Modelling brain activation during a psychopharmacological challenge based on molecular targets

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Background

In the past century, major improvements in the treatment and understanding of mental disorders were preceded by, often unanticipated, discoveries in neuropsychopharmacology. Despite their extensive application in psychiatry, sufficient understanding of the antidepressant mechanisms of selective serotonin reuptake inhibitors (SSRIs) and ketamine is still lacking, and a significant fraction of patients does not respond to treatment. Therefore, there is an urgent need for robust approaches which allow for the prediction of drug efficacy in individual patients. Recent breakthroughs in human brain imaging (PET/, fMRI) and transcriptomics have provided molecular and functional measures for integrated investigation of the distribution of drug targets, activation and connectivity on a systems level.

Specific aims

The aim of this project is to develop novel models to assess changes in brain activation and networks induced by a pharmacological challenge with SSRIs or ketamine. Proceeding previous work, the approach will include a multitude of drug-specific targets based on the distribution and engagement of corresponding molecular targets. In a subsequent step, resulting models will be applied in a clinical sample of depressed patients with the aim to discover specific differences in pharmacological responses which are related to treatment outcomes (**Figure 1**).

Research methods

In the proposed project, two different drug challenges will be investigated in a randomized double-blind, placebo-controlled, cross-over study design. Forty healthy controls (HC) will receive ketamine and a further 40 HC and 40 MDD patients citalopram. Each subject will undergo two scans with a minimum of 45 min of resting-state pharmacological MRI (phMRI) data acquisition during which an acute intravenous drug challenge or placebo will be applied (**Figure 2**).
The phMRI data acquired will be analysed using dual regression models of increasing complexity. The approach will combine predictors based on drug pharmacokinetics such as plasma levels and occupancy as well as the distribution and affinity of relevant molecular targets i.e. serotonin transporter and serotonin receptors for citalopram and glutamate receptors for ketamine (**Figure 3**). This will allow to assess the specific contribution of each target to acute drug responses. In the final step, depressed and healthy participants will be compared within this framework to assess disease specific parameters of pharmacological responses.

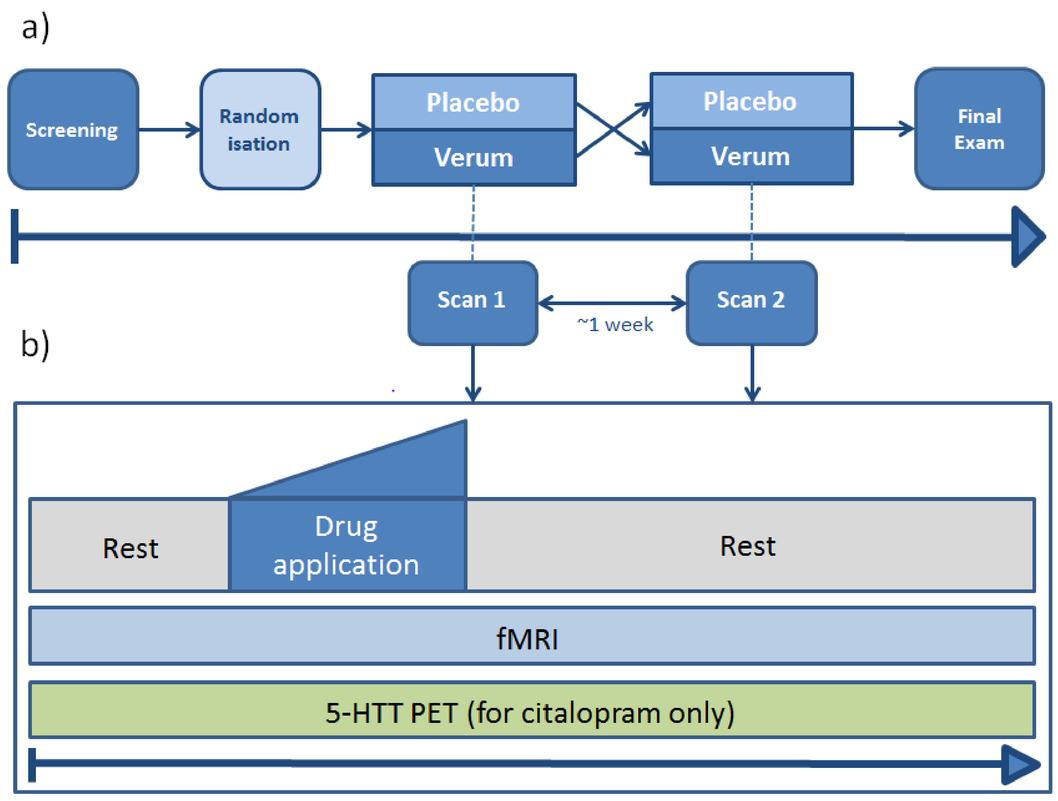

Figure 1: Graphical representation of the general study design. (a) Displays an overview of each appointment in the study which follows a randomized double-blind, placebo-controlled, cross-over design with two drug challenge scans. (b) Shows the timing for the data acquisition and drug application during each scan.

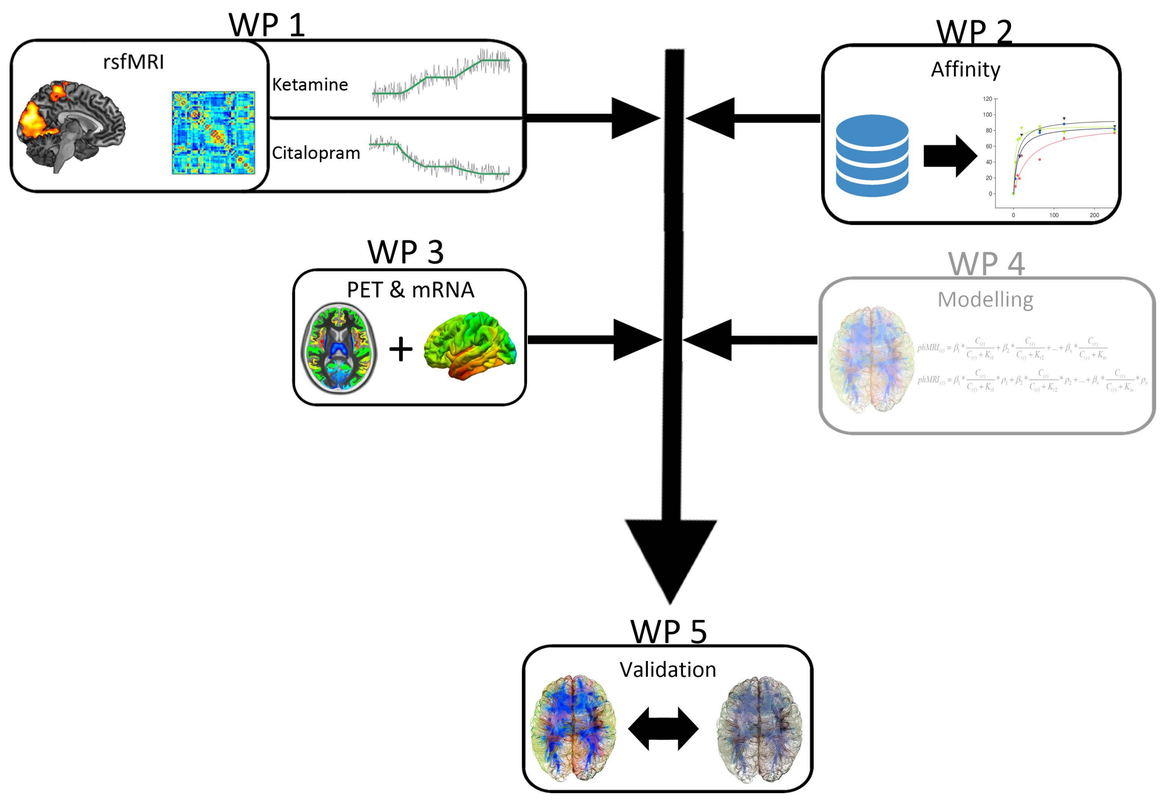

Figure 2: Overview of all work packages of the project and how they are interconnected. Work package 1 represents the preprocessing and preliminary analysis of the phMRI data, WP 2 represents the collection of the affinity data of each target and WP 2 the preparation of PET and mRNA data. The first 3 WP's are then used as parameters for the model in healthy subjects in WP 4. In the final WP 5, the data is clinically validated on patients with depression.

Relevance and implications

In the current project, a systematic and technology-driven approach is proposed in order to ultimately derive a clear picture of the molecular-functional coupling of the human brain. Establishing models for integrated analysis of pharmacological effects based on brain activation responses, regional expression of molecular targets and their occupancy is a valuable research paradigm that may substantially aid clinical practice. In contrast to animal models, the clinical relevance of such models in patients can be directly assessed and ample data on the function of human brain areas is already available to aid the interpretation of results. The estimation of the individual contribution among multiple molecular drug targets will provide novel insight into the mechanism of action of antidepressants. This technique may be further used to guide drug development and provide a rationale for psychopharmacological treatment in clinical practice.

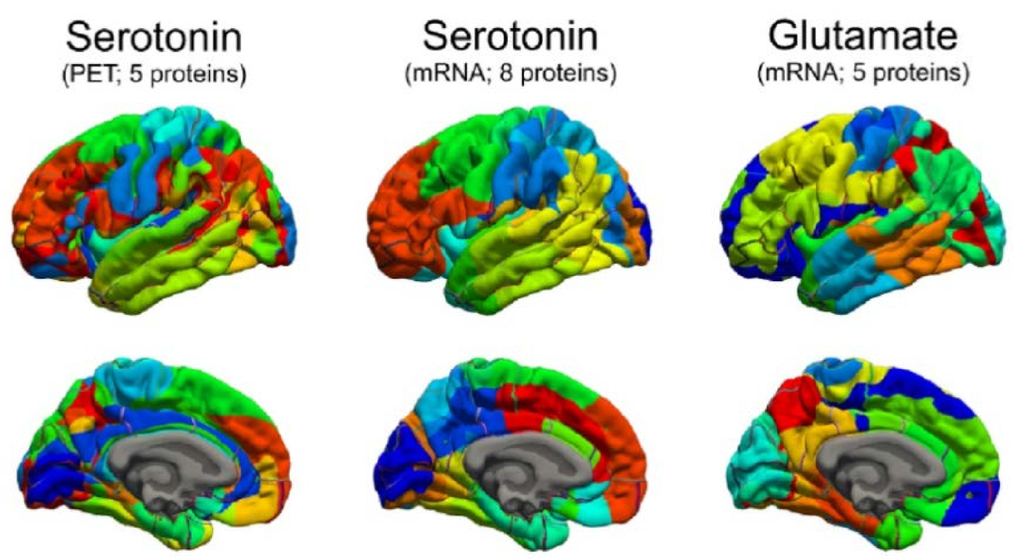

Figure 3: Clustering of brain regions based on expression of molecular targets within different neurotransmitter systems based on our database. Cluster membership was determined for each point on the surface based on expression of each target using k-means clustering. For comparison the, number of clusters was fixed to 16. PET data for proteins shown in Figure 1 (5-HT1A, 5-HT1B, 5-HT2A, 5-HTT, MAO-A) was used for clustering of drug targets within the serotonergic system. As for other proteins no PET data is currently available, mRNA expression from the Allen Human Brain Atlas was interpolated on the cortical surface. Clusters are shown for an extended set of serotonin receptors (5-HT1A, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2C, 5-HT3, 5-HT4, 5-HT7) and a sample of glutamate receptors (NMDA, AMPA, mGluR1, kainate, HCN1) and the hyperpolarization-activated cation channel (HCN1) involved in the regulation of glutamate levels