Placebo modulates regional power of BOLD oscillations in chronic low back pain patients.

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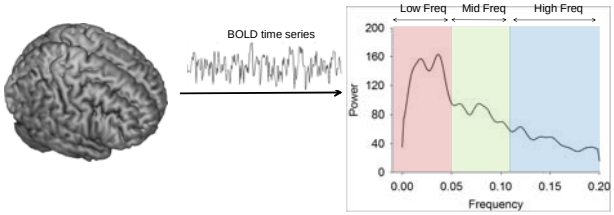
INTRODUCTION

Our lab has shown that BOLD frequency band distribution reflects anatomical and functional organization, with each brain network exhibiting distinct frequency structure (Baria A et al.,2011). Moreover, we have demonstrated that chronic back pain is associated with increased fluctuation in 0.12 – 0.2 Hz in the mPFC (Baliki et al, 2011). This increase in high frequency oscillation is tightly coupled with changes in functional connectivity in brain regions involved in nociception. Here we investigate whether high frequency oscillations in the frontal cortex play a role in chronic pain modulation. We studied two CBP patient groups: the first group responded to the placebo treatment with more than 60% pain reduction (CBP decreasing group; n=15), and the second group showed little or no change in pain (3.9%) after placebo treatment (CBP persisting group; n=13). First, we discovered that the left DLPFC showed significantly greater power in the high frequency band in the CBP decreasing group. The DLPFC has been repeatedly implicated for its role in pain modulation and in the placebo response. Building on this finding, we investigated whether 1) the power in the high frequency band predicts the placebo response, 2) the DLPFC modulates pain by affecting other brain regions in a frequency dependent manner, 3) anxiety, depression or pain intensity affect the DLPFC related pain modulatory networks resulting in group differences in placebo response

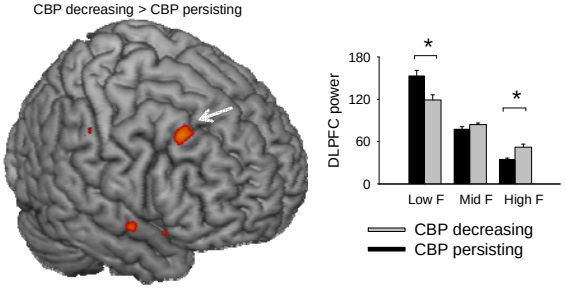
1 Frequency Power Measurement



BOLD fMRI time-series are extracted at each voxel. Time-series data are Fourier-transformed into frequency space. Power at 3 different frequency bands (0.01-0.05, 0.05-0.12, 0.12-0.20 Hz) is averaged and assigned to each voxel, generating 3 frequency distribution maps for each subject. Maps are transformed into standard space and averaged across subjects. Comparisons between the groups were done using an unpaired t-test (random effects analysis and were corrected for multiple comparisons).

2 CBP decreasing group show greater high frequency power in the DLPFC

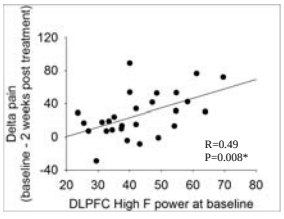
F3 power
CBP decreasing > CBP persisting



Whole brain contrast between the two groups at baseline was significant in the DLPFC (Brodmann area 8: see arrow) for two contrasts: CBP decreasing > CBP persisting at high F band power and CBP persisting > CBP decreasing for low frequency band power, Bar graph shows power extracted from DLPFC region. (Map corrected at z > 2.3; p<0.001).

3 DLPFC high frequency power predicts placebo response

A



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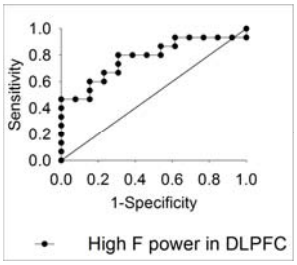

Receiver operating curve (ROC) characteristics for discriminating two groups: CBP persisting and CBP decreasing based on DLPFC high frequency power measured at baseline. The DLPFC high frequency power strongly predict future outcomes of placebo treatment (accuracy >78%), p=0.012.

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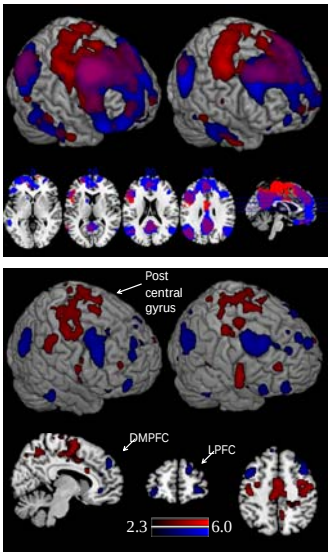
METHODS

- 30 chronic back pain patients (avg duration 5 years, 14 females) were scanned while they continuously rated magnitude of their chronic back pain with a finger span device. These subjects were scanned at baseline and after treatment with a placebo patch applied to the lower back for two weeks. Pain intensity was measured at baseline and post treatment.
- Anxiety and depression scores were measured with the Beck Depression Inventory & Beck Anxiety Inventory.
- Whole-brain functional MR data was acquired with a 3T Siemens Trio whole-body scanner.40 slices were obtained in the axial plane covering the entire brain. flip angle = 90°, in-plane resolution = 64×64, TR/TE = 2500/30 msec and slice thickness of 3mm.
- Time-series of the BOLD signal was extracted at every voxel. Power spectral density of the BOLD signal at each voxel was determined using Welch's method and the average power at 3 frequency bands: low (LF, 0.01-0.05 Hz), mid (MF, 0.05-0.12 Hz) and high (HF, 0.12-0.2 Hz) were computed. Group average PSD maps for each group were generated by averaging the power of each voxel across all subjects within each group after transformation of individual maps in standard space. Comparisons between the groups were done using an unpaired t-test (random effects analysis and were corrected for multiple comparisons).
- Relationships were determined using principal component analysis with promax rotation and with linear regression. Predictive capacity of the measurements were determined with ROC curves.

4 DLPFC network in CBP persisting and decreasing groups



In addition to different power in the left DLPFC, the brain networks correlated with the DLPFC also differed significantly between the CBP decreasing and persisting groups.

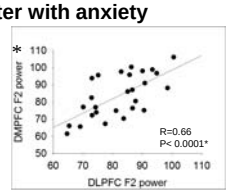
Top panel shows mean DLPFC connectivity in CBP persisting (blue) and decreasing (red) groups. Purple regions show over lap between the two groups.

Lower panel shows contrast between the two groups. Blue represents DLPFC connectivity in CBP persisting > CBP decreasing, and red CBP decreasing > CBP persisting. DLPFC connectivity in CBP decreasing group mapped onto somatosensory networks, ACC and SMA. On the other hand in CBP persisting group, DLPFC showed connectivity with LPFC, DMPFC, the insula and the parietal cortex. (Whole brain F-test analysis, , corrected for multiple comparisons at z >2.3, p<0.01)

5 Power in regions identified to be linked with DLPFC in CBP persistent group cluster with anxiety

Factors	Principal Components				
	Comp 1	Comp 2	Comp 3*	Comp 4	Comp 5
Variance explained	(34 %)	(15%)	(13%)	(9%)	(8%)
DLPFC LF		-0.851			
DLPFC MF			0.784		
DLPFC HF		0.866			
DMPFC LF	-0.788				
DMPFC MF			0.829		
DMPFC HF	0.860				
LPFC LF	-0.904				
LPFC MF	0.790				
LPFC HF	0.818				
MPFC LF	-0.626			-0.358	
MPFC MF	0.363				-0.487
MPFC HF	0.553			0.611	
Pain				0.853	
Delta pain	-0.371	0.691		0.487	
Depression					0.909
Anxiety	0.317		-0.686		

DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsal medial prefrontal cortex; LPFC: lateral Prefrontal cortex; MPFC:medial prefrontal cortex: l a INS: left anterior insula. Promax rotation, KMO test for sampling adequacy =0.51, sig at p<0.0001



Left panel: each principal component comprises a unique combination of factors consisting of measurements of regional power in cortical regions (selected from analysis shown in section 4) and measures of placebo effect (delta pain), pain intensity, anxiety and depression.

Top panel: correlation identified from component 3 demonstrates relationship between DLPFC and DMPFC specifically in the mid frequency band, this correlation is linked with decrease in anxiety.

CONCLUSION

1. CBP subjects that show decrease in pain after a placebo treatment show greater high frequency power in the left DLPFC before treatment and the high frequency power from this region predicts the placebo response with a high level of accuracy.

2. The left DLPFC shows greater connectivity with somatosensory regions at baseline in subjects that show decrease in pain after placebo treatment. In contrast subjects with persisting pain despite of placebo treatment show greater connectivity between DLPFC and affective regions (DMPFC, insula) and cognitive regions (LPFC).

3. The principal components analysis confirms finding 1 (see component 2), confirms the relationship between the MPFC and CBP identified by Baliki et al, 2011 (component 4). Also suggests that anxiety is linked with brain regions identified in CBP persisting group (component 1), and that an interaction between the DLPFC, DMPFC and anxiety may interact to decrease the placebo response (component 3).