#3_Modulation of functional connectivity by propofol, dexmedetomidine, and fentanyl: A randomized controlled 7 T functional MRI study in healthy young adults

Presenting Author: Keith M. Vogt
Co-authors: Marcus A. Simmons, Courtney N. Kozdron, James W. Ibinson, Helmet T. Karim.
Department of Anesthesiology, University of Pittsburgh School of Medicine; Pittsburgh, PA, USA

Introduction: Anesthetic and analgesic drugs have distinct clinical profiles and are well-accepted to affect the brain and cognition, even at subanesthetic doses. This analysis sought to characterize the systems-level changes in resting brain connectivity for three different anesthetic agents using high-field functional MRI (fMRI). Functional connectivity can be calculated on any neural timeseries data, with temporal correlations well accepted to reflect brain areas that are interacting. Changes in resting-state connectivity can be calculated between experimental conditions, including under different anesthetics.

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/). Participants 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). Blood oxygen-weighted images (1 s temporal resolution, 2 mm isotropic spatial resolution) were obtained at 7 T using a custom head coil. Data is from an 8-min resting scan obtained at the end of a session, after subjects experienced a painful stimulation paradigm (previously reported). Connectivity analysis was performed using atlas-defined regions of interest (ROIs) including, bilaterally, the anterior cingulate, posterior cingulate, insula, primary somatosensory cortex (S1), thalamus, hippocampus, and amygdala. A linear mixed effects model was run with subject as a random effect and drug as a fixed effect. Fixed effects were corrected using an FDR-adjusted $p < 0.05$.

Results: There were significant changes in resting-state connectivity between the selected ROIs, compared to the no drug scan, described in the Figures and Table, below. No drug-associated connectivity differences were seen for the thalamus, posterior cingulate, or amygdala. Propofol was associated with decreased connectivity between the right hippocampus and several subdivisions of the anterior cingulate. Both dexmedetomidine and fentanyl were associated with decreased connectivity between the left posterior insula and right S1. Somewhat unexpectedly, **IN**creases in connectivity for the right hippocampus were seen with dexmedetomidine (to the left insula) and fentanyl (to the anterior cingulate).

Conclusions: Even using very conservative thresholding, propofol, dexmedetomidine, and fentanyl distinctly modulate resting brain connectivity, with significant changes commonly affecting the right hippocampus. Given the well-known hippocampal role in explicit memory formation, this suggests that all three drugs have the potential to affect long-term memory. Additionally, both fentanyl and dexmedetomidine decreased connectivity between the posterior insula and S1, two brain areas characteristically involved in the sensory-discriminative dimension of the pain experience. These results further demonstrate that distinct anesthetic agents modulate connectivity of memory and pain-processing brain circuits, even in the absence of experimental tasks or specific cognitive effort engaging these areas.

==========

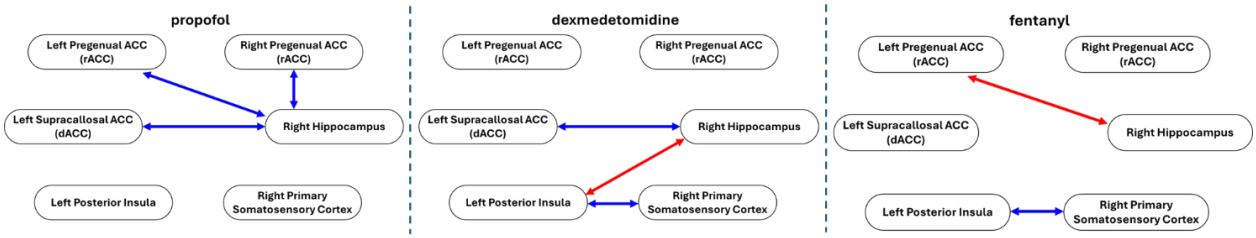

Figure 1. Connectivity changes shown by ROI. Blue lines indicate decreases and red indicate increases in functional connectivity, after overall false detection rate correction.

Table 1: Significant connectivity changes between drug and placebo sessions Legend: ROI= region of interest, CC= correlation coefficient, SE= standard error, t-stat= t-statistic, FDR-p= p-value corrected for false detection rate, L= Left, R= Right, ACC_sup= supracallosal division of the anterior cingulate cortex, AAC_pre= pregenual division of the anterior cingulate cortex

ROI 1	ROI 2	Drug	CC change	SE	t-stat	FDR-p
ACC_sup_L	Hippocampus_R	propofol	-0.1025	0.0394	-2.60	0.010600
ACC_sup_L	Hippocampus_R	dexmedetomidine	-0.0999	0.0393	-2.54	0.012386
ACC_sup_L	Hippocampus_R	fentanyl	0.0847	0.0395	2.14	0.034026
ACC_pre_L	Hippocampus_R	propofol	-0.1845	0.0434	-4.25	0.000039
ACC_pre_L	Hippocampus_R	dexmedetomidine	-0.0798	0.0434	-1.84	0.068464
ACC_pre_L	Hippocampus_R	fentanyl	0.0530	0.0434	1.22	0.224445
ACC_pre_R	Hippocampus_R	propofol	-0.1665	0.0423	-3.94	0.000128
ACC_pre_R	Hippocampus_R	dexmedetomidine	-0.0339	0.0423	-0.80	0.424073
ACC_pre_R	Hippocampus_R	fentanyl	0.0559	0.0423	1.32	0.187998
Hippocampus_R	Insula_L_posterior	propofol	0.0323	0.0380	0.85	0.397179
Hippocampus_R	Insula_L_posterior	dexmedetomidine	0.1585	0.0377	4.21	0.000057
Hippocampus_R	Insula_L_posterior	fentanyl	-0.0161	0.0382	-0.42	0.673917
Insula_L_posterior	Postcentral_R	propofol	-0.0136	0.0497	-0.27	0.784493
Insula_L_posterior	Postcentral_R	dexmedetomidine	-0.1034	0.0494	-2.09	0.038664
Insula_L_posterior	Postcentral_R	fentanyl	-0.2102	0.0498	-4.22	0.000049

Note: Corrected p < 0.05 are highlighted in green. Significant drug-related changes in connectivity are highlighted: decreases in blue and increases in red.

==========

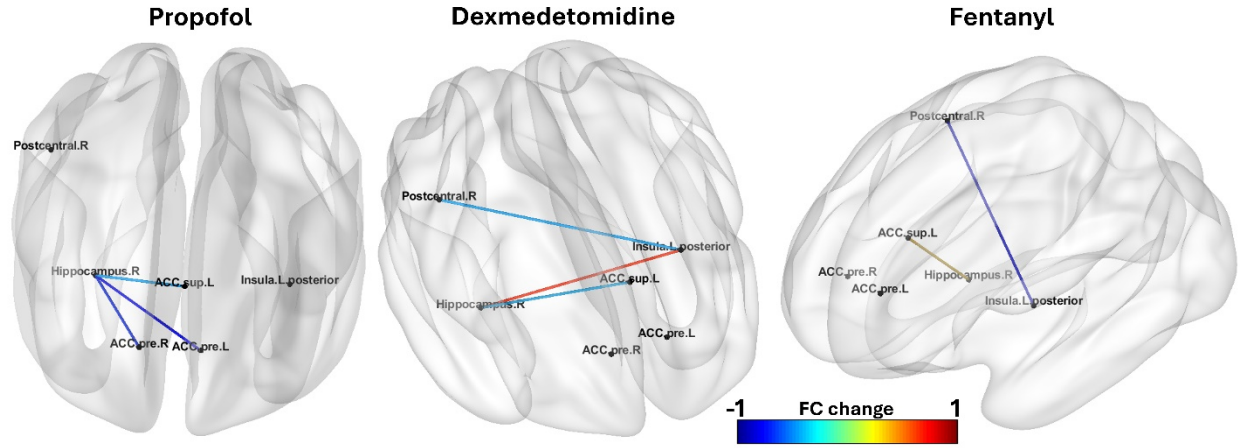

Figure 2. Connectivity changes by drug shown on brain underlays, to illustrate anatomical relationships between involved regions. Dots are located at central coordinates within the ROI they represent. ROI labels are as in Table 1 legend. Color bar represents change in functional connectivity (FC), based on numerical difference in correlation coefficients between no-drug and drug scans, with cool colors showing decreases under drug, and warm colors showing increases.