Modulation of human brain areas for memory and pain by propofol, dexmedetomidine, and fentanyl: A randomized controlled 7 T functional MRI study in healthy young adults

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Introduction: Anesthetic and analgesic drugs have distinct clinical profiles and are well-accepted to impair memory and relieve pain to varying degrees. However, anesthetic effects on the human brain systems for memory encoding and pain processing are less well demonstrated. We developed a novel paradigm with periodic painful stimulation during an auditory memory encoding task which reflects the clinical conditions under which anesthetic and analgesic agents are commonly used. This framework was used to study the effects of three different anesthetic agents using high-field functional MRI (fMRI).

Methods: This was an IRB-approved, pre-registered clinical trial (NCT04062123) of healthy adults age 40 and under. There were two separate scan sessions, both with crystalloid infusion. In one session, a constant effect-site concentration (ESC) was targeted using stanpumpR (https://stanpumpr.io/). Subjects were blinded and randomized to propofol (n= 22; ESC=1.0 mcg/ml), dexmedetomidine (n=25; ESC=0.15 ng/ml), or fentanyl (n=25, ESC=0.9 ng/ml). A nerve stimulator connected to the left index finger was set to 7/10 intensity rating. Subjects listened to a series of 80 words and while creating a mental picture involving the word, adding more detail as the word repeated over 6 s. Thirty of the words were accompanied by a 2 s painful shock, and pain ratings and sedation scores were recorded throughout. Blood oxygen-weighted images (1 s temporal resolution, 2 mm isotropic spatial resolution) were obtained at 7 T using custom hardware. Testing 1 day afterwards included 80 not previously-heard words, and assessed recognition 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 $Z > 2$ and cluster significance adjusted to $p < 0.05$.

Results: Due to inter-subject variability, pain ratings were not significantly different under any drug. Memory performance (Fig. 1) was reduced under propofol. The fMRI signature of successful memory (Fig. 2, top row) included activity in (predominantly right-sided) hippocampus (Hpc) and parahippocampal (PHC) areas. The Hpc/PHC memory areas were modulated by: propofol (right brain, decrease), dexmedetomidine (right brain, increase) and fentanyl (left brain, increase). Amygdala (bilateral) activity decreased with propofol, for the memory task. Shock-related activity (bottom half of Fig. 2) was decreased with fentanyl, in the right primary somatosensory cortex, and insula (predominantly left brain, inferior). Propofol decreased shock-related activity in the anterior cingulate, insula (bilateral), and amygdala (bilateral).

Conclusions: Propofol, dexmedetomidine, and fentanyl distinctly modulated brain areas for memory and pain processing, despite achieving similar levels of sedation. This suggests that anesthetic effects on specific aspects of cognition are mediated through different brain circuits when agents with different pharmacology are administered. Specific findings that do not match clinical intuition are: decreased activity in affective pain processing areas under propofol and modulation in memory areas under fentanyl. Further neuroimaging studies under broader anesthetic conditions will help to further elucidate the systems-level neural correlates of action for these agents.

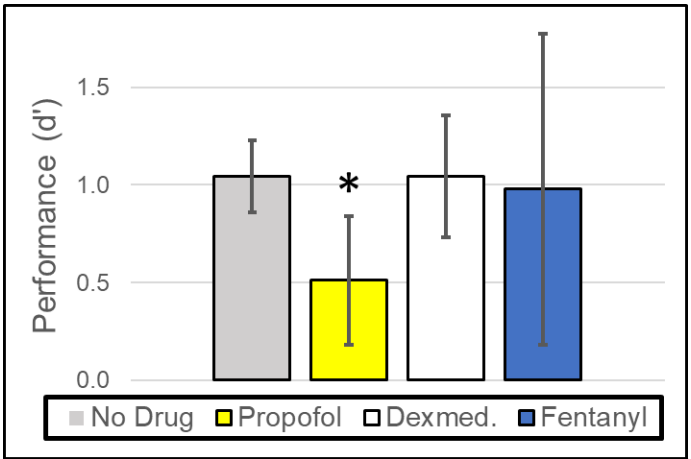

Fig. 1. Memory performance by drug, mean +/- 95% confidence interval. Dexmed.= dexmedetomidine.

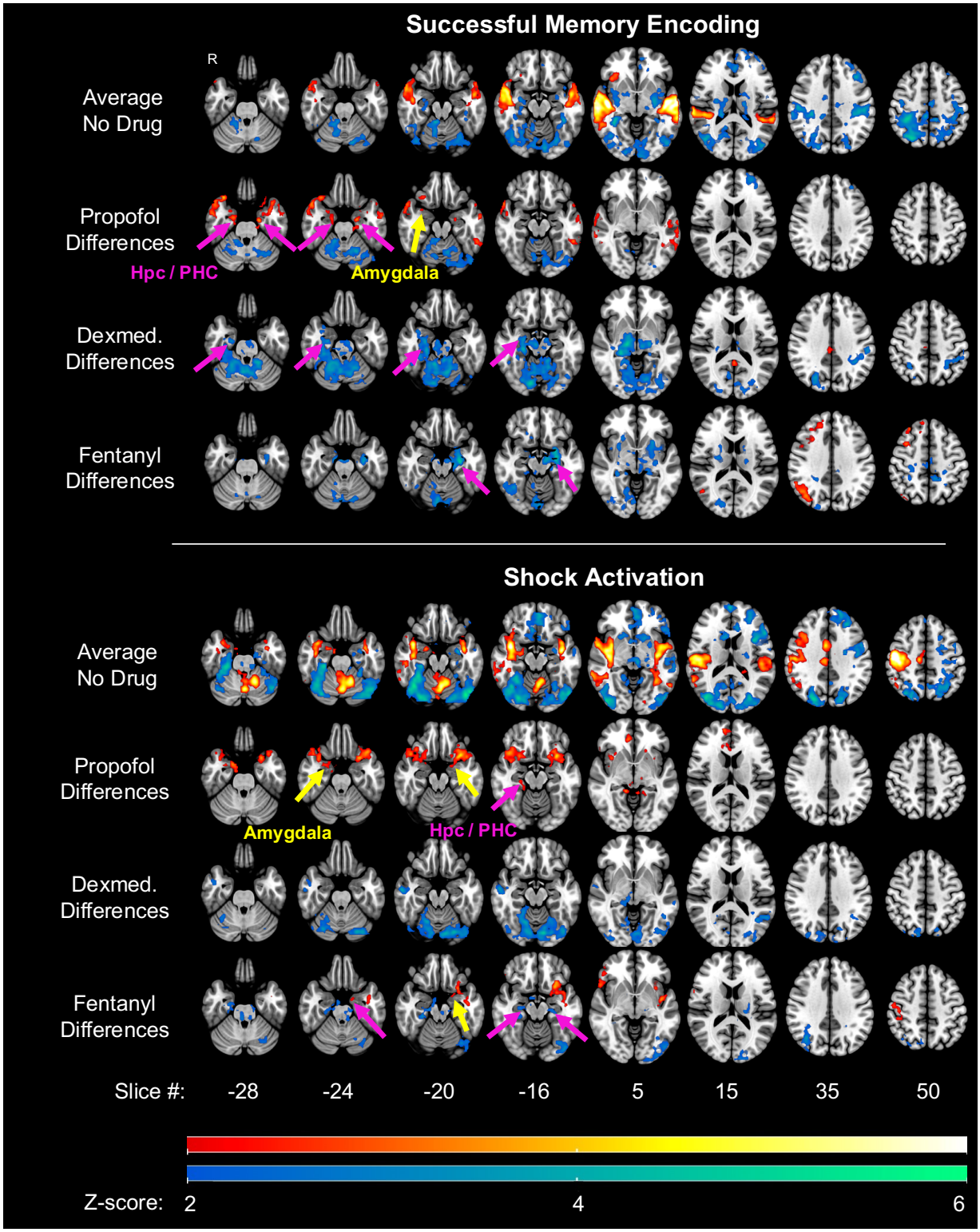

Fig. 2. All-subject average fMRI task activation for words successfully encoded (top) and during periods experiencing painful electric nerve stimulation (bottom) for selected axial slices (left brain on right side of figure), with MNI-152 slices shown. The color bar indicates Z-score, according to the scale shown. The top row in each sub-panel show 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 no-drug > drug and cool colors indicate drug > no-drug differences. Color-coded arrows indicate changes in key areas. Hpc= hippocampus, PHC= parahippocampus, Dexmed.= dexmedetomidine