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Use of magnetic resonance imaging in pharmacogenomics

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Because of the large variation in the response to psychoactive medication, many studies have attempted to uncover genetic factors that determine response. While considerable knowledge exists on the large effects of genetic polymorphisms on pharmacokinetics and plasma concentrations of drugs, effects of the concentration at the target site and pharmacodynamic effects on brain functions in disease are much less known. This article reviews the role of magnetic resonance imaging (MRI) to visualize response to medication in brain behaviour circuits *in vivo* in humans and assess the influence of pharmacogenetic factors. Two types of studies have been used to characterize effects of medication and genetic variation. In task-related activation studies the focus is on changes in the activity of a neural circuit associated with a specific psychological process. The second type of study investigates resting state perfusion. These studies provide an assessment of vascular changes associated with bioavailability of drugs in the brain, but may also assess changes in neural activity after binding of centrally active agents. Task-related pharmacogenetic studies of cognitive function have characterized the effects in the prefrontal cortex of genetic polymorphisms of dopamine receptors (*DRD2*), metabolic enzymes (*COMT*) and in the post-synaptic signalling cascade under the administration of dopamine agonists and antagonists. In contrast, pharmacogenetic imaging with resting state perfusion is still in its infancy. However, the quantitative nature of perfusion imaging, its non-invasive character and its repeatability might be crucial assets in visualizing the effects of medication *in vivo* in man during therapy.

Introduction

Notwithstanding the large effects of genetic polymorphisms on the pharmacokinetics of drugs [1], individual response is still poorly characterized [2]. For this reason, there is a need for tools that visualize response in brain behaviour circuits *in vivo* in humans. Over the last 15 years, magnetic resonance imaging methods (MRI) have been used to assess the effects of centrally acting pharmacological agents on brain networks *in vivo*, giving rise to the kind of studies collectively known as pharmacological MRI (phMRI, [3, 4]). In parallel with the development of phMRI, imaging methods have also provided biomarkers of genetic variability of relevance for psychiatric disorders [5–7]. In this article, we will focus on the potential importance for the field of pharmacogenomics of the simultaneous investigation of pharmacological and genetic variability with phMRI, and its potential contribution in understanding how the genetic makeup of patients may affect their response to pharmacological therapy. Even if they may never rival positron emission tomography (PET, [8]) in molecular specificity, MRI techniques offer superior temporal and spatial resolution. Furthermore, they are cost-effective, radiation-free and widely available. These properties are essential for the collection of large samples (as required by clinical research or genetic imaging), and for the applicability of these methods in both preclinical models and in patients. For this reason, they may be of use not only in research on pharmacological effects, but also in future applications in the clinic.

A unifying concept underlying both pharmacological and genetic imaging research is that of 'intermediate phenotype' [6, 9], corresponding to the notion of 'endophenotype' of psychiatric geneticists [10, 11]. Endophenotypes are state-independent heritable traits, not visible to the unaided eye but measurable with the

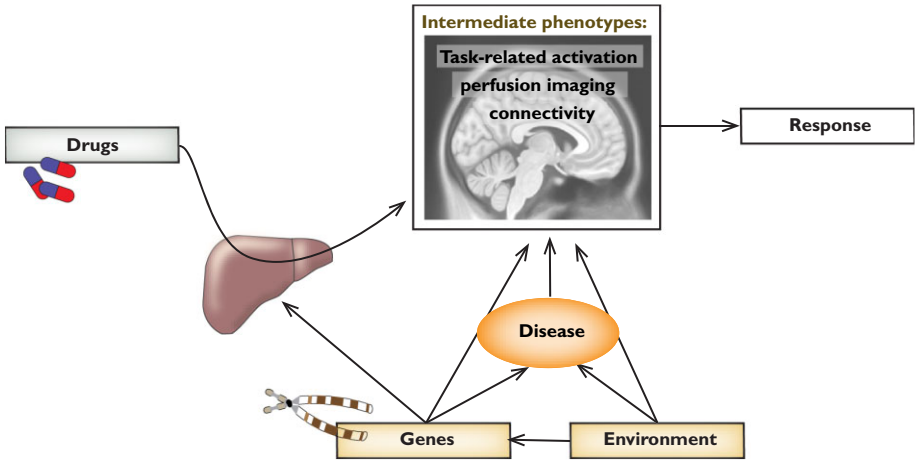

Figure 1

Intermediate phenotypes provided by imaging techniques are biological markers of brain function that may clarify the association between therapy, individual factors, including the genetic makeup, and response. In this article we review mainly the role of task-activated and resting perfusion phenotypes. A third emerging phenotype, connectivity, has just begun to be applied to pharmacological imaging studies in man

appropriate instrumentation, that co-segregate with disorders within families [11]. In contrast, the term intermediate phenotype is typically used in the context of neuroimaging research, where the role of intermediate phenotypes as biomarkers is not restricted to an association with genotype. Intermediate phenotypes are functional and quantifiable biomarkers of brain activity obtained *in vivo* with neuroimaging methods that may provide an assessment of brain function that is closer to the biological substrate affected by brain-related disorders, their treatment or genetic variation (Figure 1). The importance of this notion lies in the relative lack of specificity of symptomatic indices of improvement or remission from psychiatric disorders. Furthermore, by mapping these markers to what is known about brain circuits active during healthy functioning, intermediate phenotypes may provide proof-of-concept models of processes affected by therapy or individual differences. A related notion is that of Research Domain Criteria (RdoC). These are well-defined tasks recruiting fundamental processes, whose systematic investigation has been advocated as key to establish valid diagnostic criteria [12].

A typology of imaging studies of pharmacological and genetic effects

Task-related activation studies

Pharmacological and genetic imaging studies belong into two broad categories, assessing intermediate phenotypes with different properties. In the first type of study, participants are asked to perform a task while in the scanner (task-related activation studies). A control condition allows the identification of the brain structures associated with the recruitment of processes required by the task [13]. Participants or scan sessions are further randomized to treatment with the active agent or placebo to assess the effect of the drug on the neural correlates of the process elicited by the task [4]. For example, this approach successfully demonstrated modulation of the brain response to a painful stimulus under increasing analgesic concentrations [14]. An advantage of this approach is the specificity of the brain function circuits assessed by the task, although the real degree of specificity depends on a careful choice of the task and control conditions (for a critical discussion, see [15]). Because many such circuits may exist, studies of this type are usually guided by previous knowledge on the process that may be affected by the drug, or on the function of the polymorphic gene. Note, however, that the existence of learning or habituation effects in most tasks [16–18] complicates the longitudinal monitoring of the effects of medication.

The physiology and methodological underpinning of the signal in task-related activation studies has been extensively investigated [19]. This signal is based on the blood oxygenation level dependent (BOLD) haemodynamic response [20, 21] and on the tight coupling between brain metabolism and perfusion [22] (here we use the term 'coupling' to refer specifically to the mechanism through which a change in brain function is translated into an MRI signal). The increased glucose consumption accompanying neural activity brings about a vascular adjustment response, which increases blood oxygenation in the involved areas with a latency of 2–3 s. The MRI signal is generated by the different magnetic properties of haemoglobin at different oxidation levels [23]. Task-related differences in metabolism or perfusion

may also be detected with PET techniques or arterial spin labelling (ASL, [24]) that measure the changes of these physiological parameters directly.

Resting state studies

A second approach historically preceded task-related activation studies and was common at the time when PET and related techniques were the only available neuroimaging probe. In this approach, an index of brain function such as metabolism or blood perfusion at rest provides the intermediate phenotype to associate with the effects of the pharmacological agent or to predict response [25]. A possible disadvantage here is the lack of specificity of brain metabolism or perfusion at rest, compared with the former approach. In the absence of compelling hypotheses on the function affected by the drug or the genetic polymorphism, however, this may be an asset. In contrast, task-related activation studies are restricted to testing the modulation of the drug on one neural substrate among many, and one that was specified *a priori*. Furthermore, the signal from metabolism or perfusion at rest is stable over time, making it suitable to longitudinal investigations [26]. More recently, the MRI technique of ASL [24] has been used as an alternative to PET for the assessment of brain perfusion at rest (Figure 2). While as yet less used than task-related phMRI, the coming of age of ASL may greatly expand the type of information obtainable with neuroimaging in pharmacogenetic research [27, 28].

Studies of brain metabolism or perfusion at rest have shown that psychoactive substances affect the brain according to different regional patterns. Neuroleptics, for example, bring about an increase of metabolism and perfusion in the basal ganglia, and a variable degree of decrease in the cortex, especially in the frontal lobes (see [29, 30] for a review of early work, and [31–33] for more recent ASL studies). These differences may be due to the very different receptor profiles of neuroleptics accompanying dopaminergic antagonism [33, 34]. Likewise, comparative studies of brain perfusion at rest of antidepressants with different profiles show different perfusion patterns [35].

While all task activation studies are based on the well-understood BOLD response neurovascular coupling, several mechanisms may be responsible for the rest perfusion changes associated with the administration of an active agent (Table 1). An unfavourable setting is when the mechanism is a direct action on vascular regulation. For example, a serotonomimetic compound may bind to vascular receptors and alter perfusion directly, masquerading as, or obscuring, a neural effect. However, the potential relevance of the effect on vascular tone and its informative value is dramatically different if it is serotonin itself which binds to vascular receptors. Then the study may assess the extracellular availability of the neurotransmitter, for example after transporter blockade [36], or the activation of intrinsic neurovascular regulatory circuits [37], thus providing an indirect assessment of drug activity in the brain. Most neurotransmitters have an effect on the regulation of cerebrovascular tone [37], so that the haemodynamic effect of the drug on vascular regulation through changes in the bioavailability of neurotransmitters [38] replaces the BOLD haemodynamic response as the coupling between stimulation (by the drug) and the signal (perfusion changes) [39]. Validation of this concept comes from studies in laboratory animals showing the dependency of rest perfusion haemodynamic response on lesion of key receptor systems [36, 39–41]. In a third possibility, centrally acting compounds may alter neural activity, thus leading to changes detectable through the BOLD haemodynamic response coupling. For example, in an ASL rest perfusion

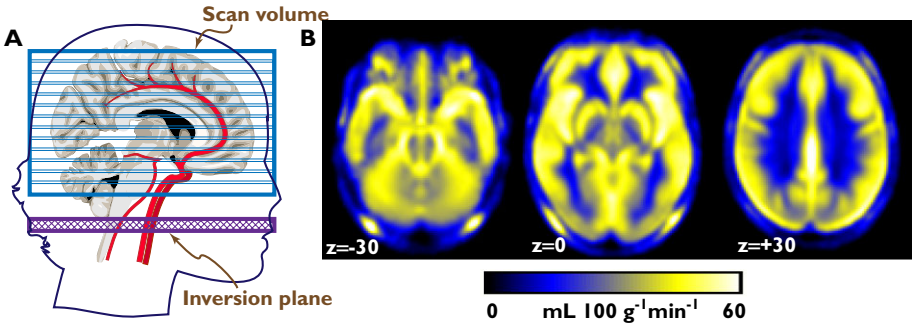

Figure 2

(A) Schematic illustration of the ASL technique. An inversion pulse inverts the spins of the water molecules in the blood in the neck, disrupting the signal from these molecules when they are sampled after reaching the brain. The cerebral blood flow (CBF) is estimated from the difference between two images, one taken with and one taken without the inversion pulse. (B) Regional CBF maps created from the ASL signal, averaged from about 300 hundred individuals. The maps represent transversal slices taken at the level of the midbrain, the thalamus and basal ganglia, and the cerebral hemispheres immediately above the corpus callosum (the coordinates are in Montreal Neurological Institute space). The figure shows that cortical and subcortical grey matter and regions rich in vessels are brighter than white matter and ventricular spaces, reflecting higher regional perfusion values

Table 1
Neurovascular couplings leading to signal changes in rest perfusion MRI

Mechanism	Interpretive model	Representative reference
Direct binding of drug to vascular receptor	Confound, since rarely of interest	Caffeine [60, 105]
Direct binding of transmitter to vascular receptor	Assessment of central transmitter availability or vascular effector activation; assessment of central drug activity	Dopaminergic agents and vascular modulation [36, 40]; changes in dopamine function after nicotine withdrawal [106]
Changes in activity of target cell detected through hemodynamic response	Functional changes across networks	Brainstem nuclei after transporter blockade [35]
Essentially unknown, or a mixture of the above	Detection of signatures or fingerprints of receptor profiles	Cortical modulation of metabolism/perfusion by neuroleptics [42]

study, changes in the brainstem under paroxetine and bupropion were observed that were consistent with neurophysiological changes in the firing rates observed in laboratory animals [35]. A final interpretive strategy takes into account the broad range of receptor affinities of many drugs in clinical use. Because the effects on these receptors might involve any of the previous couplings, sometimes simultaneously, one may view changes in rest perfusion as multi-determined signatures or fingerprints of the receptor profiles of these drugs. An example of the issues tackled by this interpretive model arises in rest perfusion studies of neuroleptics, where the comparison of cortical decrements involves the discussion of notions of atypicality and the associated receptor profiles [32, 33, 42, 43].

Connectivity studies

Recently, a third type of study has emerged based on the estimation of correlations between seed voxels and the rest of the brain ('intrinsic connectivity', [44]), which may be due to vasomotor activity reflecting structural or functional associations between brain areas [45]. These correlation maps are obtained by regressing the signal in each voxel separately on the signal of a predefined voxel ('seed') in data collected with standard BOLD-sensitive techniques. These analyses show that variations of the BOLD signal, not due to changes in activity elicited by experimental tasks, tend to correlate with variations in other specific areas of the brain. These correlation patterns are stable, being qualitatively unchanged at rest and during the execution of a task [46]. Several studies have shown modulation of strength of connectivity by pharmacological agents [47–54] and by genetic variation [55, 56]. However, little is known about the nature of the physiological coupling between pharmacological or genetic variability on the one hand and signal changes in intrinsic connectivity on the other. Because they are usually collected at rest, intrinsic connectivity studies are sometimes assimilated to rest studies. However, no association has been found between mean levels of perfusion at rest and connectivity patterns elicited by common seeds [57]. It therefore appears that intrinsic connectivity and rest activity levels provide information about distinct properties of the brain. This result, however, like others in this field, may be dependent on the seeds chosen to elicit the connectivity maps. Key studies in laboratory animals are starting to investigate the physiological bases of connectivity changes caused by pharmacological agents [58], showing that connectivity analyses may profit from the use of specific seeds located in the subcortical centres most directly affected by the drug.

Methodological issues in interpreting imaging studies of drug effects and genetic polymorphisms

Several issues may compromise the valid interpretation of results in genetic or pharmacological MRI studies, but affect task-related and baseline perfusion studies differently. For the inference in task-related activation studies to be valid, the medication or the genetic polymorphism should not alter the BOLD haemodynamic response mechanism. Furthermore, effects detected in task-related phMRI studies may be caused by the effects of drugs on the vascular tree or its regulation, rather than by changes in the functional activity of neurons [59]. Two well-known cases are caffeine [60–62] and indomethacin [63]. These effects are readily detectable with rest perfusion studies [27], where, as noted above, they constitute a powerful instrument to assess drug activity at target sites [39].

Several observations suggest that results of task-related phMRI are not all due to confounding effects of this nature. In a study measuring both electrophysiological and functional imaging effects, these two measures provided comparable assessments of the cortical response to stimulation [64]. Medication-induced changes were present in both measurements, indicating that changes in the functional imaging signal reflected changes in the response of cortical neurons, not in the BOLD haemodynamic response mechanism through which neural activity is detected.

Another indirect line of evidence for the validity of task-related phMRI is given by the sparseness of task-related activation effects, in contrast to vascular effects that may be expected to be distributed across large regions. The same argument may be applied to regionally identifiable effects in rest perfusion phMRI. For example, rest perfusion under serotonin transporter inhibitors is characterized not only by diffuse cortical decrements that are consistent with the vascular activity of serotonin [65], but also by regionally specific effects [35, 66].

A limitation of the BOLD approach in task-related activation studies lies in the non-quantitative character of detected signal changes. Hence, it is impossible to tell if changes in signal amplitudes associated with the task are due to changes in the activation or in baseline levels. Several laboratories have demonstrated that reduction in baseline perfusion levels is associated with higher activation responses [67–69]. This difficulty is overcome by quantitative approaches such as ASL that can provide baseline measurements in task-related studies. However, ASL currently suffers from lower signal : noise ratio and slow acquisition times, which makes it unsuitable for the detection of fast activity changes of some task-related studies [70].

Pharmacogenetic MRI studies

Because of differences in the intermediate phenotype they expose through different couplings, task-related activation phMRI and rest perfusion phMRI have different applicability. The former can identify a brain behavioural circuit that may be affected by neuro-psychiatric disorders, and therefore provide an index of change related to a cognitive or emotional process affected by pathology or therapy. The latter is closer to the physiological substrate of centrally active agents, and may be more appropriately used to assess their biological activity. This broadly suggests the suitability of task-related activation phMRI and rest perfusion phMRI for the investigation of individual variation in pharmacodynamic and pharmacokinetic factors, respectively.

Pharmacogenetic MRI studies with focus on pharmacodynamics

Reflecting the state of research in phMRI, most pharmacogenetic studies conducted to date have adopted a task-related approach, and targeted the neural substrates of specific processes affected by medication and pharmacogenetic polymorphisms to identify the pharmacodynamic mechanisms underlying individual variation in response (Table 2). Most efforts have been directed to study the effects of dopaminergic agonists and antagonists on intermediate phenotypes exposed by cognitive function. In contrast, pharmacogenetic imaging studies of affect and antidepressants are in the early stages [71].

The study by Mattay *et al.* [72] was among the first to demonstrate the genetic modulation of the response to a centrally active drug on a task-related intermediate

Table 2

Task-related phMRI studies with pharmacogenetic implications

Intermediate phenotype/gene	Drug	Main findings	Ref.
Working memory/*COMT*	Amphetamine	Performance improvement and modulation of working memory network (PFC) in carriers of the high activity allele (see text)	[72]
Working memory + declarative memory/*COMT*	Tolcapone	Performance improvement and modulation of working memory network (PFC) in carriers of the high activity allele	[107]
Working memory/*DRD2*(*C957T*)	Nicotine	Polymorphism modulates changes in ventral associative areas	[108]
Working memory/*COMT*	Nicotine abstinence	Smokers with the high activity allele were more sensitive to withdrawal and had larger effects in working memory network (PFC)	[109]
Reward/*DRD2*(*TaqIA*)	Bromocriptine	Increased ventral striatum reward prediction signal in carriers of the low density D_2 receptor allele	[110]
Reversal learning/*DRD2*(*TaqIA*)	Cabergoline	Increased striatal signal in carriers of the low density D2 receptor allele	[111]
Working memory/*COMT*	Olanzapine	Response in carriers of the high activity allele, and modulation of attentional networks (see text)	[78]
Working memory/*DRD2*(*rs1076560*), *AKT1*, *GSK-3*β	Olanzapine	Epistatic interactions associated with response and attentional networks (see text)	[84]
Working memory connectivity/*AKT1*, *COMT*, *DRD2*(*rs1076560*)	Neuroleptics	Epistatic interactions associated with response and cortical-subcortical connectivity (see text)	[85]
Declarative memory/*AKT1*, *COMT*, *BDNF*	Lithium/valproate addition to neuroleptics	Epistatic interaction associated with response and structural brain changes	[104]
Perception emotional stimuli/*CNR1*	Antidepressants	Association with response paralleled by subcortical signal changes	[112]

D_2, dopamine D_2 receptor; PFC, prefrontal cortex.

phenotype with phMRI. The cortical activation was assessed in participants carrying out a working memory task and receiving amphetamine, a dopamine agonist that increases alertness and modulates attention, and is member of a class of drugs used in the clinic to treat attention deficit hyperactivity disorder [73]. Mattay and colleagues hypothesized that individual differences in the response to amphetamine reflected differences in baseline dopamine tone [74, 75], associated with prefrontal cortex function [76]. They therefore tested the modulation of the effect of amphetamine by the val^{158}-met COMT polymorphism, the drug metabolizing enzyme (DME) that removes endogenous dopamine, on the prefrontal brain circuit known to be associated with working memory function [77]. Homozygous carriers of the high activity COMT allele were characterized by improved reaction times and a decrease of the prefrontal BOLD signal in the working memory task under amphetamine, consistently with a compensation of a lower basal dopamine tone. In contrast, these improvements were not observed in homozygous carriers of the low activity *COMT* allele, whose performance degraded at high levels of task difficulty. The authors concluded that these findings accounted for an increased risk of adverse response to amphetamine in the low activity COMT allele carriers [72].

Following this seminal work, several innovative studies have explored the genetic modulation of the dopamine system under neuroleptic medication. Bertolino *et al*. assessed the working memory intermediate phenotype to locate the mechanism through which the same COMT polymorphism may affect response to olanzapine in a sample of schizophrenic patients [78]. They reported that response to treatment was limited to patient carriers of the high activity allele, and a corresponding modulation of the signal elicited by the working memory task in the prefrontal and parietal attentional network. The authors concluded that the effects of olanzapine on working memory capacity interact with its response profile. The same group extended these results with an in-depth investigation of post-synaptic dopamine D_2 receptor transmission, involving polymorphisms of the dopamine D_2 receptor (*DRD2*, [79]), and of AKT1, a kinase in the signalling pathways of post-synaptic D_2 [80] and in the growth factor-induced cell survival in the developing nervous system [81]. Polymorphism in these genes was previously associated with differences in cognitive performance [82, 83]. They found that interactions between polymorphisms in these two genes were associated with response to olanzapine treatment in schizophrenic patients. In both polymorphisms as in the previous COMT study, the alleles associated with response were those leading to reduced dopaminergic function. They also reported a modulation of the signal in the medial prefrontal cortex by the interaction of these two polymorphisms in an attentional task [84]. These results were confirmed by subsequent work by Tan *et al*. [85], where a sophisticated connectivity analysis traced the effect of AKT1 polymorphism on dopaminergic function in the efficiency of the interactions between prefrontal cortex and striatum in a working memory task. In schizophrenic patients receiving neuroleptic treatment, they replicated the association of D_2 receptor and *AKT1* polymorphism with response in the form of a dose-response effect on cognitive change.

Imaging studies with focus on pharmacokinetics

In contrast with pharmacogenetic studies targeting pharmacodynamic mechanisms, applications of MRI to study genetic variation in pharmacokinetics belong to the future. An issue affecting response is the concentration of a drug at the target site, which may be only loosely related to plasma concentrations due to the existence of anatomical and functional structures such as the blood–brain barrier. Transporters at the blood brain barrier such as the organic cation transporters (OCTs, [86]) display functional polymorphisms that affect the distribution of the drug at the target site and therapy response [87, 88]. Imaging methods are valuable here because they provide a means to quantify changes in function *in vivo*. One approach exploits the vasoactive coupling of rest perfusion phMRI to assess drug activity indirectly, provided that the active compound does not itself alter vascular tone [40]. An alternative, a few phMRI studies have been conducted to estimate the pharmacokinetic curve of the drug in the brain [14, 89–91]. Beyond MRI approaches, PET may be used to assess receptor occupancy [92] or drug distribution at the target tissue, provided that radiolabelling does not alter its pharmacokinetic properties [93]. This listing shows that there are several potential approaches that may be exploited to target the possible effects of genetic polymorphisms on the pharmacokinetics of drugs at their target.

Another important issue for response concerns the activity of DMEs in the brain, a consequence of the common existence of endogenous substrates of DMEs [94]. Psychotropic DMEs, especially those in the cytochrome P450 group (CYP), are expressed not only in the liver, but also in the brain [95, 96], where they may contribute to the local drug metabolism and the local biochemical homeostasis. Many endogenous neurotransmitters and neurohormones are metabolized by CYPs [97], possibly explaining their reported roles in neurodevelopment [98], neuroprotection [99] and behavioural affective traits [100]. In man, variation in brain levels of CYPs among individuals, either through genetics [101] or regulation [97], may contribute not only to differences in drug response [96, 101], but may also explain the reported associations between genetic polymorphisms of CYPs and cognitive function, personality and vulnerability to mental disorders [96]. The importance of these associations lies not only in their intrinsic value in explaining individual variability in vulnerability to affective disorders and risk for

drug-induced neurotoxicity, but also to the fact that many drugs commonly used in the treatment of mental disorders are either metabolized by these enzymes and/or actively inhibit these enzymes in the brain. A comprehensive account of the effects of DME polymorphism on drug effects may therefore be more complex than the one provided by the observation window on plasma concentrations, crossing the distinction between pharmacokinetics and pharmacodynamics.

Two imaging studies have provided evidence on the modulation of brain function by CYP2D6 polymorphism. The first study provided evidence of differences in rest perfusion levels in the brain, primarily affecting the thalamus and the posterior cortical regions [102]. The effect of CYP2D6 polymorphism in the same region was found also in a second study, which used task-related activation in a cognitive and emotional processing task [103]. As would be expected from the influence of baseline levels on task-related activation, task-related activation was larger in the individuals whose genetic make-up was associated in the previous study with lower baseline perfusion.

Conclusion

The joint investigation of genetic and pharmacological variates in a MRI design is still rare, requiring large samples for genetic analysis and sophisticated experimental manipulations for pharmacological treatment. As the recent pharmacogenetic studies on the effects of neuroleptics demonstrate [84, 85, 104], extremely valuable information may be obtained by combining analysis of samples of patients obtained in a relatively naturalistic design with larger samples of healthy participants, genetic databases [85] and biobanks for the validation of genetic polymorphisms and investigation of genetic expression [84].

A conceptual attraction of pharmacogenetic MRI is the triangulation of outcome measures, genetics and intermediate phenotypes, which provides a link with the neurobiological mechanism mediating the effects of medication and genetic polymorphisms on response. Furthermore, since the methods would be available in the clinic, discoveries in research programmes of this kind may be translated to the clinic without the need of additional infrastructure.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. RV received consultancy fees from the BfArM, Bonn. All other authors declare no other relationships or activities that could appear to have influenced the submitted work. This paper was prepared without recourse to extramural funding sources.

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