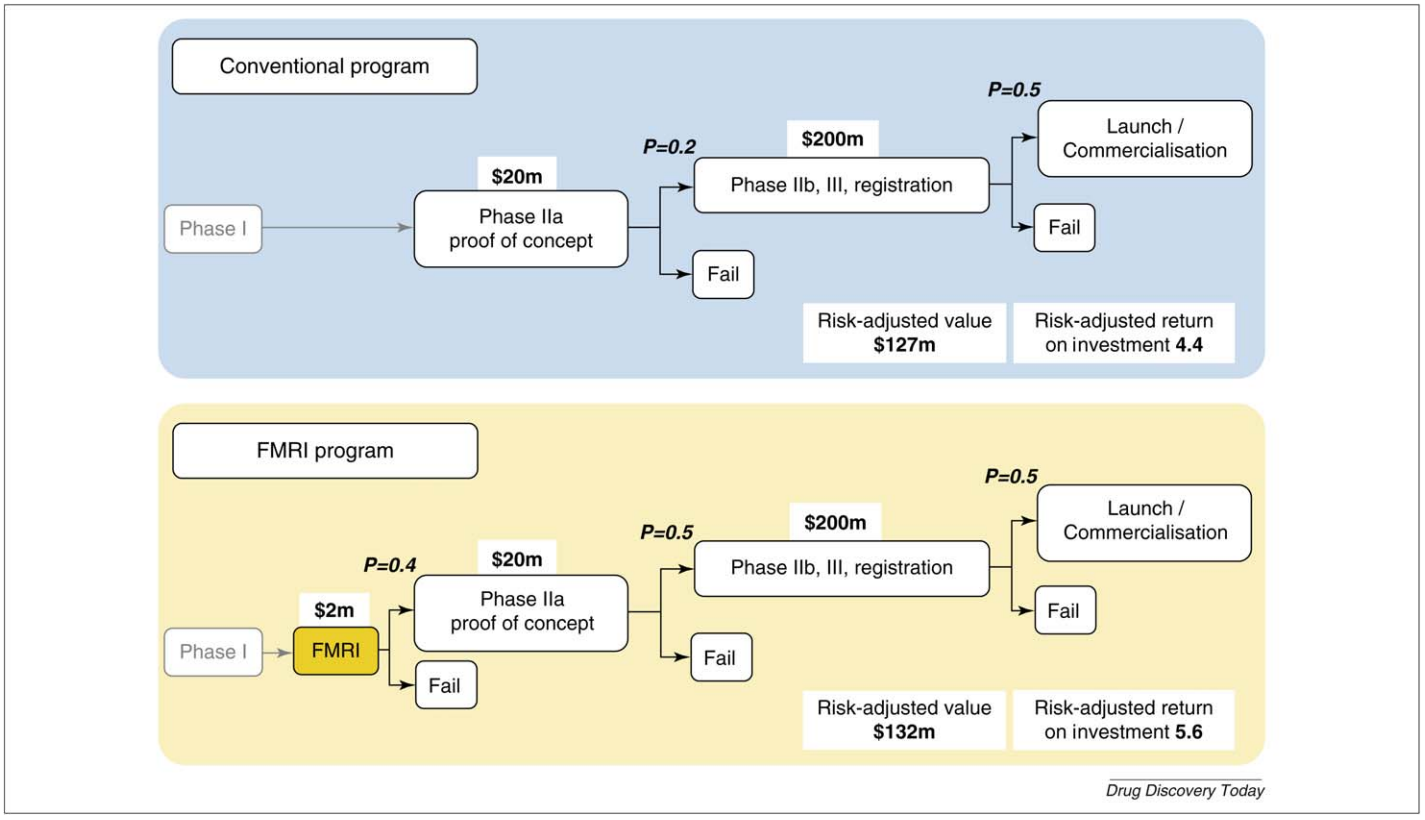

FIGURE 3

FMRI as a simple filter. An example comparison between the 'base case', a conventional drug development program and one including an FMRI filter stage, assuming that phase I has already been successful. We suggest that the use of FMRI might increase the probability of success at phase IIa. Values are after tax.

value of the project (risk-adjusted net present value, or rNPV) and the efficiency (risk-adjusted return on investment).

The rNPV metric (also frequently referred to as 'expected net present value') takes into account both the timing and the uncertainty associated with future cash flows. It is calculated by first taking all future costs or revenues and applying discount factors to convert them into their equivalent in today's money. These discounted figures are then risk-adjusted by multiplying them by their probability of occurrence and summed to give a single figure, which represents the overall value of the project [51]. Calculating risk-adjusted return on investment (also referred to as 'expected productivity index') requires the additional step of dividing the rNPV by the development costs (which are also discounted and risk-adjusted to reflect the probability they will be paid). This gives a ratio that reflects the efficiency of the investment, in which zero is the break-even point and positive figures represent attractive investments.

The next step in the analysis is to determine how the FMRI study will be incorporated into the development program and how the results of the FMRI study will change the pattern of cost, risk and timing relative to this base case. One key observation is that from a decision-analytic perspective, information itself is not intrinsically valuable. Information only has value to the extent that it can influence a decision. In the current example, the best place to insert an FMRI study is before the phase IIa proof-of-concept study, to resolve as much of the efficacy risk as possible for minimal cost. The value of the FMRI study will consequently depend on the decisions that are made on its outcome; if the decision is to proceed to the proof-of-concept study anyway (albeit perhaps with increased confidence in the probable result), then the FMRI study is worthless. An example of this approach is illustrated in Fig. 3, which contrasts the base-case plan in the top panel with an FMRI-based plan below. In the example, for simplicity's sake, it is assumed that the FMRI study has no appreciable false negative rate and, therefore, that the overall chance of reaching the market is unchanged; it is also assumed that the study can be inserted into the development program without being on the crucial path. In an analysis of a real example, either or both of these simplifying assumptions could be relaxed. Also for simplicity, in the example the development steps after proof-of concept are depicted as one block whereas, in reality, each phase has its own cost and associated probability of success.

The final step in such an approach should typically involve sensitivity analysis around the assumptions involved. This can frequently be the most important step of all because it reveals which assumptions are crucial for making the investment decision and which do not matter. The procedure involves systematically varying one of the assumptions (such as the cost or duration of the FMRI study) until the economics no longer favour the FMRI approach over conventional development. From the current example, it should be obvious that the cost of the FMRI study is important, and if it approaches the cost of the proof-of-concept study then FMRI offers no benefit. Likewise, if the FMRI study forms part of the critical path and produces a substantial increase in the length of the drug development program then its benefits will be eroded. Perhaps less intuitively, the value of the FMRI study will also depend on the prior probability that the drug will successfully achieve proof-of concept because the main benefit of the FMRI study is in providing a relatively cheap means of terminating projects destined to fail. For example, to take an extreme case, if a project is certain to succeed then inclusion of the FMRI study simply adds $2m to the development cost, which results in a net

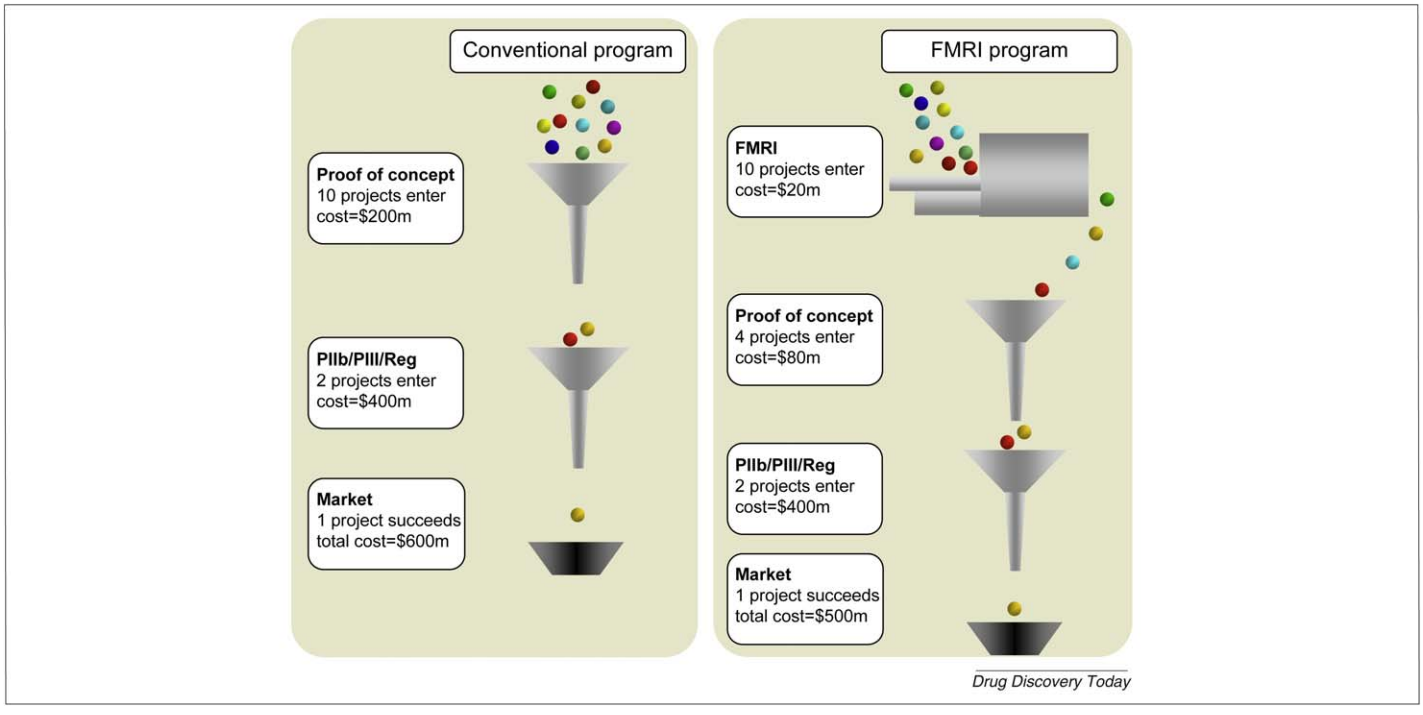

FIGURE 4

The FMRI filter: analysis of costs. In this example, using FMRI can save US$ 100 million per successful project, or an average of US$10 million for each project that completes phase I. These savings could, in turn, be used to fund more projects in the portfolio.

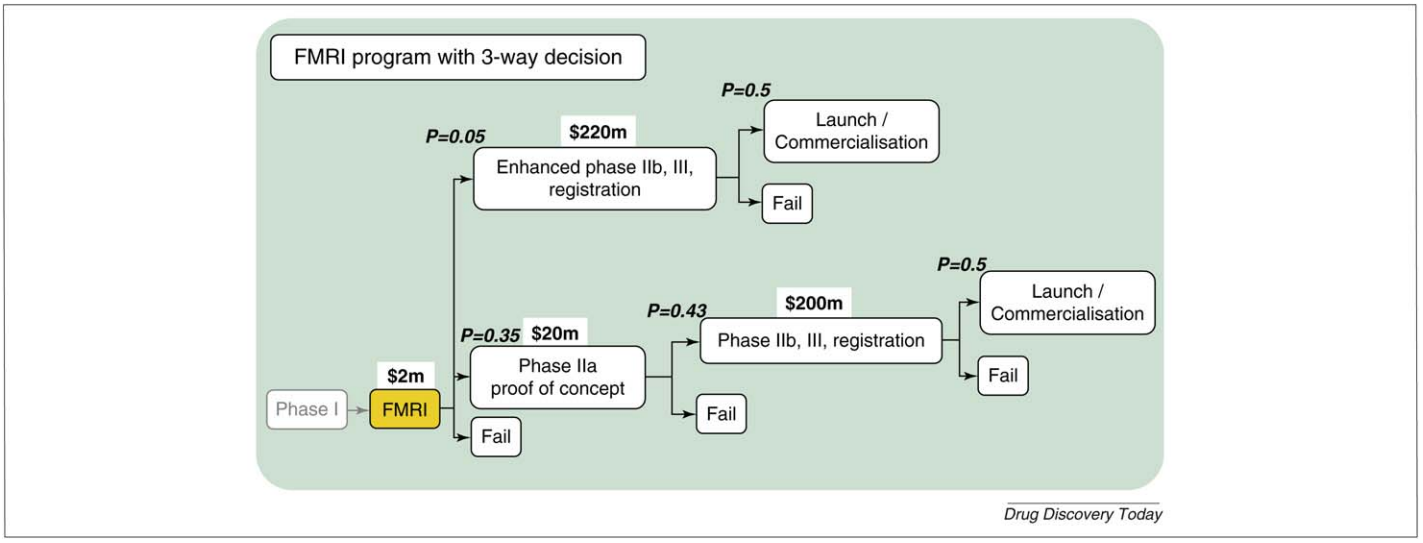

FIGURE 5

FMRI could also support a decision for fast development. Simple success in the FMRI study leads to the full proof-of-concept study, as before (Fig. 3). A superior result in the FMRI study could provide sufficient confidence to proceed directly to phase IIb, theoretically enabling an earlier launch and higher commercial value, which further adds value to the FMRI-based decision. For clarity, it is again assumed here that the FMRI study does not change the overall chance of launch, but in this example it can influence timing.

decrease in the value of the project. The 'sweet spot' for using FMRI will be for projects that have a moderate chance of success. Sensitivity analysis can also help determine acceptable false positive and false negative rates from the FMRI study. Too high a false negative rate will result in missed opportunities through the termination of some projects that could potentially become successful drugs. Too high a false positive rate will simply result in extra cost because more projects destined to be unsuccessful progress to (and fail in) the phase IIa proof-of-concept study. The valuation framework can be used to help decide whether the FMRI study should be incorporated in any particular project and, if so, what success criterion should be used to best trade-off these possible outcomes.

In the current example (Fig. 3), because the FMRI study does not affect time to market or the overall probability of success, a shortcut can be used that simply compares the average or risk-adjusted cost of the two programs. This is easy to calculate, particularly if one applies the thinking to a collection of projects and then tracks their fate through the developmental cascade. Figure 4 shows an example of this, in which use of FMRI saves an average of $10m per project.

In Fig. 5, a more ambitious decision framework is illustrated, in which the FMRI study could support a third branch based on superior results. This could result in the same overall success rate but a faster path to market built upon increased confidence in the magnitude of the efficacy signal. Again, sensitivity analysis can be used to help decide whether such a decision framework truly adds additional value or whether the simpler filter approach is sufficient.

Of course, these examples assume that appropriate FMRI protocols and analysis toolkits are already in place with sufficient validation to support decision-making. Before the application of FMRI to the decision-making process, a decision must have been made to invest in developing the appropriate FMRI protocol itself. That decision would typically take into account the cost and staging of the validation studies, as well as the probability that the validation will be successful. This will be compared with the average value FMRI can add to each compound it is applied to and the probable number of projects that will benefit. The number of projects might be limited if there is a danger that a new technology will emerge that has advantages over the validated model. The organization making this initial investment (or organizations, in the case of a consortium approach) will, therefore, benefit most if they have a broad range of projects to which the technology can be applied, occurring with a fair degree of certainty within a reasonably short time.

Concluding remarks

When a compound is going to fail in the development pipeline, it is desirable to have it fail as fast and as cheaply as possible. FMRI is likely to contribute to this decision-making process, but we are currently still in the phase of validating FMRI for this purpose. More experience of the technique in the context of drug development is needed to provide data to model well the cost-effectiveness of the widespread application of FMRI. This experience is being gained largely through partnerships between industry and academia and is perhaps best done in an industry-wide precompetitive phase [5]. This task is enlarged by the need to constantly challenge the assumptions underlying the measurements at every stage of their development, particularly in applying them to patient populations such as the elderly where the underlying cerebral physiology might be altered. In FMRI, however, we have a tool that has proved very valuable for neuroscience in the past 15 years and when applied strategically in the drug development pipeline could result in substantial cost savings across a portfolio of compounds.

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