Pain activation and resting-connectivity are altered by intravenous lidocaine: A functional MRI in healthy young adults

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Introduction: Intravenous lidocaine infusions have been increasingly employed as a means to provide opioid-sparing pain relief. Persistence of these effects for hours to days after termination of the infusion suggests the involvement of higher-brain processes rather than direct sodium channel blockade in the periphery as the mechanism for systemic lidocaine. Despite these unknowns, little attention has been focused on the brain response to systemic lidocaine administration in humans. This study aimed to quantify the effects of lidocaine infusion on functional MRI (fMRI) measures of the brain response to acute painful stimulation and functional connectivity.

Methods: Data is reported from 27 volunteers (13 male, range 20-55 years, mean 31.4 years) in an open-label observational study. An electric nerve stimulator was connected to the left index finger and titrated to a subjective pain rating of 7/10 intensity using a verbal numerical rating scale. After connection to standard monitors and initiation of a saline carrier infusion, participants underwent 3 T MRI. An acute pain task with five 10 s painful electric nerve stimulations was followed by an 8-minute resting-state scan. In both scans, blood oxygen-level dependent weighted fMRI images were obtained every 800 ms with 2.1 mm isotropic spatial resolution. Lidocaine was then dosed to achieve an effect site concentration of 1.5 mcg/mL using stanpumpR (//stanpumpr.io/). After steady-state was predicted, the pain task and resting-state fMRI scans were repeated under the lidocaine condition. Pain ratings obtained after each pain stimulation period were compared with the Related-Samples Wilcoxon Signed Rank Test. FMRI task analysis was done with FSL (//fsl.fmrib.ox.ac.uk/) using a paired mixed-effects model. Resulting group average maps were thresholded for an adjusted $p < 0.05$, after a cluster significance threshold of $Z > 2$, correcting for multiple comparisons. Connectivity analysis was performed with Conn toolbox (//web.conn-toolbox.org/) using a region-of-interest (ROI) to ROI approach. ROI-level inferences were based on parametric multivariate statistics, combining the connection-level random-effects statistics across all connections from each ROI with the familywise false-discovery rate set at $p < 0.05$.

Results: The total dose of lidocaine was 1.8 +/- 0.1 mg/kg (range 1.7 to 2.0 mg/kg) administered over a mean time period of 27 minutes (range= 21-33 min). No subjects experienced sedation or lasting side effects. Pain intensity scores (mean, standard deviation) at baseline (6.8, 0.8) were slightly higher than under lidocaine (6.4, 1.0), with a mean rating difference of 0.44 (95% confidence interval 0.01 to 0.88, p=0.045). Pain unpleasantness scores at baseline (6.3, 1.6) were higher than under lidocaine (5.7, 1.7), with a mean rating difference of 0.56 (95% confidence interval 0.11 to 1.0, p=0.016). Brain fMRI responses to pain were decreased under lidocaine (Fig. 1) in the insula, cingulate, left thalamus, bilateral primary somatosensory cortex, left cerebellum, bilateral putamen, right primary motor cortex, medial prefrontal cortex, and a small portion of the left hippocampus. Functional connectivity was predominantly decreased both within and between hemispheres (Fig. 2), with predominance of temporal lobe ROIs identified, However, connectivity changes were also seen in frontal, occipital, parietal, and cerebellar areas, as well as deeper brain structures such as the putamen, amygdala, hippocampus, and cingulate.

Conclusions: Intravenous lidocaine at an effect site-concentration of 1.5 mcg/mL significantly affected fMRI measures of brain function. Lidocaine was associated with broad reductions in fMRI response to experimental painful stimulation in regions commonly involved in acute pain processing. Lidocaine modulated whole-brain functional connectivity, predominantly decreasing long-range connectivity with some predominance in temporal lobe structures. Small but significant decreases in pain ratings were also observed. This suggests that lidocaine modifies the pain experience by modulating both primary sensory processing and affecting higher-level processing of the noxious stimulus. This work lays the foundation for better understanding of systems-level neuroscience changes that occur with lidocaine, working towards refining the clinical use of this important opioid-alternative analgesic agent.

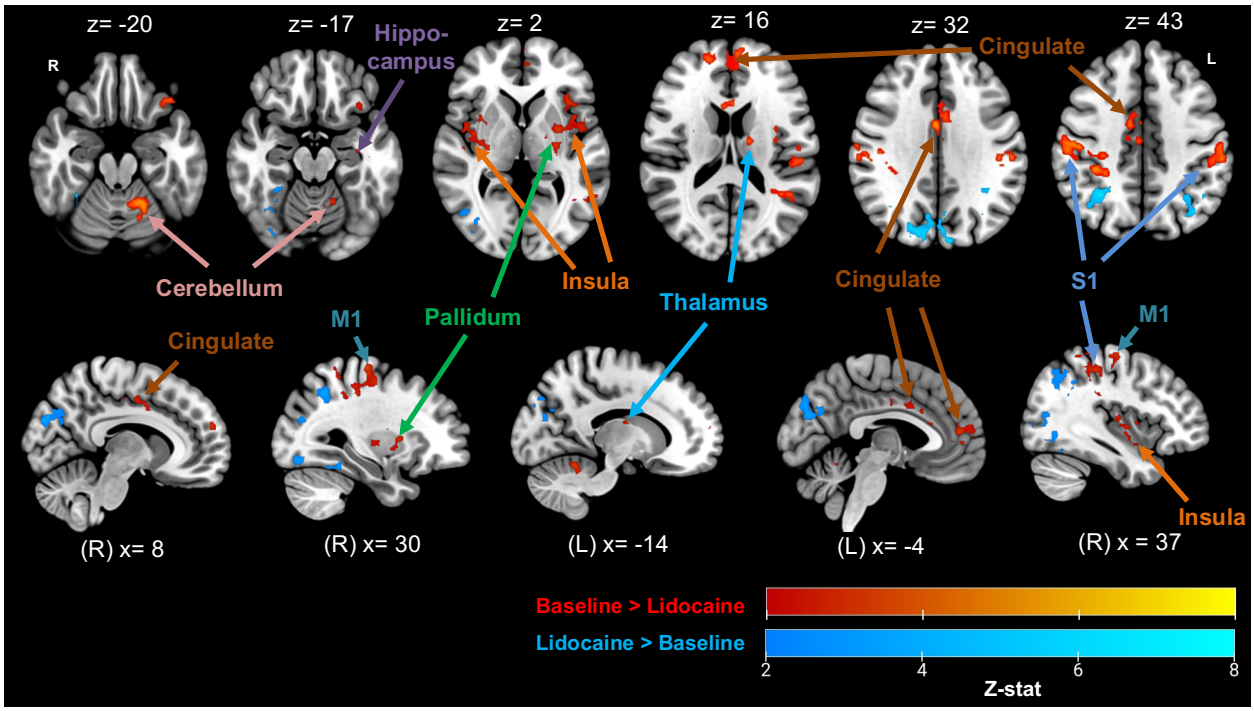

Fig. 1. Pain task functional MRI differences for baseline vs. lidocaine condition, averaged across subject. These are in radiologic orientation (right brain on left side of image). Color bars indicate strength of statistical difference, cluster corrected (for multiple comparisons) and thresholded at Z> 2, p< 0.05. Slice numbers refer to coordinates in the MNI-152 standard space template. S1= primary somatosensory cortex, M1= primary motor cortex, R= right, L=left

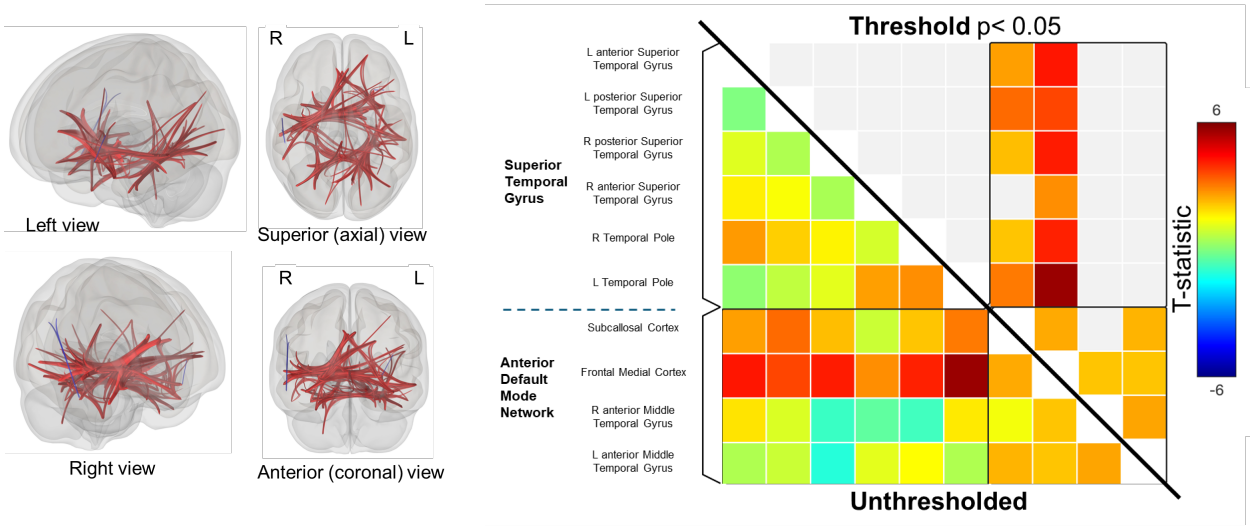

Fig 2. Group differences in resting connectivity, using hierarchical clustering with multivariate pattern analysis. Left panel shows anatomical locations; right panel shows strength of connectivity change, with unthresholded results in the bottom-left half of the grid and significant connectivity changes (FDR-p < 0.05) in the top-right half of the grid. L= left, R= right