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Co-Activation Patterns Reveal Differences In Neural Representations Of Experimental Pain

Timothy Jordan, PhD, Alia Lawhorne, Niveen Kaddoura, Priyanka Bhanushali, Daniel Harper, PhD
Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA

Pain Stimulus Processing & Research

Current Research
- Pain Stimulus chosen without explanation or based on perceived relation to condition being studied
- Considered neurologically equal

Pain Processing of Heat and Pressure
- Macroscopically similar, but microscopically unequal
  - Neural Encoding that produces differing pain sensations
  - Low vs High Threshold activations
  - Pain Onset Time differences

Innovation
- Alternative neural encoding will create separate neural patterns relating to the specific type of pain stimulus
- Development of neural activity informed pain stimulus decisions in pain research

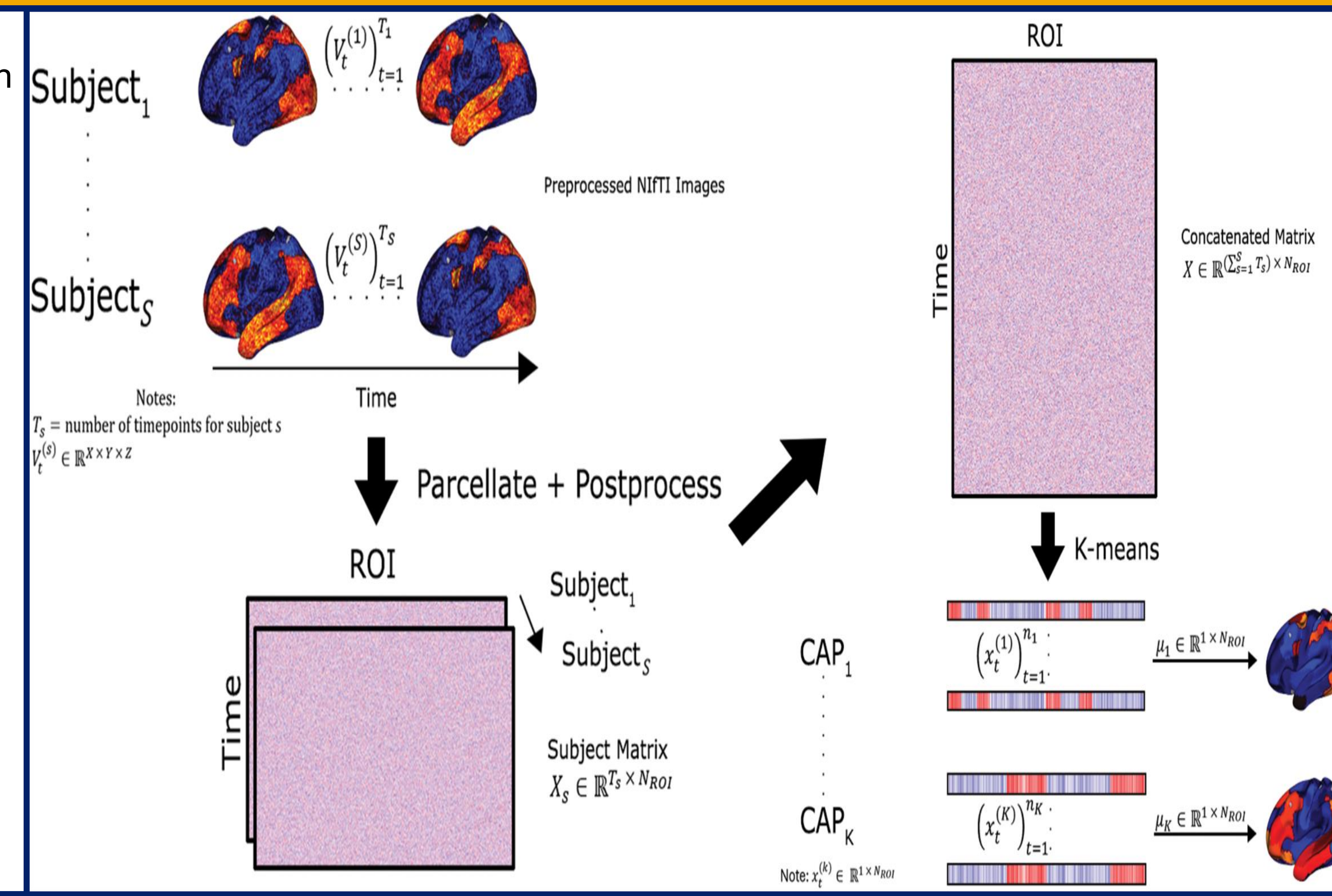
Figure 1: Application of Pain Stimuli to participant's leg. Pressure pain was delivered via blood pressure cuff (**Top**) and thermal pain delivered via thermode (**Bottom**).

Study Design & Analysis

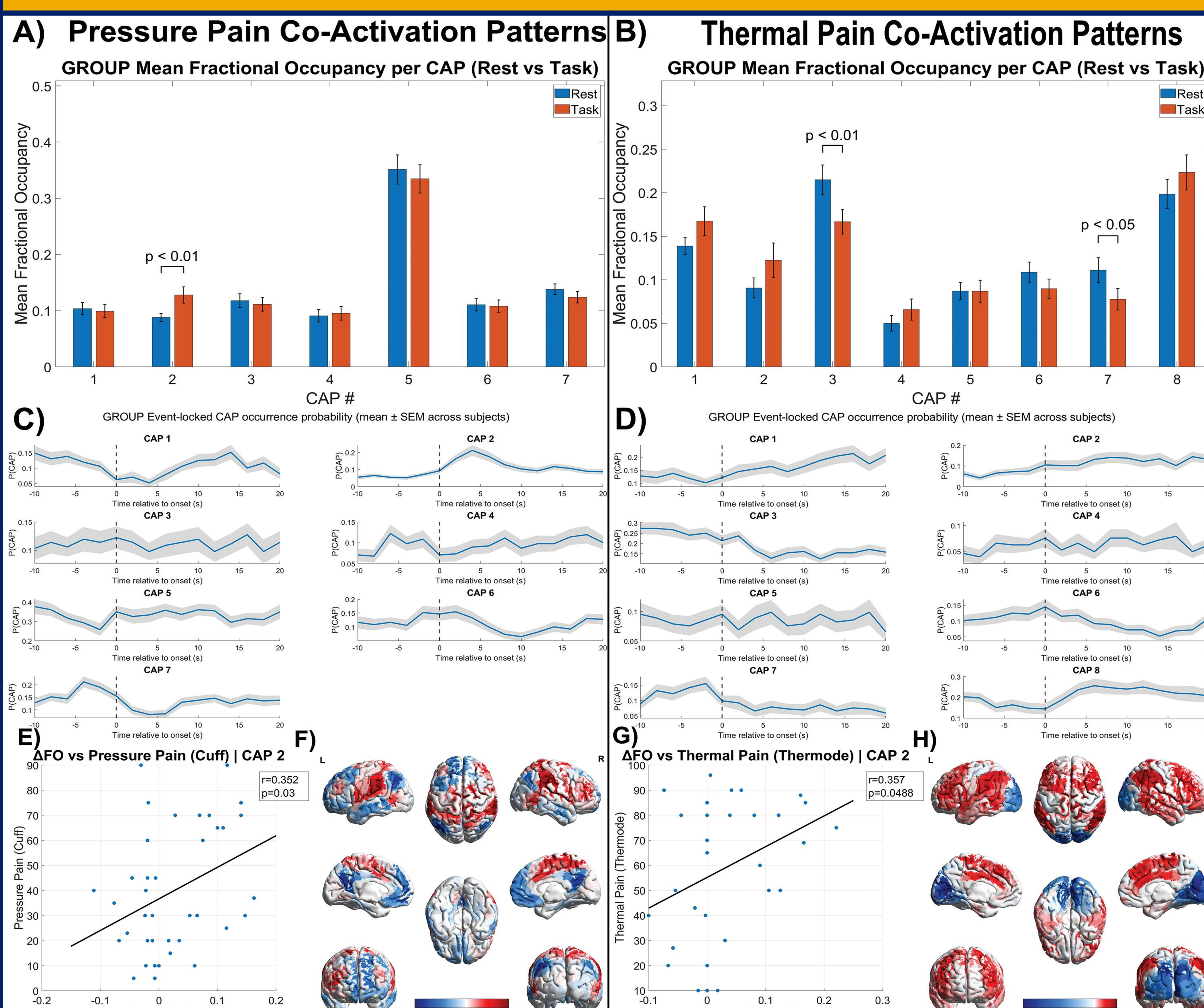
Group	Cuff	Medoc
N	46	38
Sub-Group	People w/ TMD: 27 (59%) People w/o: 19 (41%)	People w/ TMD: 22 (58%) People w/o: 16 (42%)
Sex	Male: 9 (20%) Female: 37 (80%)	Male: 6 (16%) Female: 32 (84%)
Age (mean ± std)	36 ± 14 yrs	40 ± 15 yrs

- Thermal Stimulation delivered by Medoc TSA 2 Stimulator with 30mm x 30mm thermode stimulation
- Pressure Pain delivered by PSI controlled Blood Pressure Cuff
- Schaefer 400 Atlas used for Parcellation
- NeuroCAPs[1] Software used for Co-Activation Pattern Analysis
- See preprocessing pipeline here:

Figure 2: Co-Activation Analysis Pipeline. Preprocessed fMRI data per subject is parcellated using the Schaefer 400 Atlas and then concatenated in time. All timepoints are separated into a specified number of states using a K-means algorithm to find the centroid of each state.



Task-Related Co-Activation Patterns



Co-Activation Differences Between Heat and Pressure Pain

- **7 CAPs were found for Pressure Pain and 8 CAPs were found for Heat Pain**
- **Task-Related CAPs for each stimuli were determined and found to have moderate correlations with induced pain**
- **Heat Pain induced regions in the Prefrontal and Temporal areas not seen in Pressure Pain**
- **The Heat Pain CAP had lower activations in the Visual regions, but higher in the Prefrontal and Parietal Areas**

Figure 3: Measures for Determining Task-related CAP per pain stimulus. **A-B)** Group-mean fractional occupancy of each CAP during rest (blue) and task (red) periods. **C-D)** Group-mean probability plots showing the probability of a specific CAP occurring 10 seconds prior to stimulus onset and 20 seconds after stimulus onset. **E&G)** Whole-brain view of task-related CAP for Pressure Pain and Thermal Pain, respectively. For both cases, CAP 2 was found to be task-related. Regions shown in red were activated during the task-related CAP and regions shown in blue were deactivated during task-related CAP. **F&H)** Scatter plot showing the correlation between the change in Fractional Occupancy (ΔFO) and participant self-rated pain from stimulus. Both CAPs were found to have moderate positive correlations between ΔFO and pain ratings. The more each state occurred during task periods the more pain participants reported having.

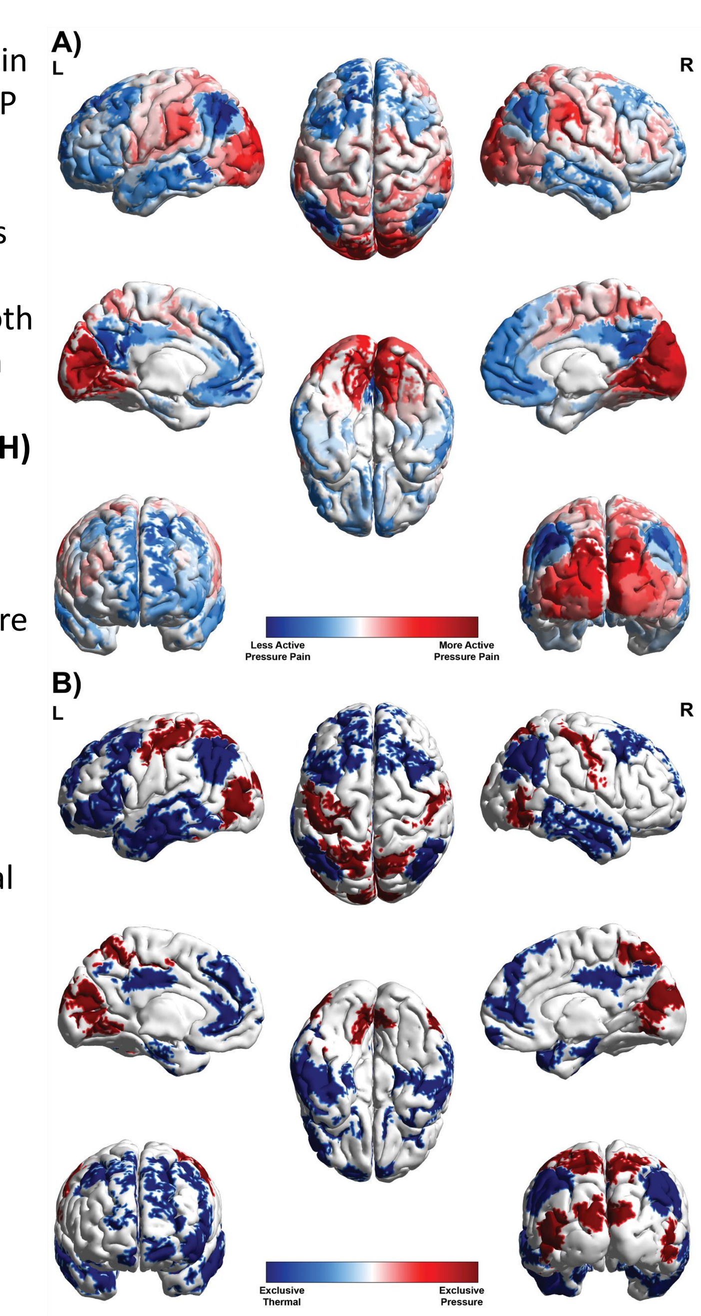
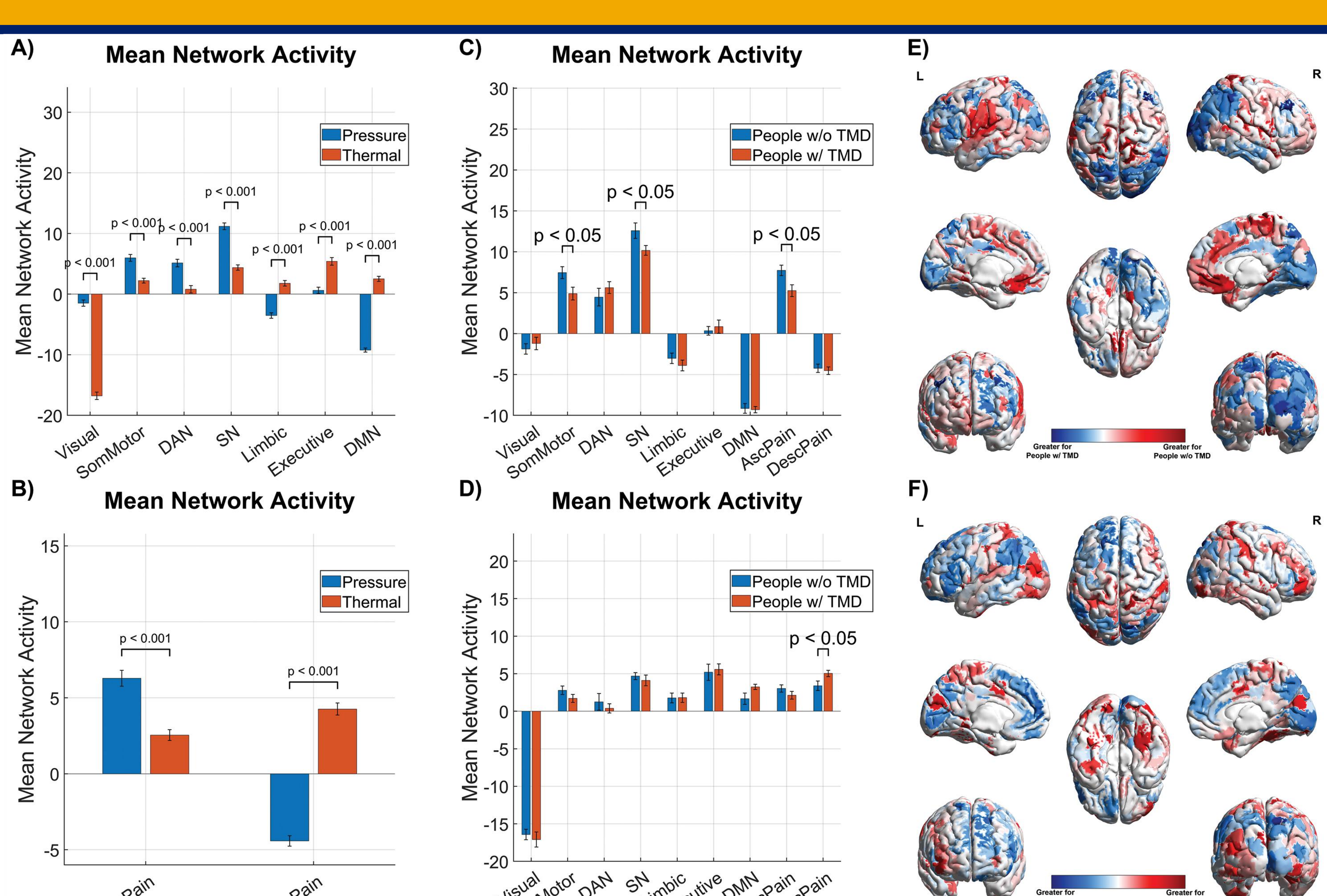


Figure 4: A) Differences in regional activity between CAP 2 from the Pressure Pain Stimulus and CAP 2 from the Thermal Pain stimulus. Regions found to be more active during Pressure Pain are shown in red, while regions found to be more active during Thermal Pain are shown in blue. **B)** Regions that are active only during the CAP of one stimulus. Regions show in red were found to be only active during pressure pain, while regions in blue were found to be active during thermal pain only.

Networks Activity Changes depending on the Pain Stimuli Delivered

Figure 8: A) Network-level activity differences between the pressure pain CAP and the thermal pain CAP for the 7 Yeo Networks. Pressure pain (blue) was found to active the Visual, Somatomotor, Dorsal Attention, and Salience Networks more than Thermal Pain (orange). Thermal pain (orange) was found to have higher activity in the Limbic, Executive, and Default-mode Networks. **B)** Network-level activity differences between the pressure pain CAP and the thermal pain CAP for the ascending and descending pain networks. Pressure pain was found to have higher activity in the ascending pain network, while thermal pain was found to have higher activity I the descending pain network. Both networks showed activity in the ascending pain network, but pressure pain showed greater deactivations in the descending pain network contrary to thermal pain. **C-D)** Network-level activity differences between People without (blue) and with (orange) TMD for pressure pain (**C**) and for thermal pain (**D**). **E-F)** Differences in regional activity between people with and without TMD for pressure pain (**E**) and thermal pain (**F**). Regions shown in red were found to have higher activity for people without TMD and regions show in blue were found to have higher activity in people with TMD.



Discussion

Conclusions:
- Heat and Pressure pain activate separate and overlapping pain processing patterns in the brain, utilizing different regions and networks.
  - Heat Pain induces more activations in the Limbic, Executive Control, and Default Mode Networks, while more greatly suppressing the Visual Network
  - Pressure Pain induces more activations in the Somatic Motor, Dorsal Attention and Salience Networks, while suppressing the Default Mode Network.
- Task-related CAP for Heat Pain activates both the Ascending and Descending Pain Networks, while the task-related CAP for Pressure Pain only utilizes the Ascending Pain network
- Pain Stimuli are encoded differently in the brain, and this must be taken into consideration during pain research designs so that regions of interest are activated during the task.

Future Directions:
- Examine neural activations of pain stimuli that activate the same microscopic pain pathways in Aδ and C Fibers to see if their patterns are similar
  - Chemical vs Heat Pain
  - Different heat stimuli (Laser-induced, Radiant, Thermode)
- Expand this analysis into dynamic functional domains to see if there are dynamic encoding differences between pain stimuli

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References
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