functional MRI correlates with self-assessment of pain intensity and reveals effect of the opioid analgesic Buprenorphine on brain processing of noxious stimulation

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Introduction: There is growing interest in exploring the potential of functional Magnetic Resonance Imaging (fMRI) as a biomarker for drug discovery and development [1]. fMRI-based biomarkers have the potential to provide a signal indicating central effect of CNS drugs in early phases of drug development and important insights into mechanism of action. In the area of pain, noxious peripheral stimuli have consistently induced CNS responses in a characteristic set of brain regions [1]. More recently, several analgesic drugs have been shown to attenuate the evoked fMRI response [2], leading to the hypothesis that this approach might provide a pharmacodynamic biomarker predictive of analgesic action. Some of these studies have shown parallel drug effects in fMRI response and subjective pain ratings. Here, we assess the relationship between perceived pain intensity and fMRI signal amplitude in response to a battery of innocuous and noxious stimulation paradigms. In particular, we show for the first time intra-subject correlations in the *change* in perceived pain and the *change* in fMRI response induced by the presence of the analgesic drug buprenorphine, a compound with mixed agonist and antagonist actions and mu- and kappa-opioid receptors.

Methods: The study was a placebo-controlled 2-way cross-over design conducted in healthy male volunteers (n=10). Each subject was scanned on two days at least two weeks apart (allowing for compound washout) in a randomized sequence when either Placebo or clinically efficacious dose of Buprenorphine, 0.2 mg/70 Kg, I.V. were administered. Three complementary paradigms, stimulating different afferent fibres and inducing different degrees of noxiousness were applied to the dorsum of the left foot in the following order 25-30 min after dosing: brush (non-noxious), von Frey (mildly noxious), and heat (noxious). Each stimulus was applied in 7 consecutive cycles in on/off fashion (on/off = 15s/25s). Whole brain images (64x64x41 matrix, 3.5x3.5x3.5 mm^3 resolution) were acquired using an EPI sequence (TR/TE=2500/30ms)., Following a General Linear Model analysis [FSL (3)], average percent-signal-change (PSC) was calculated for several Regions-of-Interest (ROIs) believed to constitute the pain processing network (4) as fMRI pain response endpoints. The ROIs included Insula (anterior and posterior), Thalamus, Medial-cingulate Cortex, and Primary Somato-sensory Cortex and were defined on the MNI standard template and transformed to the native fMRI space. Subjective Visual Analog Scale (VAS) ratings of pain were recorded for each subject during the experiment.

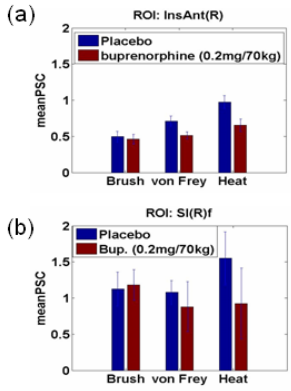

Fig. 1: Group mean VOI response (PSC) by stimulation paradigm and modulation by buprenorphine: (a) anterior insula,(b) foot representation of SI, both contralateral to stimulus. (mean±SEM).

(a)

Sub	VAS	fMRI
1	↑	↑
2	↑	↑
3	↑	↑
4	↑	↑
5	↑	↓
6	↑	↑
7	↓	↓
8	↓	↓
9	↑	↑
10	↑	↑

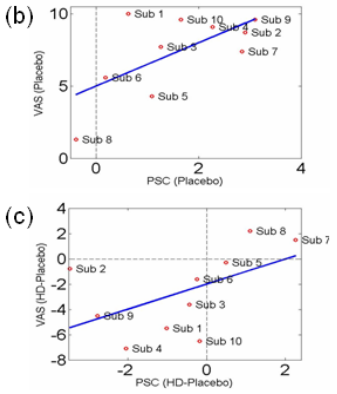

Fig. 2: Relationship between self-assessment of pain (VAS) and fMRI response, illustrated for the SIf VOI under the noxious heat paradigm. (a) Valence of drug effect (↑ Placebo > Buprenorphine, ↓ Placebo < Buprenorphine). (b) Correlation between subjective pain and fMRI in placebo condition. (c) Correlation between *change* in VAS score and *change* in fMRI induced by buprenorphine.

Results: On a scale of 0-10, average ± s.d. VAS pain ratings for brush, von Frey and heat in the placebo condition were respectively 0.8 ± 0.3, 2.1 ± 1.4 and 7.6 ± 2.0. The average threshold temperature for heat stimuli was 47.2 ± 2.1 °C. Figure 1 shows an increasing intensity of BOLD signal with increasingly noxious stimulation paradigm for two key regions in the central pain network, the anterior insula and the primary somatosensory cortex (foot representation). Moreover, an attenuation of the fMRI response by buprenorphine was preferentially observed in response to the more noxious stimuli (Fig. 1). Figure 2 shows the relationship between the self-reported VAS rating and fMRI PSC in the contralateral SIfoot VOI. There was a consistent trend between drug-induced changes in the two variables: increases in VAS were typically accompanied by increases in PSC and decreases in VAS tracked decreases in PSC (Fig. 2(a)). In the placebo condition, there was a strong correlation between fMRI response and VAS (r=0.72, p=0.02; Fig. 2(b)), consistent with a relationship between the observed BOLD changes and the perceived pain intensity. Moreover, changes in VAS and changes in fMRI following Buprenorphine treatment were also correlated, as illustrated by the intra-subject correlation in Fig. 2(c).

Discussion and Conclusions: These results, in particular the positive intra-subject correlation between the perceived analgesic effect of Buprenorphine and the detected fMRI response, further validate pharmacological fMRI as a sensitive biomarker of acute pain and its relief in healthy human volunteers. Furthermore, we demonstrated the utility and potential of fMRI-based biomarkers for discovery and early stage development of analgesic compounds.

References: 1. Apkarian AV, Semin. Neurosci., 1995, 279-293; 2. Iannetti et al, PNAS, 2005, 102(50), 18195-200. 3. Smith et al. NeuroImage, 23(S1):208-219, 2004. 4. Wise et al. NeuroImage, 2002, 16(4):999-1014.