#4_Brain modulation by sevoflurane and nitrous oxide during memory encoding and periodic painful stimulation: A 3 T functional MRI study in healthy young adults

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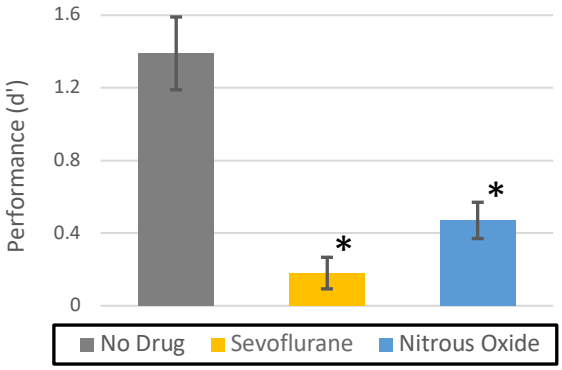
Introduction: Sevoflurane and nitrous oxide (N_2O) are mechanistically distinct inhalational anesthetic agents with different clinical profiles for memory impairment and analgesia. While both agents are known to affect cognitive function and pain perception, their effects on human brain systems for memory encoding and pain processing during concurrent aversive stimulation remain poorly characterized. In this study, we employ a novel experimental paradigm of periodic painful stimulation during an auditory memory encoding task to imitate the clinical conditions under which anesthetic agents are commonly used. This paradigm was used to study the effects of sevoflurane and N_2O using 3 T functional MRI (fMRI).

Methods: This data is from two IRB-approved, pre-registered clinical trials (NCT06702631, NCT06044740) which recruited healthy adults between ages 18 and 59. A nerve stimulator connected to the left index finger was set to the subject's personal 7/10 intensity rating. Subjects listened to a series of 35 words and were instructed to create a mental picture involving the word, adding more detail as the word repeated over 6s. Twelve of the 35 words were accompanied by a 2 s painful shock. After the no-drug baseline, this experimental paradigm was then performed under 0.5 % sevoflurane (n = 29) or 70 % N_2O (n = 15) using different words. Blood oxygen-weighted images (0.8 s temporal resolution, 2.1 mm isotropic spatial resolution) were obtained at 3 T. Testing 1 day afterwards included 70 novel words, and word recognition was assessed using the normalized signal detection metric, d-prime (d'), for which 0 indicates chance performance. FMRI analysis was performed with FSL 6 (https://fsl.fmrib.ox.ac.uk/), and group results were thresholded for $Z > 2.0$ and cluster significance adjusted to an overall $p < 0.05$.

Results: Memory performance both under sevoflurane and N_2O was reduced compared to baseline (Fig. 1). FMRI signatures at baseline included robust increased bilateral activation in the anterior cingulate cortex (ACC) and lateral prefrontal and parietal cortices, including the precuneus (Fig. 2, top). The addition of the painful stimulus produced increased bilateral activation in the amygdala and insula (Fig. 3, top). Sevoflurane was associated with bilaterally decreased activation of the superior and middle temporal lobes and increased activation in the ACC, inferior temporal lobe, and the prefrontal cortex. In response to the painful stimulus, sevoflurane was associated with decreased activation in the right secondary somatosensory cortex and bilateral insula, and increased activation in the left parietal and primary somatosensory cortex (S1). N_2O was associated with bilaterally decreased activation of the superior and middle temporal lobes. In response to the painful stimulus, N_2O was associated with bilateral decreases in the insula, anterior and posterior cingulate, posterior prefrontal cortex, S1, parietal lobes, and cerebellum.



using the normalized signal detection metric d' (d-prime). Asterisks denote statistically significant differences from the no-drug condition ($p < 0.001$).

Discussion:
Sedative doses of sevoflurane and N_2O both impaired memory performance and showed reduced auditory cortex activation. Both sevoflurane and N_2O showed decreased pain-related activation in the posterior insula, a key region in pain processing. N_2O was also associated with more widespread decreases in activation throughout the pain neuromatrix, including ACC and S1, which are consistent with their analgesic

effects. Future work, including additional subject recruitment and analyses investigating successful memory encoding, will help elucidate the systems-level neural correlates for these agents.

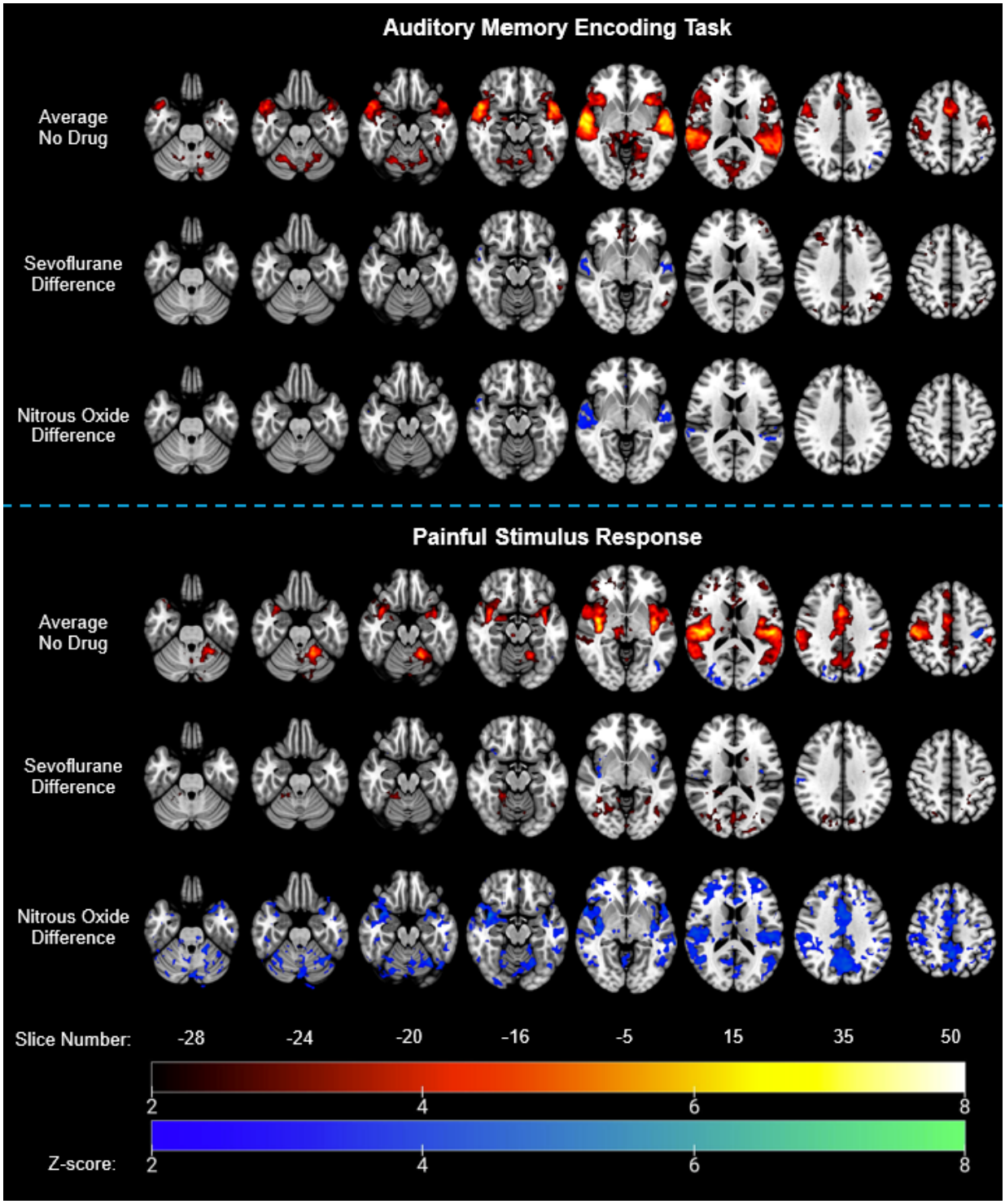


Fig. 2. All-subject average fMRI task activation for words encoded (top) and during periods experiencing painful electric nerve stimulation (bottom) for selected axial slices (left brain on right side of figure), with MNI-152 slices shown. The color bar indicates Z-score, according to the scale shown. The top row in each sub-panel shows the brain with significant positive (warm colors) or negative (cool colors) correlation to the task under the no-drug condition. The subsequent

rows display areas of significant differences under each drug condition (the no-drug vs. drug contrast). Warm colors indicate drug > no-drug and cool colors indicate no-drug > drug differences.