Exploration of Resting State fMRI Metrics as Biomarkers of Central Nervous System Activation by Drug: Placebo Controlled fMRI Study of the Effect of the Analgesic Buprenorphine

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Resting-state functional MRI experiments used for the assessment of functional connectivity in the Central Nervous System have become an area of intense research recently. There is particular interest in their potential utility as biomarkers of disease processes and/or therapeutic efficacy. In order to qualify the usefulness of functional connectivity endpoints as therapeutic efficacy tools, the sensitivity of the endpoints to treatment needs first to be established. The present work provides initial exploration of functional connectivity approaches based on Independent Component Analysis (ICA). This is done in the context of a Placebo Controlled fMRI study of Buprenorphine, a partial opioid agonist and antagonist. A set of previously reported fundamental resting state networks (RSNs) were examined comprising of medial visual, lateral visual, auditory system, sensory motor system, default mode network, executive control, dorsal visual stream (Beckmann 2005). Treatment effects of Buprenorphine on functional connectivity metrics associated with each of these fundamental RSNs were examined.

Functional MRI data was acquired in a placebo controlled 2-way cross-over design conducted in 12 healthy volunteers. Each subject was scanned in two scanning session days when, in a randomized sequence, either Placebo or clinically efficacious dose of Buprenorphine, 0.2 mg/70 Kg, were administered I.V. A pharmacological fMRI scanning session was used whereby subjects lay at rest while EPI images are acquired (TR/TE=2500/30ms, 64x64x41 matrix, 3.5x3.5x3.5 mm^3 resolution). For each subject in their respective placebo and buprenorphine challenge sessions, a total of 720 images are acquired over 30 min; the first 120 images (5 min) are acquired prior to administration of either Placebo or Buprenorphine and correspond to resting state in absence of any pharmacological challenge. The last 120 images in the experiment are used to assess the effect of treatment. In total, for each subject a set of four resting state periods were acquired: two under no treatment (baseline 1 and 2), one following placebo administration and one following Buprenorphine administration. Functional connectivity was assessed by the goodness-of-fit (GOF) parameter for the putative resting state networks. We used 8 spatial templates of the fundamental RSNs as obtained in the study by Beckmann et al 2005. GOF is derived from an independent component analysis (ICA) approach that measures degree of functional connectivity and spatial specificity of connectivity within a given network (Greicius 2004).

Figure 1 shows maps of the spatial independent components (ICs) corresponding to the fundamental RSNs in the placebo cohort. Reproducibility of the ICA approach is demonstrated as all fundamental RSNs previously reported (Beckmann et al 2005) have been robustly identified.
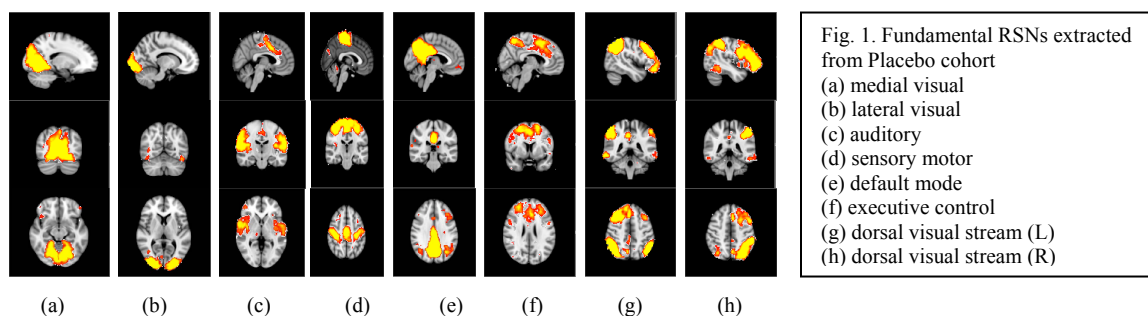

Fig. 1. Fundamental RSNs extracted from Placebo cohort
(a) medial visual
(b) lateral visual
(c) auditory
(d) sensory motor
(e) default mode
(f) executive control
(g) dorsal visual stream (L)
(h) dorsal visual stream (R)

(a)   (b)   (c)   (d)   (e)   (f)   (g)   (h)

Figure 2 shows bar plots indicating the difference in the GOF endpoint across the fundamental RSNs. Significant changes were observed in the two networks namely Sensori-motor network (d) and Default Mode Network (e, DMN). Functional connectivity in other fundamental RSNs was not affected by buprenorphine. Using the GOF to quantify the functional connectivity across all networks provides an internal control and indicates the specificity of the drug effect to specific RSNs.
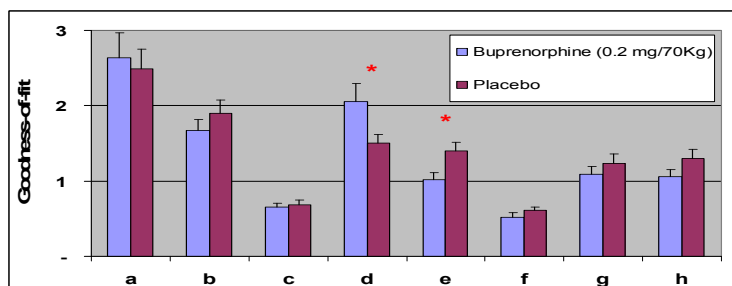

Fig. 2. Treatment effect of Buprenorphine vs. Placebo measured by the "Goodness-of-fit" (Greicius 2004) ., Significantly different changes between in the two treatment arms obtained by the paired t-test at significance level of 0.05 are denoted by (*). RSN labels are as in Figure 1.

These results reproduce Beckmann's (2005) observed fundamental Resting State Networks as defined by ICA. The sensitivity of the GOF endpoint to treatment was demonstrated by changes in the RSNs consistent with the mechanism of action of Buprenorphine. Further work will focus on the effect of sublingual administration of Buprenorphine on the fundamental RSNs as well as comparison with (non-analgesic) Fos-aprepitant.

References: Beckmann et al (2005) Phil Trans R Soc B; Greicius et al (2004) PNAS