

# Pharmacological challenge with the opioid analgesic Buprenorphine, but not Placebo, enhances resting-state functional connectivity in the pain processing network

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**Introduction:** Resting-state functional MRI (fMRI) experiments used to assess functional connectivity in the Central Nervous System (CNS) have gained much attention recently [1]. Several groups have reported on the Default Mode Network (DMN), a set of functionally connected ROIs including the posterior cingulate cortex, superior parietal regions, and superior and middle frontal gyri regions believed to be involved in cognitive processing [1]. There have also been reports of changes in functional connectivity patterns in disease (Alzheimer's Disease, Schizophrenia, Depression, Chronic Pain, [1,2,3]). However, little has been done to assess the effect of pharmacological compounds on functional connectivity parameters. In the present report we address two related issues: test-retest reliability of resting state measures of functional connectivity in the DMN and sensitivity of a functional connectivity endpoint to treatment with an opioid analgesic compound, Buprenorphine.

**Methods:** fMRI data were acquired in a placebo controlled 2-way cross-over design conducted in 10 healthy male volunteers. Each subject was scanned in two scanning session days when, in a randomized sequence, either Placebo (saline) or clinically efficacious dose of Buprenorphine, 0.2 mg/70 Kg, were administered I.V during an extended fMRI scan during which the subjects lay at rest while EPI images were acquired (TR/TE=2500/30ms, 64x64x41 matrix, 3.5x3.5x3.5 mm<sup>3</sup> resolution). For each subject in their respective placebo and buprenorphine sessions, a total of 600 images were acquired over 25 min; the first 120 images (5 min) were acquired prior to administration of either Placebo or Buprenorphine and correspond to resting state in absence of any pharmacological challenge. The last 120 time points in the time series, following signal stabilization after the infusion, were used to assess the effect of treatment on resting state BOLD fluctuations. 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 in two ways: (1) analysis of the temporal correlation across the average BOLD time signal from 6 ROIs constituting the DMN (mPFC, LP, PCC, MT, FEF, and IPS, [2]) and (2) analysis of the goodness-of-fit (GOF) parameter for the putative (anatomically defined) pain processing network (PPN, Figure 2, including thalamus, putamen, PAG, caudate, hippocampus, nucleus accumbens, amygdala and pallidum; anterior and posterior insula, primary somatosensory, anterior and medial cingulate, frontal superior orbital cortices). 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[3].

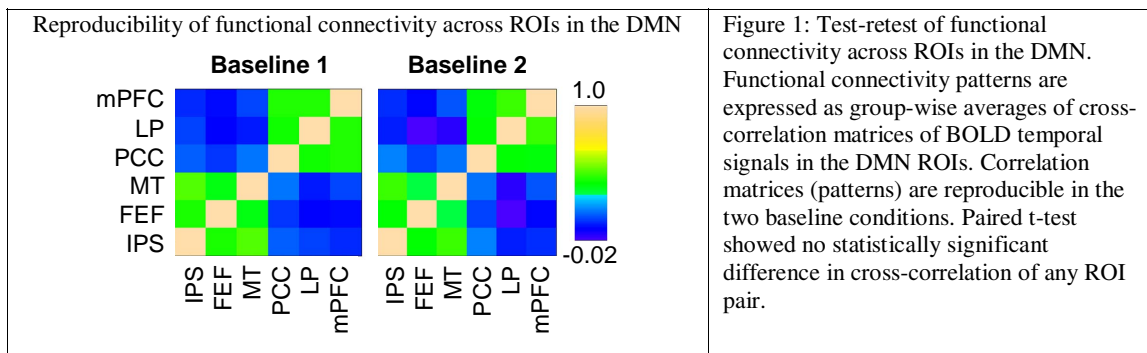


Figure 1: Test-retest of functional connectivity across ROIs in the DMN. Functional connectivity patterns are expressed as group-wise averages of cross-correlation matrices of BOLD temporal signals in the DMN ROIs. Correlation matrices (patterns) are reproducible in the two baseline conditions. Paired t-test showed no statistically significant difference in cross-correlation of any ROI pair.

**Results:** Results show that the cross-correlation matrix for DMN ROIs is stable between the two baseline scans, and pre- and post-placebo (Figure 1). Figure 2 shows the trend in GOF in the PPN. Values for GOF were  $0.43 \pm 0.18$  (mean  $\pm$  std. dev.),  $0.43 \pm 0.13$ ,  $0.43 \pm 0.16$ , and  $0.60 \pm 0.26$ , respectively for baseline 1, baseline 2, placebo and Buprenorphine conditions. There is no statistically significant difference in GOF across the two baseline scans (paired t-test  $p=0.96$ ) and placebo condition ( $p=0.89$ ). Functional connectivity as measured by GOF in the PPN increases significantly with Buprenorphine treatment ( $p<0.03$ ).

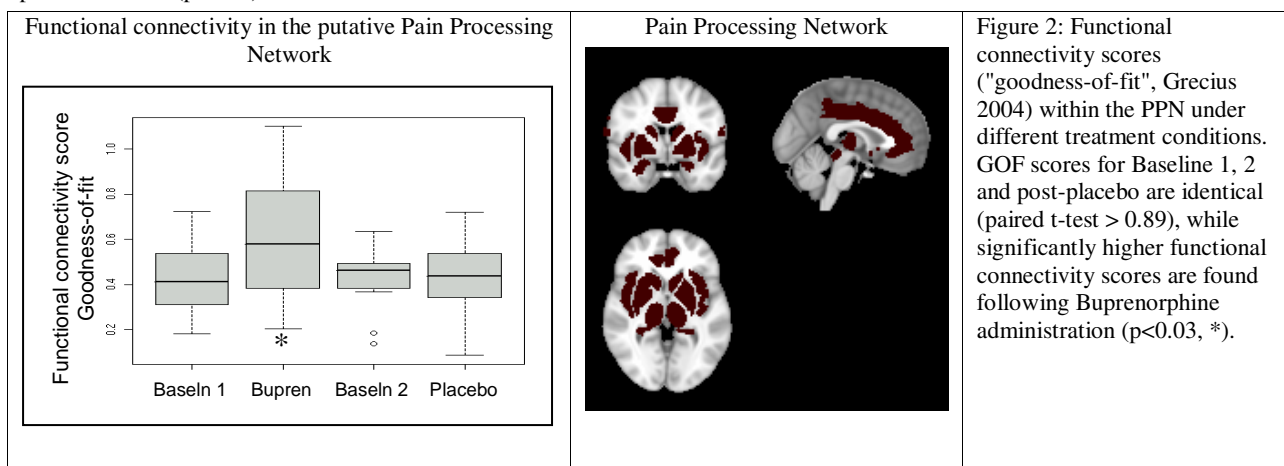


Figure 2: Functional connectivity scores ("goodness-of-fit", Greicius 2004) within the PPN under different treatment conditions. GOF scores for Baseline 1, 2 and post-placebo are identical (paired t-test  $> 0.89$ ), while significantly higher functional connectivity scores are found following Buprenorphine administration ( $p<0.03$ , \*).

**Conclusion:** The baseline DMN results from this study are in agreement with previously reports [1,2,3]. Overall, the results suggest robust test-retest reliability in functional connectivity, both between cohorts in baseline DMN and, importantly, as an insensitivity to the injection of an innocuous placebo. In contrast, sensitivity of functional connectivity endpoints to target engagement by an active compound was demonstrated by the GOF parameter. Further investigation with a different dose of Buprenorphine is on going to address possible dose response relationship.

Refs: 1. Fox and Raichle 2007; 2. Baliki et al. 2008; 3. Greicius et al 2004.