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Statistical Analysis

Analysis of numerical behavioral data, including memory performance data, was carried out with *R* software (version 4.3.1, https://www.r-project.org/). Memory and 3-back task performance were evaluated by comparing d' scores. Data were first tested for normality with the Kolmogorov–Smirnov test prior to application of two-tailed parametric statistical methods for analysis. Separate mixed models were fit for each outcome, with drug group as a fixed effect, and participant as a random effect. Interaction terms between time and drug group were fit and tested for significance and included in models if significant. $P < 0.05$ used as the threshold for significance, and values are reported both raw and P_a, indicating Bonferroni adjustment for the number of comparisons performed in the analysis.

Functional MRI data analysis

Functional MRI datasets were preprocessed using FSL 6 (https://fsl.fmrib.ox.ac.uk/) on several machines running MacOS (Apple Inc., Cupertino, CA). Subsequent acronyms are subroutines within the FSL software package. Correction for magnetic field distortion, using the acquired field maps, was performed on all functional data using TOPUP. Brain extraction was performed with BET and tissue segmentation with FAST. Based on the principle components of signal within the white matter and CSF in the functional time-series, the CompCor algorithm was used to reduce physiologic noise related to respiration and cardiac pulsatility. Motion parameters were included as a covariate of no interest in the first-level model, with censoring of any time point with root mean squared frame displacement motion over 0.9 mm. Spatial smoothing was performed with a 5 mm Gaussian kernel.

Event-related task activation was calculated based on timing of events. For the memory and conditioning task data, three subject-level contrasts were included: items subsequently recognized correctly (with either a correct Remember or Know response at next day testing), items forgotten (a false negative response at next-day testing), and the timing of all electric nerve stimulations (regardless of memory performance for the corresponding word). In the pain task data, only shock timing was used as a first-level contrast. Average task activation and drug-condition difference maps were generated by grouping data from each drug condition in a group-level mixed effects model. Two hardware and one software upgrades to the scanner over the course of the study were accounted for at the group level as effects of no interest. Clusters were initially thresholded for significance at $Z > 2$, then an additional threshold was applied that adjusted the overall analysis-level false discovery rate to $p < 0.05$. No statistical power calculation was possible for the imaging analyses; but overall sample size was based on general estimates suggesting that 24 subjects are adequate for task-based functional magnetic resonance imaging studies.