The Relation between Drug-induced Effects on Resting State Brain Connectivity and Cerebral Blood Flow

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Introduction: Resting state fMRI (RS-fMRI) and perfusion imaging are potentially important tools for central nervous system (CNS) drug development research. Emerging studies show that RS-fMRI can reveal drug effects on functional brain connectivity. Technological improvements to arterial spin labeling (ASL) methodologies offer an important alternative to costly and restrictive PET perfusion measurement methods that were primarily used by CNS-drug researchers. However, the link between effects detected with RS-fMRI and ASL is not well established. The objective of this study is to quantify and compare the regional effects of different drugs on the brain, which are detected using RS-fMRI and pseudocontinuous ASL (PCASL) [1], in the same subjects, in the same scanning sessions.

Materials and Methods: ***Subjects***: Twelve healthy young men (18-40 yrs) with no history of drug abuse, chronic illness or mental health problems were recruited from the community. ***Experimental Design:*** This was a cross-over, randomized, double blind placebo-controlled pharmacological study involving controlled doses of morphine and alcohol. Subjects were scanned using a 3T scanner in three sessions with identical experimental procedures. ***Drug Infusion:*** Alcohol and morphine were administered intravenously. Previously validated pharmacokinetic models [2] were used to ensure minimal inter- and intra-subject variation in plasma drug concentration over a period of two hours after the infusion began. ***Image Acquisition:*** PCASL and RS-fMRI were performed before drug or placebo infusion, and after morphine and alcohol had reached pseudo-steady levels after two hours. ***Connectography***: We used the dual-regression method [3] to first extract a representative resting-state signal within each of the eight common resting state networks [4]. The connectivity maps were obtained by voxel-wise regression of RS-fMRI data against signals obtained from these template networks of interest (NOI) as shown in Figure 1. This produced eight z-score maps per data set, where z=0 suggested no connectivity to the given network. ***Cerebral Blood Flow:*** PCASL subtraction maps were computed (using Matlab, Mathworks, Inc.) as described by [1] and spatially normalized to MNI152. Each perfusion map represented the absolute value of CBF (ml/100 ml tissue/min). ***Statistical Analysis***: A mixed-effect statistical model tested drug by time interactions on the connectivity and the CBF maps. A non-parametric permutation-based (5000 randomizations) was used, and the statistical threshold was set to $p < 0.05$ (cluster-corrected with t=3.2). All image processing and analyses were done using FSL4 (FMRIB, Oxford, UK).

Results and Discussion: Statistical maps of drug by time interaction with CBF and resting state connectivity are superimposed in Figure 1. The highest peak of morphine-induced CBF increase overlapped with its RS-fMRI effects in NOI4—including sensorimotor areas, part of the lateral-pain processing network [5]) and in NOI6—including the medial prefrontal cortex, which has high opiodergic receptors and is part of the medial pain processing network [5]. Similarly, the most significant alcohol induced CBF increases corresponded to connectivity changes of the paracingulate cortex to NOI3 (the auditory/insula network), the anterior cingulated cortex to NOI4 (the sensorimotor network), and the medial visual cortex to NOI1 (the visual network)—all regions that are linked to functional effects of alcohol [6]. Most but not all of the RS-fMRI effects were accompanied by an increase in the CBF. Quantitative ROI analysis in Figure 1 illustrates that although the CBF within all ROIs was increased compared to placebo, the connectivity changes (z-scores) were not unidirectional. This suggests that the correspondence between CBF increase and resting state brain connectivity is not ubiquitous. Thus, RS-fMRI provides additional information about the dynamics of functional connectivity that may be important for understanding the adaptive mechanisms involved in pharmacologically induced changes in brain activity.

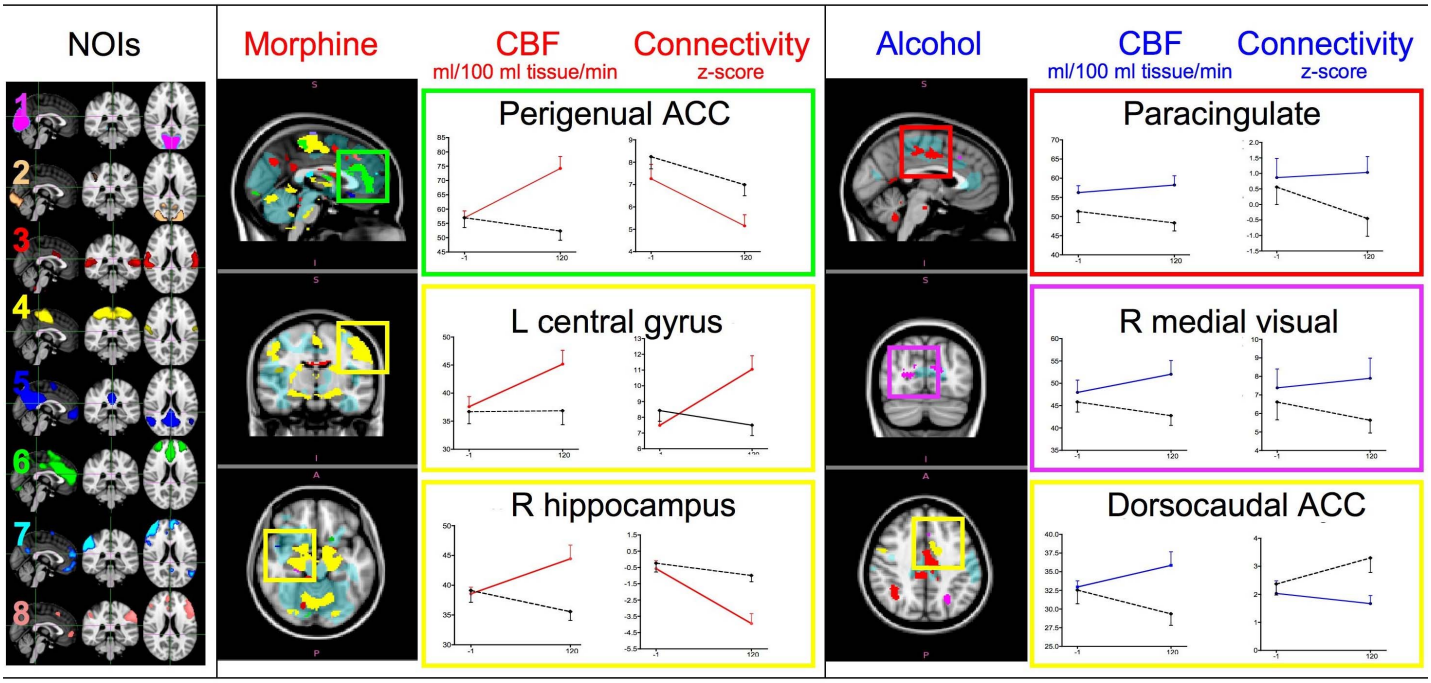

Figure 1*: Superimposed effects of each drug detected with PCASL (CBF-increase transparent cyan) and with RS-fMRI (illustrated in different colors related to each NOI in the left panel). The magnitudes of the most significant morphine and alcohol effects (corresponding to color-coded clusters within each box) are plotted to illustrate relations between CBF and RS-fMRI effects. Morphine, red; alcohol, blue; and placebo, black.*

References: [1] M. J. Van Osch *et al*, *Magnetic Resonance in Medicine* **62**, 2009; [2] E. Sarton *et al.*, *Anesthesiology* **93**, 2000 ; [3] C. Beckmann *et al*, *NeuroImage* **47**, 2009; [4] C. F. Beckmann *et al*, *Philos Trans R Soc Lond B Biol Sci* **360**, 2005; [5] R. Peyron *et al, Brain,* **122,** 1999; [6] S. A. Meda *et al*, *Hum Brain Mapp* **30**, 2009.