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Functional large-scale network analysis of fMRI for chronic pain

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INTRODUCTION

• Functional connectivity is usually used to determine the strength and/or direction of the relationship between a small number of regions identified to be active in a given task.

• Here we use *a new functional connectivity analysis method* to identify functional groupings and information flow in a network made of 35 brain regions.

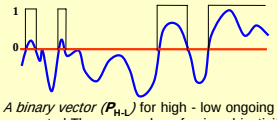
• Peaks were generated from brain activity in 12 chronic back pain patients for 1) spontaneous pain, using a finger-span device, and 2) rate the length of a bar that fluctuates in a pattern derived from their own pain ratings (visual control), using a general linear model analysis.

METHODS

• 12 CLBP patients were used in this study. In the scanner subjects either rate the spontaneous fluctuations of the intensity of their ongoing pain (signal for pain subjectivity), or rate the length of the bar that fluctuates in time in a pattern derived from their own ratings of pain (visual control signal).

• The signals for pain and visual control are used to calculate appropriate vectors used to search for the BOLD signal using FSL software (fmrib, Smith et al. 2001).

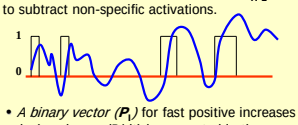
1 Vectors and covariance matrices.



• *A binary vector ($P_{H\text{-}L}$)* for high - low ongoing pain is generated.The mean value of pain subjectivity signal is calculated. Pain ratings having a value larger and smaller than the mean are designated by 1 and 0, respectively.

• *A binary vector ($V_{H\text{-}L}$)* for visual control is generated from the visual control signal in a similar fashion to $P_{H\text{-}L}$.
BOLD responses to $V_{H\text{-}L}$ control for motor component.

• *A second control vector ($S_{H\text{-}L}$)* is generated by inverting in time the original pain rating. This vector has the same statistical properties as $P_{H\text{-}L}$ but does not correlate with the pain experience. $S_{H\text{-}L}$ is used to subtract non-specific activations.



• *A binary vector (P_I)* for fast positive increases in pain (maximum dP/dt) is generated in the same fashion
as $P_{H\text{-}L}$.

• *A surrogate vector (S_I)* is generated for P_I. Again, S_I is generated by inverting P_I in time.

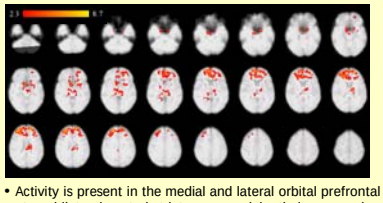
• $P_{H\text{-}L}$, $V_{H\text{-}L}$, $S_{H\text{-}L}$, P_I and S_I are convoluted with HBF and searched for in BOLD signal using FSL, and subtracted from each other.

• The Talairach coordinates of these peaks were used to search for corresponding peaks in individual subject Z-maps that were used to generate a 35x35 covariance matrix, which was thresholded to generate a binarized network. The topology of this network was studied by creating a network neighborhood dendogram and information transmission on the network was studied by calculating iterated path lengths 'traffic'. The analysis was performed for the pain condition and f the controls.

RESULTS

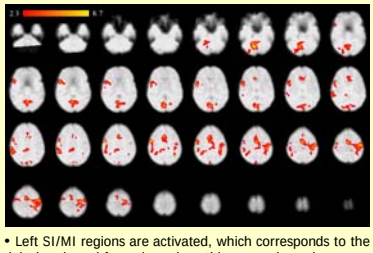
2 Activity maps for pain

High - low ($P_{H\text{-}L} - V_{H\text{-}L} - S_{H\text{-}L}$)



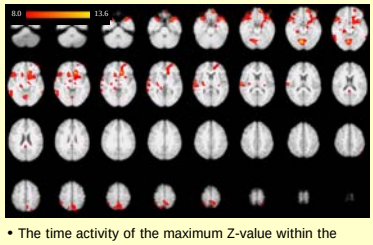
• Activity is present in the medial and lateral orbital prefrontal cortex , bilateral ventral striatum, amygdala, thalamus, and ventral tegmentum.

Fast increases in pain ($P_I - S_I$)



• Left SI/MI regions are activated, which corresponds to the right hand used for ratings since this comparison also identifies the times where the rate of hand movement rate is maximal. Multiple cingulate areas are activated as well as, bilateral SII, anterior insula, thalamus, and cerebellum.

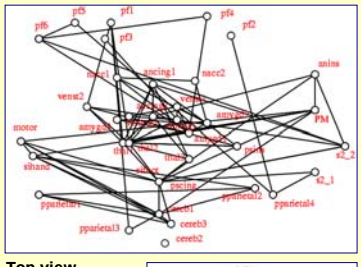
Activity synchronized to prefrontal peaks in $P_{H\text{-}L}$



• The time activity of the maximum Z-value within the prefrontal cortex identified in P(high-low) is correlated with the rest of the brain to identify brain regions that may be active in synchrony with the prefrontal activity.The only additional area observed in this comparison was bilateral leg/foot SI.

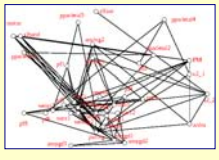
3 Network analysis

Topological representation of the connectivity between 36 brain regions (activity peaks) during $P_{H\text{-}L}$



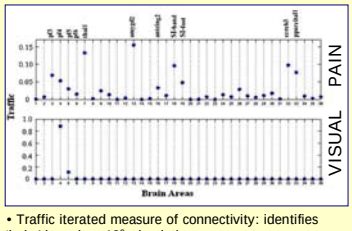
Top view

Frontal view



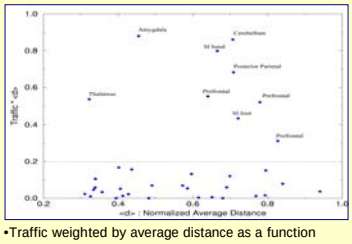
• Correlation matrix for 35 peaks. Thresholded at r = 0.6. Distances are preserved. Effective Connectivity thresholded to a 0/1 state.

Traffic across the 36 selected brain areas during $P_{H\text{-}L}$ and $V_{H\text{-}L}$



• Traffic iterated measure of connectivity: identifies 'hubs' based on 10^6 simulations.

Traffic as a function of separation distance between nodes



•Traffic weighted by average distance as a function of average distance of a node from the rest of the nodes.

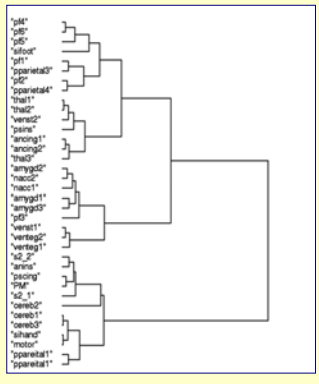
Traffic ranking

Pain:
Amygdala_2
Thalamus_1
SI (hand)
Cerebellum_3
Posterior Parietal_1
Prefrontal Cortex_3
Prefrontal Cortex_4
SI (foot)

Pain Surrogate:
Prefrontal Cortex_4

Visual Surrogate:
Prefrontal Cortex_2

Network neighborhood dendogram for the 36 brain regions during $P_{H\text{-}L}$



4 Groups of communities

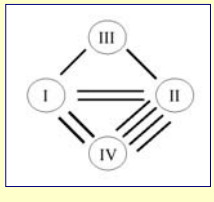
Group I: pf1, pf2, pf4, pf5, pf6, s1-foot, pparietal3, pparietal4

Group II: thal1, thal2, thal3, venst2, psins, ancing1, ancing2

Group III: amygd1, amygd2, amygd3, nacc1, nacc2, pf3, venst1, venteg1, Venteg2

Group IV: s2_1, s2_1, anins, pscing, PM, cereb1, cereb2, cereb3, s1-hand, motor, pparietal1, pparietal3

Connections between communities:



CONCLUSIONS

The results indicate that studying fMRI activity as networks with a relatively large number of elements can provide new ideas regarding information transmission and integration across multiple brain areas. This network analysis clarifies the multiple functional circuits involved in chronic pain perception.

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