

Increasing pharmacological knowledge about human neurological and psychiatric disorders through functional neuroimaging and its application in drug discovery

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Functional imaging methods such as fMRI have been widely used to gain greater understanding of brain circuitry abnormalities in CNS disorders and their underlying neurochemical basis. Findings suggest that: (1) drugs with known clinical efficacy have consistent effects on disease relevant brain circuitry, (2) brain activation changes at baseline or early drug effects on brain activity can predict long-term efficacy; and (3) fMRI together with pharmacological challenges could serve as experimental models of disease phenotypes and be used for screening novel drugs. Together, these observations suggest that drug related modulation of disease relevant brain circuitry may serve as a promising biomarker/method for use in drug discovery to demonstrate target engagement, differential efficacy, dose-response relationships, and prediction of clinically relevant changes.

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Current Opinion in Pharmacology 2014, **14**:54–61

This review comes from a themed issue on **Neurosciences**

Edited by **David G Trist** and **Alan Bye**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 8th December 2013

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<http://dx.doi.org/10.1016/j.coph.2013.11.009>

Introduction

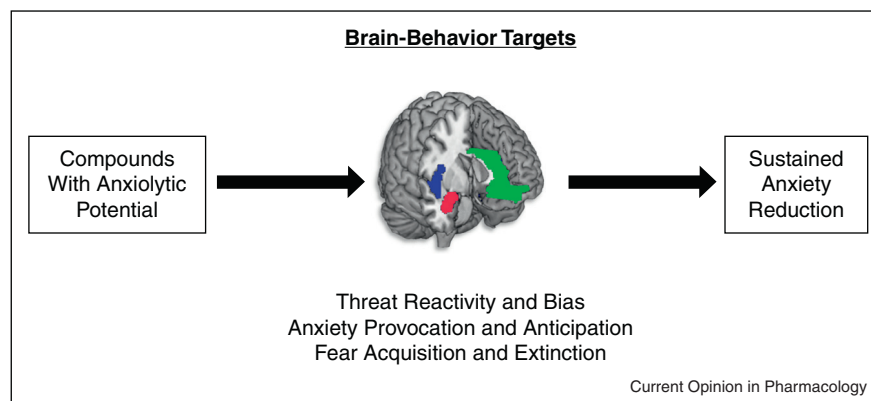
Functional neuroimaging methods including functional magnetic resonance imaging (fMRI) are increasing used as a research method or biomarker in early clinical development to gain greater understanding the *functional* mechanism of action of drugs, the ability of drugs to

modify brain circuits involved in CNS diseases, and as a surrogate marker of drug efficacy. In phases 1 and 2 studies, fMRI and other functional imaging methods are used to demonstrate target engagement, a critical first step in establishing proof of mechanism, and subsequently to demonstrate that a drug can normalise abnormalities in brain activity at rest or in response to disease relevant cues (e.g. emotional cues, food and alcohol) (i.e. proof of concept). While in its infancy, fMRI has also been shown to be useful in demonstrating differential efficacy (i.e. when making a comparison of the drug in development with a gold standard or a competitor drug), as well in predicting long-term behavioural or clinically relevant changes from acute or early responses of the drug on brain circuitry.

It is now well established that fMRI can be used to indirectly probe neuronal activity, through the measurement of Blood Oxygenation Level Dependent (BOLD) activity [1], as a result of changes in deoxyhaemoglobin concentration linked to the metabolic demands of neuronal function. Using advanced techniques in brain imaging analysis, the resultant activity can be quantified at a regional level (i.e. voxel-wise or region of interest analysis) or at a brain network level (i.e. functional connectivity analysis or graph theory) to examine the effects of pharmacological manipulation on neuronal activity in target brain areas or brain networks.

In this review, we provide an overview of the work conducted in a number of CNS disorders including Depression, Anxiety disorders, Schizophrenia and disorders of compulsive consumption (i.e. addiction), where fMRI together with pharmacological challenges have been used to examine the neurochemical basis of abnormal brain activity in disease relevant circuits as well as studies in early clinical development where the efficacy of new drugs have been tested using disease relevant biomarkers of brain circuit activity. These studies suggest that functional imaging methods like fMRI are sensitive biomarkers of abnormal regional or brain networks activity in CNS disorders and can add value in early clinical development to examine key drug discovery questions related to target engagement, differential efficacy, dose response relationships and prediction of behavioural and clinical relevant changes.

Figure 1



Brain-behavioural targets for compounds with anxiolytic potential for treatment development.

Anxiety disorders

Despite remarkable advance in our understanding of the neurobiology of anxious states and of anxiety disorders [2–4], few new anxiolytic compounds have reached the clinic in the past two decades [5]. Using positron emission tomography (PET), there is some *in vivo* evidence to suggest that the most commonly used pharmacologic agent used for anxiety disorders (and for major depressive disorders) — selective serotonin reuptake inhibitors (SSRIs) — do mechanistically exert their action on the putative neurochemical target (transporter site) [6,7]. However, for several other known anxiolytic compounds (tricyclic antidepressants [TCAs], dual serotonin norepinephrine reuptake inhibitors [SNRIs], dopamine reuptake inhibitors [DRIs], benzodiazepines), clinically used doses do not match receptor/transporter occupancy levels (for review see, [8]), suggesting that it remains an unresolved issue if these compounds exert their clinical effects through mechanisms other than reuptake inhibition or receptor binding.

If antidepressant and anxiolytic medications exert their more functional ‘downstream’ effects, then other imaging modalities (regional blood flow/metabolism PET, functional fMRI) capable of detecting localised brain ‘activity’ could play an important role in elucidating an alternative mechanism of action based on regional changes in function, particularly in relation to the brain-behaviour effects at a systems neuroscience layer of analysis that is independent of the effects at the neurochemical/receptor level. These methodologies generate mechanism-related ‘activation’ maps that could serve as functional targets to test drug, existing and new, effects [9]. Like functional neuroimaging studies of depression [10], those examining anxiety disorders [11] have elucidated a set of key brain regions — amygdala (AMYG), anterior insula (aINS), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC) — as dysfunctional using behavioural probes

(i.e. tasks during fMRI/PET) of socio-emotional perception of and bias towards threat signals, fear learning and extinction or anxiety provocation particularly in those anxiety disorders that are characterised by dysregulated fear. Thus, neuropathophysiologically based interventions should aim to restore the function of these specific regions (or the network of these functionally and anatomically connected regions) (see Figure 1).

Consistent with studies that combine functional neuroimaging with pharmacological clinical trials in depressed subjects [12,13] there is evidence that effective treatment with SSRIs reduces the exaggerated (observed pre-treatment) amygdala, insula and ACC responses to signals of social/evaluative threat and other forms anxiety provocation in anxious patients [14,15^{*}]. These data match the evidence that acute administration of SSRIs appears to downregulate amygdala hyper-responsivity to threat-relevant stimuli and during anticipatory anxiety in healthy participants [16^{*},17,18], similarly observed with fast-acting anxiolytics such as the benzodiazepine lorazepam [19^{*}]. Interestingly, the extent to which these same set of regions (AMYG, aINS, and ACC/mPFC) are functional at baseline (pre-treatment) predicts the likelihood that anxious patients will respond to SSRI [20,21] and SNRIs [22,23].

With converging *in vivo* translational evidence that functional PET and fMRI can prove useful in identifying ‘nodes’ of brain dysfunction that can be targets and predictors of anti-anxiety compounds, there is a need to leverage this approach towards further validation, fine-tuning pharmacofMRI strategies and discovery of new compounds. First, studies are needed to further establish the validity and reliability of the neural mechanism of action — via AMYG, aINS, ACC/mPFC ‘functional’ circuits that instantiate fear regulation — of SSRIs in the across all anxiety disorders for which they are

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