Chronic back pain intensity is associated with hub disruption of small world brain networks

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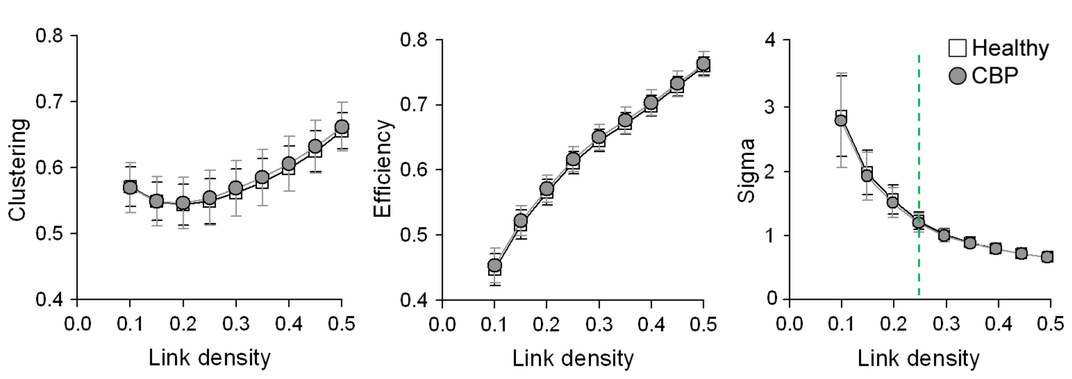
INTRODUCTION

- The brain can be conceptualized as a massive network, connected across all scales. Recent advances in our understanding of the architecture of neural networks have revealed how these different hierarchies of networks can coordinate neural processing.
- Chronic pain is associated with central neuronal plasticity. It modifies structural and functional brain properties and affects the flow of information across various brain regions.
- Here we used graph theoretical methods to explore brain network topology in resting state fMRI in back pain patients and animal models to investigate what aspects of brain network organization are fundamental for transition and maintenance of chronic pain state

METHODS

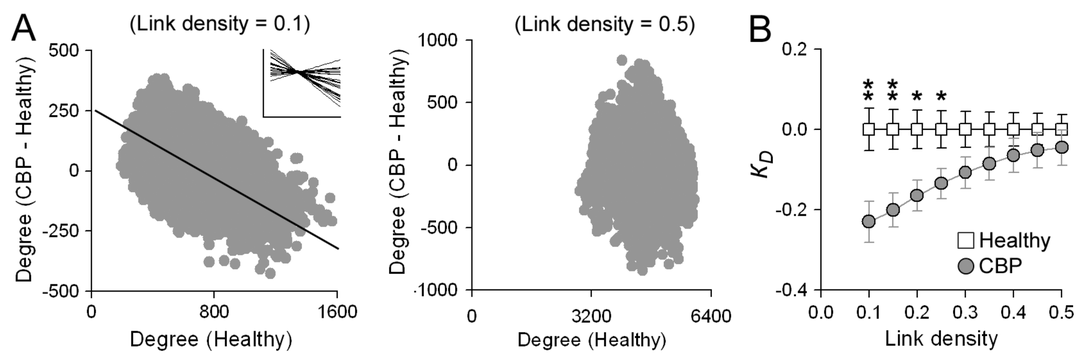
- 25 chronic back pain (CBP) patients (mean age 47.5 years, 16 females, mean pain duration = 15.4 years) and 25 matched healthy controls were scanned once during resting state fMRI (300 volumes, 10 minutes).
- An additional 12 sub-acute back pain (SBP) patients (mean age 42.7, 7 females, mean pain duration = 10.7 weeks) were scanned four times over a year as they transitioned into a chronic state (same scan parameters as above).
- Resting state fMRI was also collected in rats, under isoflurane anesthesia, 5 or 28 days following peripheral nerve injury (spared nerve injury, SNI) or sham (12 animals per group).
- Human fMRI data was preprocessed (skull extraction, spatial smoothing, slice time correction , motion correction, global BOLD signal correction), registered to standard space and subsequently sub-sampled so as to yield 7900 isometric (6*6*6 mm) voxels (nodes). Animal fMRI data was preprocessed in a similar fashion and sub-sampled to 15000 isometric (0.4*0.4*0.4 mm) voxels.
- Functional correlation matrices were generated using pair-wise Pearson correlations and thresholded over a range of values, to generate binary undirected graphs with connection densities (number of edges proportional to the maximum possible number of edges) in the range 0.1 (10% of total links, sparsely connected) to 0.5 (50 % of total links, highly connected).
- Differences in the global network properties(clustering coefficient, efficiency and mean degree) between groups were computed using the Sporn connectivity toolbox. In addition, the hub disruption index (Kd) , which estimates the global pattern of abnormally increased or decreased nodal properties (Achard et al 2012), was computed and contrasted between groups at all link densities

1 CBP and healthy controls exhibited similar global functional connectivity properties

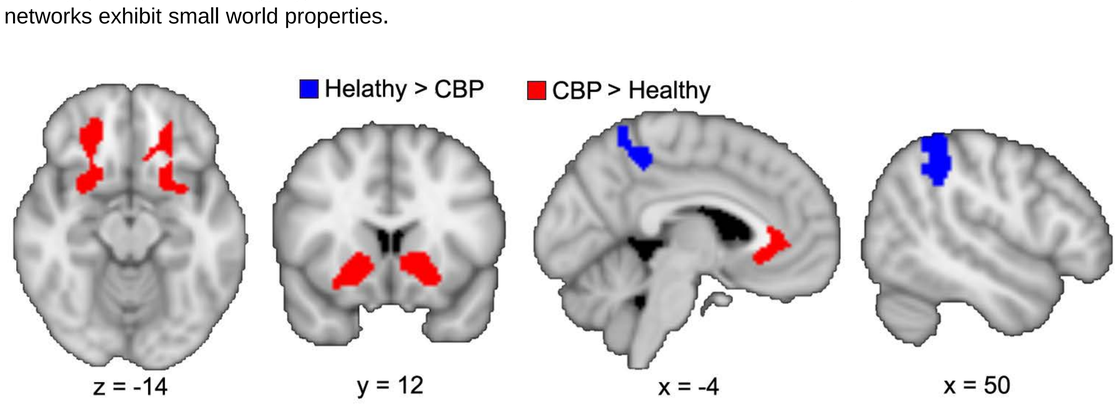


Clustering (a topological measure of segregated information transfer) and efficiency (a topological measure of integrative information transfer inversely related to characteristic path length)did not show any differences between healthy volunteers (white) and CBP patients (gray). Right panel show the sigma across all link densities. Note that both healthy and CBP patients start exhibiting small world properties (defined as sigma >1) around link density >= 0.25 (green line).

2 CBP showed significant hub disruption only when brain networks exhibit small world properties



(A) Hub disruption of functional networks in CBP patients at two link densities. The mean degree of each node in the healthy group (x axis) is plotted versus the difference between groups (CBP –healthy) in mean degree of each node (y axis). The slope (black line) of the fitted data is the hub disruption index (Kd). **(B)** Mean±s.e.m. for Kd in healthy (white) and CBP (gray) across all link densities. Note that differences are only observed when the brain networks exhibit small world properties.



Brain images show difference in mean degree between patient and volunteer groups. Maps represent all areas that showed differences for link density 0.1 to 0.25 (i.e. all link densities that showed Kd difference). Maps were generated for the conjunction of t-test p<0.05 corrected for multiple comparisons. CBP exhibit increased degree in bilateral nucleus accumbens (NAc), orbital frontal cortices, and rostral anterior cingulate cortex (ACc) and decreased degree in primary sensory cortex (foot region) and lateral posterior parietal cortex (PCc).

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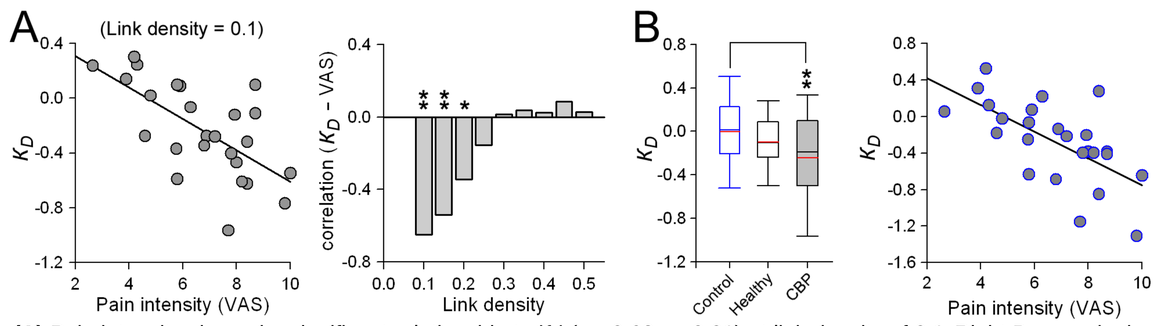
Refs

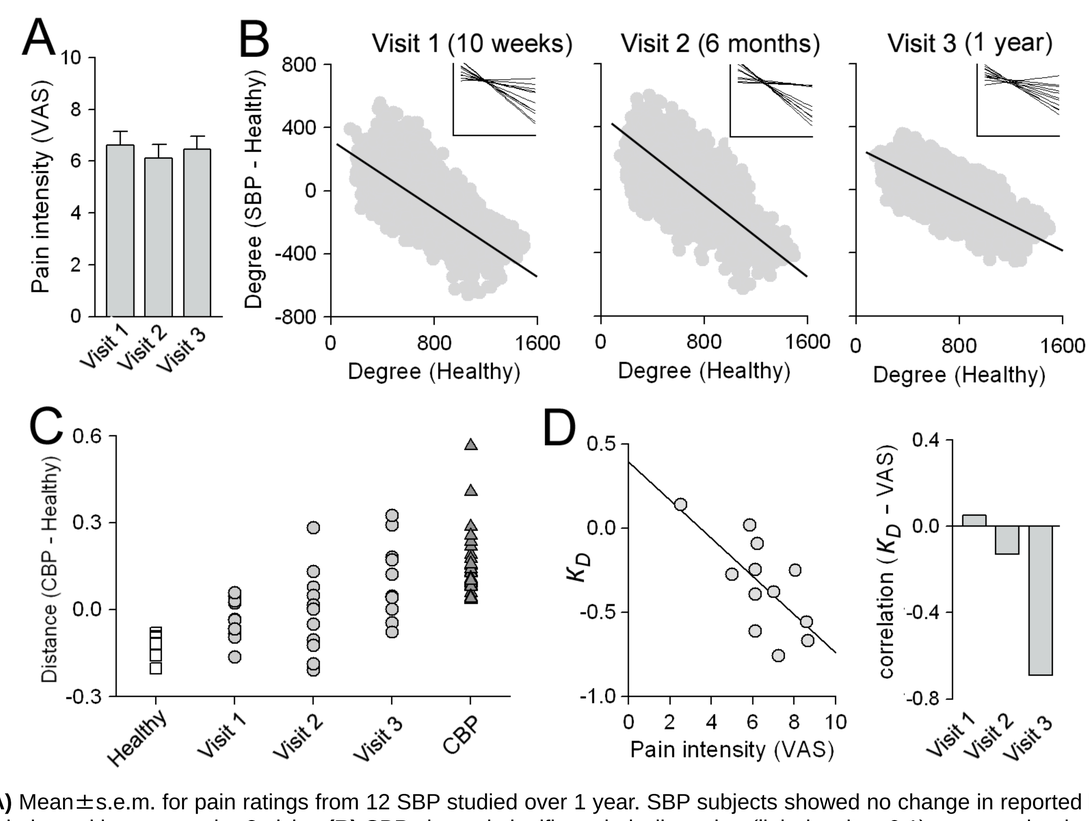
Achard, S., Delon-Martin, C., Vertes, P.E., Renard, F., Schenck, M., Schneider, F., Heinrich, C., Kremer, S., and Bullmore, E.T. (2012). Hubs of brain functional networks are radically reorganized in comatose patients. Proc Natl Acad Sci U S A 109, 20608-20613.

3 Hub disruption in CBP is related to pain intensity



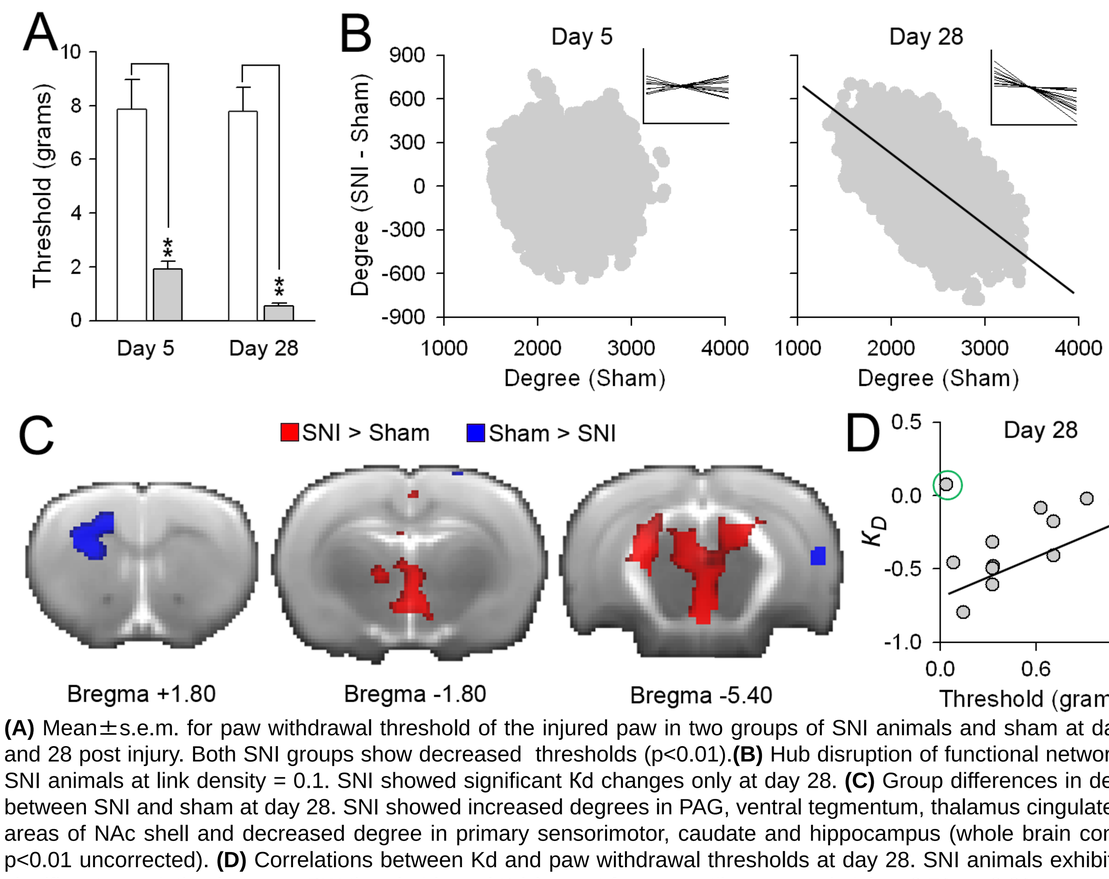
(A) Pain intensity showed a significant relationship to Kd (r= -0.68, p<0.01) at link density of 0.1. Right Bar graph show the correlation between Kd and pain across all densities. **(B)** Kd for healthy (white) subjects and CBP (gray) patients calculated using a control group selected from different subjects across different sites. CBP patients showed significant Kd compared to the control group. Kd showed a significant correlation (r= -0.71, p<0.01) when computed from an independent control group.

4 SBP showed significant hub disruption changes as pain transitioned into a chronic state



(A) Mean±s.e.m. for pain ratings from 12 SBP studied over 1 year. SBP subjects showed no change in reported back pain intensities across the 3 visits .**(B)** SBP showed significant hub disruption (link density =0.1) compared to healthy for all 3 visits (p<0.01). **(C)** Similarity between individual SBP patients computed relative to healthy controls and CBP mean group degree maps. SBP patients degree maps increase in similarity to CBP mean degree map in time. **(D)** Pain intensity showed a significant relationship to Kd at visit 1 (r= -0.69, p<0.05) but not visit 2 (r =0.5, p=0.88) and visit 3 (r=-0.13 p =0.67).

5 SNI animals exhibit significant hub disruption 28 days following nerve injury



(A) Mean±s.e.m. for paw withdrawal threshold of the injured paw in two groups of SNI animals and sham at days 5 and 28 post injury. Both SNI groups show decreased thresholds (p<0.01).**(B)** Hub disruption of functional networks in SNI animals at link density = 0.1. SNI showed significant Kd changes only at day 28. **(C)** Group differences in degree between SNI and sham at day 28. SNI showed increased degrees in PAG, ventral tegmentum, thalamus cingulate and areas of NAc shell and decreased degree in primary sensorimotor, caudate and hippocampus (whole brain contrast p<0.01 uncorrected). **(D)** Correlations between Kd and paw withdrawal thresholds at day 28. SNI animals exhibited a significant correlation between PW thresholds and Kd (except for one outlier, green circle) r= 0.71, p<0.01.

CONCLUSIONS

- Chronic pain must be viewed as a whole brain phenomenon, and directly proportional to the anatomical location and extent of reorganization of hubs in brain functional networks.
- Chronification of pain is an emergent property observed at a time when the network has stabilized into a new chronic pain state. Here we demonstrate that chronicity for back pain seems to come about sometime between 6-12 months after onset of symptoms.
- SNI animals show hub disruption in in close similarity to humans. This suggests that (1) allodynia may be considered a valid rodent parameter equivalent to pain in humans and (2) hub disruption may be used as an index for pain chronicity in rodents.
- The data add to growing body of literature that evaluates brain networks at small world scales by suggesting that only at the critical threshold at which the brain is indeed small world does the information teased out bare significant behavioral correlates.