Functional connectivity MRI can distinguish experimental pain from the resting state with seed ROI in the posterior insula, but not the anterior insula

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Introduction: The insula is well known for its role in the processing of acute and chronic pain[1]. Chronic pain is a prevalent and costly medical problem, but is difficult to experimentally model and challenging to study with functional imaging. Functional connectivity MRI (fcMRI) holds promise as a possible technique to compare brain states across distant time points, and an ability to explore brain states without an imposed experimental task. Recent work using fcMRI during painful and innocuous thermal stimulation demonstrated anatomically different connectivity: the anterior insula (aIns) was more strongly correlated to the anterior cingulate cortex (ACC), while the posterior insula (pIns) better correlated to the primary somatosensory (S1) and motor (M1) cortices[2]. This present study compares resting fcMRI maps to those during painful electric nerve stimulation (ENS), examining both correlations and anti-correlations to seed regions in the contralateral aIns and pIns. We hypothesized that insula-ACC connectivity would increase during pain processing, with a greater change seen in the aIns compared to the pIns, based on previous work[3].

Methods: BOLD data was acquired at 3 T in 14 healthy adults during REST and while painful ENS (PAIN), self-rated at 7/10, was delivered to the right index finger. Seed time courses for the contralateral aIns and pIns were extracted and functional connectivity was determined for both data sets using FSL 5.0. An optimized analysis pipeline was used[3], including low pass filtering, spatial smoothing, and regression of the global signal, motion correction parameters, and the pain stimulation model as effects of no interest. Group average and PAIN vs. REST difference maps were generated with cluster thresholds of $Z > 4$ and $p < 0.0001$.

Results: Group average functional connectivity is shown in Fig. 1 and described in the table to the right. Connectivity between the aIns and ACC was present in REST and PAIN, while only present for the pIns and ACC in REST. Notably the difference maps (Fig. 2) show almost no statistically significant PAIN versus REST differences in aIns connectivity. In contrast, the pIns showed stronger correlation to the ACC in REST compared to PAIN. Further, the pIns shows strong anti-correlation to the posterior cingulate cortex during REST, making the PAIN > REST difference significant.

Discussion: This demonstrates the impact that seed region selection can have on functional connectivity maps. Our data suggests that aIns connectivity is similar between PAIN and REST. In contrast, the pIns had dynamic connectivity changes, as evidenced by multiple areas of significance in the PAIN vs. REST difference maps; including the ACC.

Seed Region	fcMRI ROI	Dataset	
		Rest	Pain
		Max Z	Max Z
Anterior Left Insula	Right Insula	19.60	17.39
	ACC	14.25	14.54
	Left SI	-	7.02
	Left SII	11.29	10.45
	Right SII	12.73	6.78
	PCC	-11.25	-13.01
Posterior Left Insula	Right Insula	14.67	10.95
	ACC	9.19	7.26
	Left SI	10.01	10.73
	Left SII	13.13	9.74
	Right SII	12.07	11.64
	PCC	-9.20	-8.02

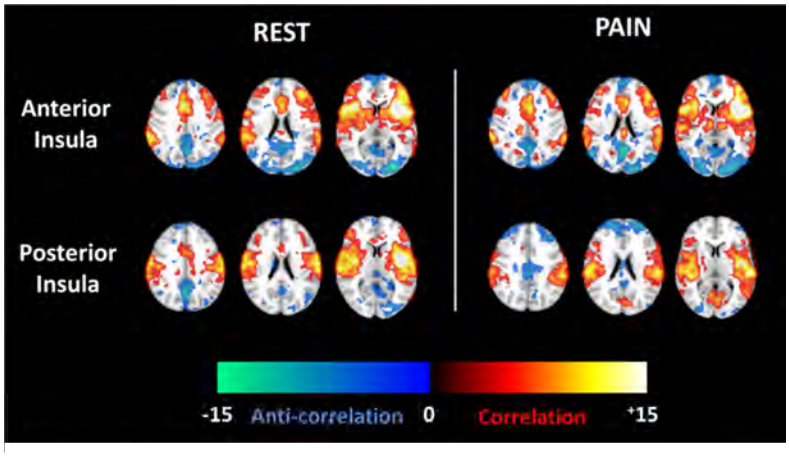

Fig. 1. Group average functional connectivity maps with color bar showing Z-score of significant correlations to the two left insula seed regions.

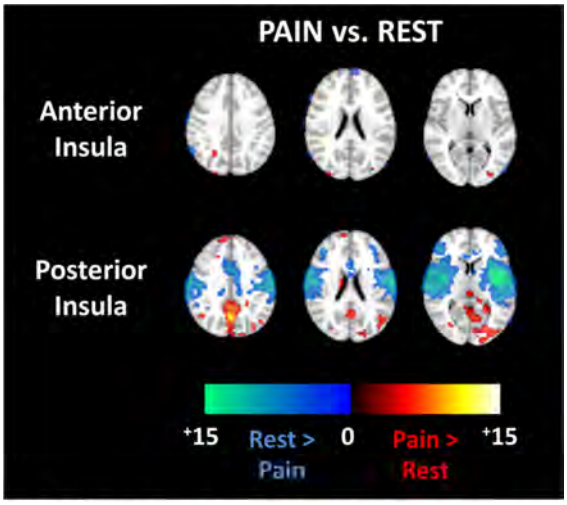

Fig. 2. Maps of significant connectivity differences for the Pain > Rest (red-yellow) and Rest > Pain (blue-green) comparisons, with Z-scores as shown on the color bars.

Conclusion: Seed region analysis using the posterior, but not anterior, portion of the insula can differentiate the presence or absence of pain.

References: 1. Apkarian AV, et al. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463-84.
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3. Vogt KM, Ibinson JW. fcMRI maps during pain tasks vary based on the inclusion of paradigm modeling in analysis. J Pain 2014;15:S57.