

Propofol selectively modulates functional connectivity signatures of sustained attention during rest and narrative listening

Taylor A. Chamberlain ^{1,*}, Monica D. Rosenberg ^{1,2,*}

¹Department of Psychology, The University of Chicago, 5848 S University Ave, IL 60637, Chicago,

²Neuroscience Institute, The University of Chicago, 5812 South Ellis Ave., MC 0912, Suite P-400, IL 60637, Chicago

*Corresponding authors: Email: tchamberlain@uchicago.edu and mdrosenberg@uchicago.edu

Abstract

Sustained attention is a critical cognitive function reflected in an individual's whole-brain pattern of functional magnetic resonance imaging functional connectivity. However, sustained attention is not a purely static trait. Rather, attention waxes and wanes over time. Do functional brain networks that underlie individual differences in sustained attention also underlie changes in attentional state? To investigate, we replicate the finding that a validated connectome-based model of individual differences in sustained attention tracks pharmacologically induced changes in attentional state. Specifically, preregistered analyses revealed that participants exhibited functional connectivity signatures of stronger attention when awake than when under deep sedation with the anesthetic agent propofol. Furthermore, this effect was relatively selective to the predefined sustained attention networks: propofol administration modulated strength of the sustained attention networks more than it modulated strength of canonical resting-state networks and a network defined to predict fluid intelligence, and the functional connections most affected by propofol sedation overlapped with the sustained attention networks. Thus, propofol modulates functional connectivity signatures of sustained attention within individuals. More broadly, these findings underscore the utility of pharmacological intervention in testing both the generalizability and specificity of network-based models of cognitive function.

Key words: resting-state functional connectivity; individual differences; attention networks; connectome-based predictive modeling; fMRI; propofol.

Introduction

Attention fluctuates within individuals not only due to natural changes in arousal, such as dozing off during a long lecture, but also due to pharmacological intervention, such as in the use of methylphenidate in the treatment of attention-deficit hyperactivity disorder (ADHD). Pharmacologically induced differences in attentional state have measurable real-world consequences; children who are prescribed methylphenidate for ADHD show significant improvement in academic performance metrics such as math accuracy and reading speed (Kortekaas-Rijlaarsdam et al. 2018).

To what extent are pharmacologically induced changes in cognitive and attentional state reflected in patterns of whole-brain functional connectivity? Work suggests functional connectivity is dominated by stable individual traits, with relatively little contribution of state-related variance to an individual's functional connectome. For instance, Gratton et al. contrasted subject-dependent, task-dependent, and session-dependent variation in the functional connectome and found that the vast majority of variation could be attributed to subject-dependent effects (Gratton et al. 2018).

At the same time, other work has provided evidence that functional connectivity does, in fact, vary meaningfully with changes in mental states. For instance, recent work found an increase in the network strength of a functional connectivity-based model of mind-wandering over the course of four runs of rest scans, in tandem with a decrease in ratings of thoughts related to the external world (Kucyi et al. 2021). The sustained attention connectome-based predictive model (CPM), a model of individual differences in sustained attention, has also been shown to be sensitive to within-subject attention changes (Rosenberg, Finn, et al. 2016). The model consists of two functional networks, both defined in a data-driven manner, which predict better and worse attention, respectively. The model has been validated in its prediction of individual differences in attention function across multiple independent datasets and is sensitive to the effects of methylphenidate administration such that individuals given a single dose before functional magnetic resonance imaging (fMRI) show functional connectivity signatures of better sustained attention (Rosenberg, Zhang, et al. 2016). Furthermore, individuals under deep sedation with propofol and light

anesthesia with sevoflurane showed functional connectivity signatures of worse sustained attention compared to when they were resting while awake (Rosenberg et al. 2020).

Here, with a preregistered replication in an independent fMRI dataset, we add to this growing body of evidence by examining the effect of propofol on the sustained attention CPM—as well as the selectivity of this effect—during rest. Furthermore, we examine the effect of propofol on the sustained attention networks in an entirely new context: listening to a suspenseful movie clip from an action-thriller film. We test the hypothesis that connectome-based models do not always capture equal state-like and trait-like variability in the behavior they were defined to predict. Instead, networks defined to predict more trait-like abilities, such as fluid intelligence, may be less sensitive to within-subject cognitive and attentional state changes. Finally, we investigate the effect of propofol on functional connectome patterns more broadly, characterizing the degree to which propofol administration increases or decreases connectome similarity between individuals and across task states. Together, these results illuminate the effects of propofol sedation on the strength of networks predicting cognitive performance and on functional connectome similarity. They also demonstrate the feasibility of testing the generalizability and selectivity of brain-based predictive models in independent datasets using preregistered hypotheses.

Materials and methods

Dataset

We performed secondary analyses of data available on [Openneuro.org](https://openneuro.org/datasets/ds003171) (https://openneuro.org/datasets/ds003171) (Naci et al. 2018; Kandeepan et al. 2020). In this dataset, fMRI data were acquired while participants rested and listened to a 5:12-min audio clip from the film “Taken” at four different levels of sedation with the anesthetic agent propofol.

Participants

Seventeen healthy, right-handed, native English speakers (4 women; mean age: 24 years, SD = 5) participated in the original study, which was approved by the Health Sciences Research Ethics Board and Psychology Research Ethics Board of Western University (REB #104755). All participants completed a magnetic resonance imaging (MRI) and propofol safety screening questionnaire provided by both the attending MR technician and anesthesiologist, provided informed consent and were paid for their participation. Secondary analysis of these data was approved by the University of Chicago Institutional Review Board. Scans for which >50% of frames were censored for head motion (see “Functional MRI data preprocessing”) were excluded from analyses. Of the 17 participants, 10 had “awake” and “deep sedation” resting-state scans that passed motion exclusion, and 10 partially

overlapping participants had “awake” and “deep sedation” narrative-listening scans. All analyses were performed on these 2 sets of 10 participants, with the exception of the “Functional connectivity similarity analyses” (see below).

Task protocol

fMRI scans were acquired during four different levels of sedation: “awake, mild, deep,” and “recovery.” During each level of sedation, rest and narrative-listening scans were acquired (8 and 5 min, respectively). During the rest scan, participants were instructed to relax with their eyes closed without falling asleep. During the narrative-listening scan, participants listened to an audio excerpt from the movie “Taken.” In this emotionally evocative clip, listeners hear a teenage girl being kidnapped while speaking to her father on the phone. During each of the four sedation conditions, the narrative scan preceded the rest scan.

Propofol administration and sedation assessment

Before fMRI data acquisition for each of the 4 levels of sedation, 2 anesthesiologists and 1 anesthesia nurse evaluated volunteers’ Ramsay level, which classifies a person’s level of sedation on a scale from 1 (severe agitation) to 6 (deep coma). Scanning for each session began once the 3 anesthesia assessors agreed on the participant’s sedation level. During the “awake” session, no propofol was administered. Propofol infusion began prior to the “mild” session, and the “mild” session commenced once participants reached Ramsay 3 level of sedation in which participants’ response to verbal communication slowed. Prior to the “deep” session, propofol target effect-site concentration was increased until participants reached a Ramsay 5 level of sedation in which participants stopped responding to verbal commands. Following the “deep” sedation scan, propofol infusion was discontinued, and once a Ramsay 2 level of sedation was achieved, the “recovery” session commenced. At Ramsay level 2, participants exhibited quick responses to verbal commands. For detailed descriptions of propofol administration protocol, see Naci et al. (2018).

fMRI data acquisition

Participants wore noise-canceling headphones, and volume was adjusted to each participant’s level of comfort (Naci et al. 2018). MRI data were acquired with a 3-Tesla Siemens Tim Trio scanner (32-channel coil). Functional images were collected with the following parameters: voxel size = $3 \times 3 \times 3$ mm³, inter-slice gap of 25%, time repetition (TR) = 2,000 ms, time echo (TE) = 30 ms, matrix size = 64×64 , FA = 75°. Narrative scans and resting-state scans had 155 and 256 volumes, respectively. Anatomical images were acquired as well with a T1-weighted 3D MPRAGE sequence (32-channel coil, voxel size: $1 \times 1 \times 1$ mm³, TE = 4.25 ms, matrix size = $240 \times 256 \times 192$, FA = 9°).

Preregistration

Primary hypotheses, planned tests, and fMRI preprocessing steps were preregistered on the Open Science Framework prior to data analysis (<https://osf.io/5jpgc> last accessed: Jan 27th 2022). Hypotheses and tests described in the Network strength calculation and Network strength as a function of sedation level sections of the Materials and methods were preregistered. Follow-up analyses described in the Selectivity of propofol effects, Propofol network identification, and Functional connectivity similarity analyses sections were not preregistered.

fMRI data preprocessing

fMRI preprocessing steps (with two minor changes, detailed below) were preregistered prior to data analysis. AFNI was used to preprocess fMRI data. First, three volumes were removed from each run, followed by despiking and head motion correction. Then, functional images were aligned to the skull-stripped anatomical image with a linear transformation and then to the Montreal Neurological Institute atlas via nonlinear warping. Covariates of no interest were regressed from the data, including a 24-parameter head motion model (6 motion parameters, 6 temporal derivatives, and their squares) and mean signal from subject-specific eroded white matter and ventricle masks and the whole brain. Because head motion in this sample was relatively high (mean frame-to-frame displacement before participant, run, or frame exclusion = 0.153 mm; [Supplementary Fig. 1](#)), the final preprocessing pipeline deviated from the preregistered pipeline in 2 ways: the addition of censoring of high-motion volumes and the removal of band-pass filtering. Volumes in which >10% of voxels were outliers and volumes for which the Euclidean norm of the head motion parameter derivatives exceeded 0.25 were censored from the time-series. Voxel-wise blood oxygen level-dependent (BOLD) signal time courses were averaged within regions of interest using a 268-node whole-brain parcellation ([Shen et al. 2013](#)).

Network strength calculation

Functional network nodes were defined with the 268-node functionally defined whole-brain Shen atlas ([Shen et al. 2013](#)). We conducted our primary replication analysis in 2 ways: first, including all 268 nodes, and second, including 238 nodes, dropping any node (30 in total) that was missing in any scan (see [Supplementary Fig. 2](#) for the latter analysis). Functional connectivity, defined as the Fisher z-transformed Pearson correlation between the fMRI signal time courses of pairs of atlas parcels, was calculated for each fMRI run separately.

Network strength as a function of sedation level

To characterize the degree to which volunteers expressed functional connectivity signatures of sustained attention defined in previous work, sustained

attention network strength was measured in each functional connectivity matrix. This was performed with the high- and low-attention network masks available at https://github.com/monicadrosenberg/Rosenberg_PNAS2020, which comprise the predefined sustained attention CPM. These masks consist of 268×268 binary matrices, where a value of 1 indicates a functional connection, or edge, in the mask. We applied each mask to the functional connectivity matrix, then averaged the values in each network for each functional connectome separately, yielding high- and low-attention strength values. Prior work has demonstrated that attention network strength tracks both interindividual and intraindividual differences in sustained attention, where higher high-attention network and lower low-attention network scores are associated with better sustained attention function ([Rosenberg, Finn, et al. 2016](#); [Rosenberg et al. 2020](#)). This analysis resulted in our main variables of interest: eight separate high-attention and low-attention network strength values for each participant with complete data (two tasks [rest, narrative listening] \times four sedation conditions ["awake", "mild", "sedation", "deep sedation", "recovery"]).

To directly replicate previous work showing that propofol sedation significantly modulates sustained network strength ([Rosenberg et al. 2020](#)), we performed paired t-tests comparing high-attention network strength in the awake and deep sedation conditions and low-attention network strength in the awake and deep sedation conditions during rest. To test if this effect generalized to a different task state, we repeated both tests with narrative-listening data.

Although the t-tests directly replicate the analysis of [Rosenberg et al. \(2020\)](#), they have the disadvantage of excluding two of the four levels of sedation ("mild" and "recovery") and fail to test for possible interactions between the effect of task and sedation. To examine the effect of all four levels of sedation and task manipulations simultaneously, we assessed the main effects of sedation level and task and their interaction with two mixed-effects models using the lme4 package in R ([Bates et al. 2015](#)), one for normalized high-attention network strength and one for normalized low-attention network strength. Sedation level and task were included as fixed effects, and participants were included as random effects. Including random slopes for participants with respect to the effect of sedation prevented model convergence and including random slopes for participants with respect to the effect of task did not improve (i.e., decrease) the model's AIC. Thus, random slopes were not included in the models.

Selectivity of propofol effects

We tested whether any effects of propofol administration were selective to networks that predict sustained attention. We consider the effects of propofol to be selective to the sustained attention networks if they are greater in magnitude than effects on other functional networks. We

examined selectivity in three ways. First, we examined the effect of sedation on a connectome-based model defined to predict another central cognitive measure, fluid intelligence (Greene et al. 2018). This fluid intelligence CPM was defined using fMRI data from the Human Connectome Project sample (collected while participants performed an *n*-back working memory task) to predict individual differences in performance on a 24-item version of the Penn Progressive Matrices test. Fluid intelligence has been shown to be relatively stable across the lifespan and is not thought to vary from one moment to the next (Kazlauskaitė and Lynn 2002; Schaie et al. 2004). Consequently, networks that predict fluid intelligence may not vary with short-term state changes, akin to the kind induced by propofol, to the same degree as do networks defined to predict attention. Thus, we predicted that strength in the fluid intelligence networks would be less affected by the sedation manipulation than strength in the sustained attention networks. To test this hypothesis, we repeated the analysis described above to generate high- and low-fluid intelligence network strength values for every fMRI run and compared these values between sedation conditions.

Second, replicating previous work (Rosenberg et al. 2020), we calculated strength in canonical resting-state networks, defined in (Finn et al. 2015), such as the default mode network (DMN) and frontoparietal network, to compare the relative effect of sedation on these networks with the sustained attention network.

Third, we identified sets of functional connections that significantly differed between individuals' "awake" and "deep" sedation scans and asked whether these networks overlapped with the predefined sustained attention networks (see "Propofol network identification" and "Network overlap" sections below). We predicted that a network whose strength decreased with propofol administration would overlap with the network predicting better sustained attention, whereas a network whose strength increased with propofol administration would overlap with the network predicting worse sustained attention.

Propofol network identification

Using the Network Based Statistic Toolbox (RRID:SCR_002454; sites.google.com/site/bctnet/comparison/nbs), we identified functional networks that differed between the awake and deep sedation conditions. This procedure aids network detection by controlling for the large number of multiple comparisons necessary to test for differences in every edge in a functional connectome by comparing the size of the fully connected networks that differ between two conditions of interest (here, "awake" and "deep sedation") to the size of fully connected networks that differ between randomly assigned conditions (Zalesky et al. 2010).

First, we identified edges that were greater in the "deep sedation" or "awake" condition by performing paired, one-tailed *t*-tests, and retaining edges that fell above a predetermined significance threshold. Then, we selected the largest fully connected network of edges

from this group. Next permutation testing was performed by shuffling condition labels 5,000 times and running a *t*-test at every permutation to generate 5,000 sets of edges that differed between the random groups. The *p*-value of the sedation network was calculated by computing $(n_{\text{fully_connected_random}} + 1) / (n_{\text{permutations}} + 1)$, where $n_{\text{fully_connected_random}}$ is the number of fully connected random network components of the same size, or larger than the observed fully connected network component, and $n_{\text{permutations}}$ is 5,000, which is the number of permutations. We classified the resulting networks as significant at $P < 0.05$.

We repeated this process for each task condition (rest and narrative listening) and for three different significance thresholds at the edge-selection step ($P < 0.001$, $P < 0.01$, and $P < 0.05$), resulting in three "Awake" and three "Deep Sedation" networks for each task.

Network overlap

Considering the marked impacts of sedation on cognitive and attentional states, we predicted significant overlap between the high-attention network and the Awake propofol network and significant overlap between the low-attention network and the Deep Sedation propofol network. Furthermore, we expected less overlap between the propofol networks and the fluid intelligence networks since the fluid intelligence networks may be more reflective of trait-like differences in functional connectomes rather than the temporary state changes in the connectome caused by propofol sedation.

To test these hypotheses, we examined the overlap between the propofol networks and the sustained attention and fluid intelligence networks. For each pair of networks, we counted the number of edges shared between the networks. The significance of the overlap was determined with the hypergeometric cumulative density function, which provides the probability of drawing up to x of K possible items in n drawings without replacement from a population with M items. This was implemented in MATLAB as $P = 1 - \text{hygecdf}(x, M, K, n)$, where x is the number of overlapping edges, K is the number of connections in the given CPM network, n is the number of connections in the given propofol network, and M is the total possible number of edges in the matrix (35,778; all possible functional connections, given 268 nodes). We repeated this process for all three versions of the propofol networks (thresholded at $P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively) and both tasks (rest and narrative). To determine which CPM (sustained attention or fluid intelligence) had greater overlap with the propofol networks, permutation testing was performed. We compared the difference in percent overlap between the networks by shuffling the propofol network 1,000 times, creating a network of equal size from edges randomly selected from the whole connectome. The amount of overlap with the randomly generated networks was then used as a null distribution. Again, this was repeated for all propofol networks and both task conditions.

Functional connectivity similarity analyses

In addition to examining the effects of task state and sedation level on functional connectivity signatures of sustained attention, we were interested in understanding the effects of the drug and task manipulations on functional connectivity patterns more broadly. That is, how does sedation and task state affect the similarity of functional connectivity patterns across individuals? Do individuals show more similar connectivity patterns when awake or when under sedation? One possibility is that sedation *increases* similarity across individuals by reducing ongoing cognitive, attentional, and perceptual processes that may otherwise differ between people and drive unique patterns of functional brain organization. Another is that sedation *decreases* similarity between individuals by muting these processes, revealing idiosyncratic underlying patterns of functional brain organization. In the same vein, do individuals show more similar connectivity patterns when listening to the same story or resting? We might expect that participants listening to the same story would exhibit more similar patterns of functional connectivity because they are engaged in similar auditory and cognitive processing.

To investigate how propofol sedation affects between-subject connectome similarity, participants' fMRI time series were limited to 73 TRs per run to match the number of TRs per condition. All nodes missing in any scan were excluded from analysis (30 in total). Next, for both task conditions, we excluded participants who did not pass our motion threshold (<50% of frames censored for motion) for the "awake" and "deep sedation" conditions, resulting in 10 (rest) and 10 (narrative listening) participants, respectively (7 participants included in both conditions). We then calculated the Spearman correlation of each participant's functional connectivity pattern for the "awake" resting-state scan with that of all other participants. We averaged the Fisher z -transforms of these values to get a single similarity value per participant. We repeated this process for the "deep" condition and for the narrative-listening task, yielding four lists of subject-level similarity values. Finally, similarity while participants were "awake" was compared to similarity under "deep sedation" using two paired t -tests, one for each task condition.

To investigate how the task manipulation affects between-subject similarity, we again limited participants' time series to 73 TRs, excluding all nodes missing in any scan. Next, for each of the 4 sedation conditions, we excluded participants who did not pass our motion threshold for both task conditions, resulting in 16 ("awake"), 13 ("mild"), 8 ("deep"), and 15 ("recovery") participants, respectively (6 participants in all conditions). We calculated the Spearman correlation of each participant's functional connectivity pattern during the "awake" resting-state scan with that of all other participants. We averaged the Fisher z -transforms of these values to get a single similarity value per participant. We repeated this process for all 4 sedation

conditions and for the narrative-listening task, resulting in 8 lists of subject-level similarity values. Finally, similarity during resting-state scans was compared to similarity during narrative listening using four paired t -tests, one for each sedation level.

Results

Propofol decreases functional connectivity signatures of sustained attention

As predicted, during rest, high-attention network strength was higher ($t_9 = 3.22$, $P = 0.010$) and low-attention network strength was lower ($t_9 = -4.09$, $P = 0.003$) in the "awake" than in the "deep sedation" condition. This pattern of results replicated during narrative listening (high-attention: $t_9 = 2.50$, $P = 0.034$; low-attention: $t_9 = -3.83$, $P = 0.004$).

Also as predicted, mixed effect models of propofol's effect on sustained attention network strength revealed a main effect of sedation condition wherein less sedation was associated with functional connectivity signatures of stronger attention (high-attention: $b = -0.75$, $SE = 0.16$, $F[3,93.5] = 8.01$, $P = 8.26 \times 10^{-5}$; low-attention: $b = 0.84$, $SE = 0.15$, $F[3,92.4] = 13.24$, $P = 2.91 \times 10^{-7}$; Fig. 1). There was no main effect of task (i.e. rest vs. narrative listening) or interaction of sedation condition and task on high-attention or low-attention network strength.

To account for potential effects of head motion on functional network strength, we performed two control analyses. First, we regressed mean framewise displacement and fraction of censored frames from high- and low-attention network strength scores. We then repeated the analysis described above with the residuals of this regression, performing paired t -tests comparing residualized attention network strength while individuals were awake and under deep sedation during rest and narrative listening. Demonstrating that effects of propofol on attention network strength are robust to effects of head motion, residualized high-attention network strength during rest was higher during the "awake" than the "deep sedation" condition (rest: $t_9 = 3.56$, $P = 0.006$; narrative: $t_9 = 2.73$, $P = 0.023$). We observed the opposite pattern of results for residualized low-attention network strength (rest: $t_9 = -2.34$, $P = 0.044$; narrative: $t_9 = -3.59$, $P = 0.006$).

As a second motion control, we replicated the mixed effects analysis, including mean framewise displacement and fraction of censored frames in each run as predictors. Results were consistent with those described above: Models revealed a main effect of sedation condition wherein less sedation was associated with functional connectivity signatures of stronger attention (high-attention: $b = -0.82$, $SE = 0.16$, $F[3,93.7] = 9.87$, $P = 1.02 \times 10^{-5}$; low-attention: $b = 0.68$, $SE = 0.15$, $F[3,92.9] = 8.5$, $P = 4.73 \times 10^{-5}$). There was no main effect of task or interaction of sedation condition and task on high-attention network strength. For low-attention network strength, there was a main effect of task ($b = -0.15$, $SE = 0.07$, $F[1,92.3] = 4.1$,

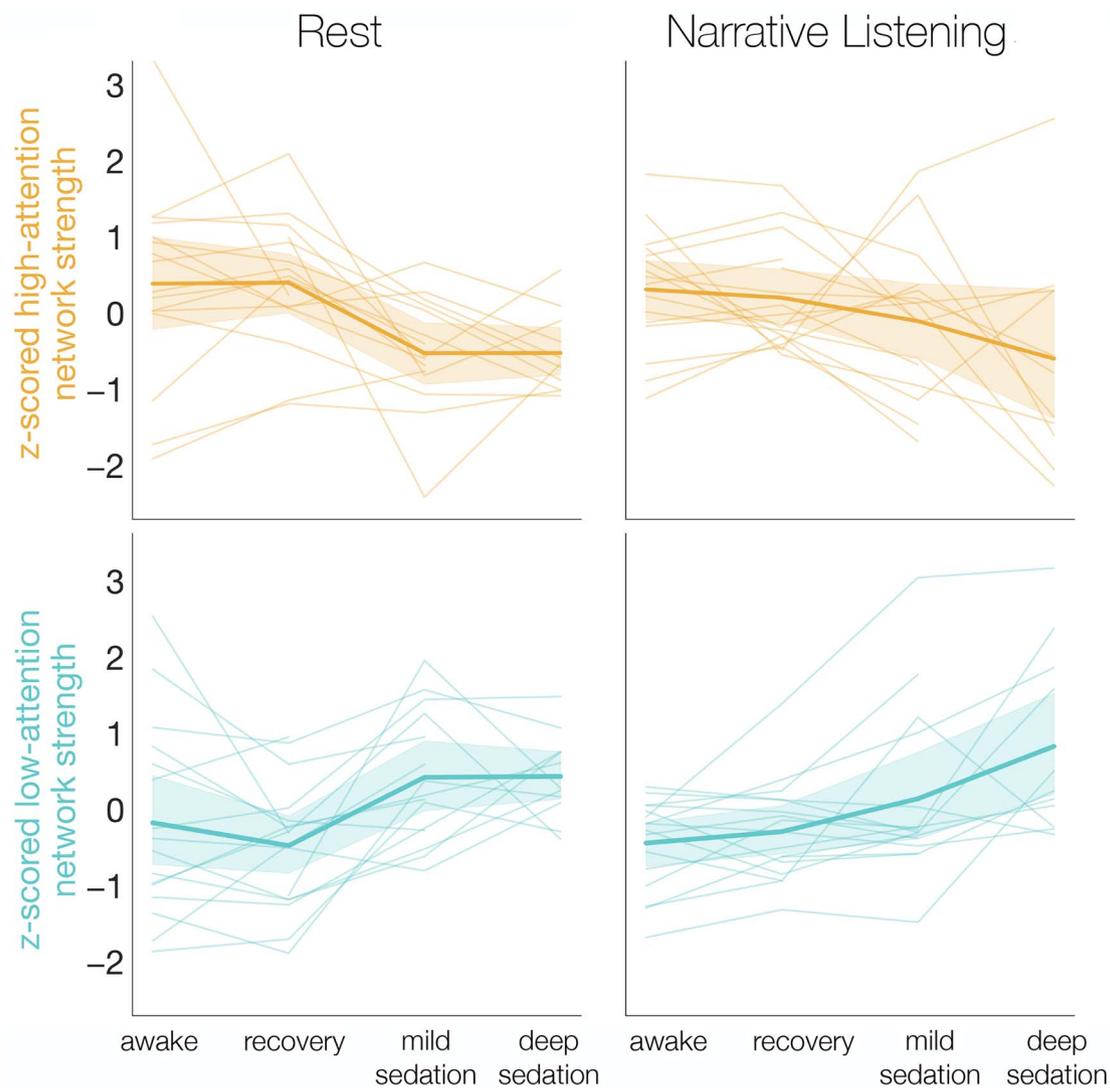


Fig. 1. High-attention and low-attention network strengths during two tasks (rest and narrative listening) and four sedation conditions (“awake,” “recovery,” “mild sedation,” and “deep sedation”). Network strength values were z-scored within graph for visualization. Semi-transparent lines represent individual participants and bold lines represent average across participants, with the shaded region indicating the 95% confidence interval. Some semi-transparent lines do not extend the full length of the plot as not all participants had complete data for all sedation and task conditions.

$P = 0.045$) such that low-attention network strength was higher during rest than narrative-listening scans.

Propofol selectively modulates functional connectivity signatures of sustained attention

Propofol modulates sustained attention networks more than fluid intelligence networks

Is propofol’s effect on the connectome selective to networks predicting sustained attention? We tested this question in three ways. First, we investigated propofol’s effect on a functional connectivity network defined in previous work to predict fluid intelligence (Greene et al. 2018). Attention function varies across individuals but also varies within a single individual over time, and the sustained attention CPM is sensitive to both these individual differences and intraindividual variability (Rosenberg et al. 2020). Fluid intelligence, by comparison, may reflect a more trait-like aspect of behavior, as evidence suggests it is relatively stable within an individual over

time (Kazlauskaitė and Lynn 2002; Schaie et al. 2004). Consequently, drug-induced changes in cognitive state may modulate the fluid intelligence networks to a lesser degree than they do the sustained attention networks.

In both the resting-state and narrative-listening conditions, high-fluid intelligence network strength did not significantly differ between “awake” and “deep sedation” scans (rest: $t_9 = 0.32$, $P = 0.76$, narrative listening: $t_9 = 0.62$, $P = 0.55$) (Fig. 2). Low-fluid intelligence network strength was significantly greater in the “deep sedation” scans for the narrative-listening condition only (rest: $t_9 = -1.89$, $P = 0.09$, narrative listening: $t_9 = -2.63$, $P = 0.03$). A mixed effect models of propofol’s effect on fluid intelligence network strength did not show a main effect of sedation condition for high-fluid intelligence network strength but did show a main effect of sedation for low-fluid intelligence network strength wherein greater sedation was associated with higher low-fluid intelligence network strength scores (high-fluid intelligence: $b = -0.20$,

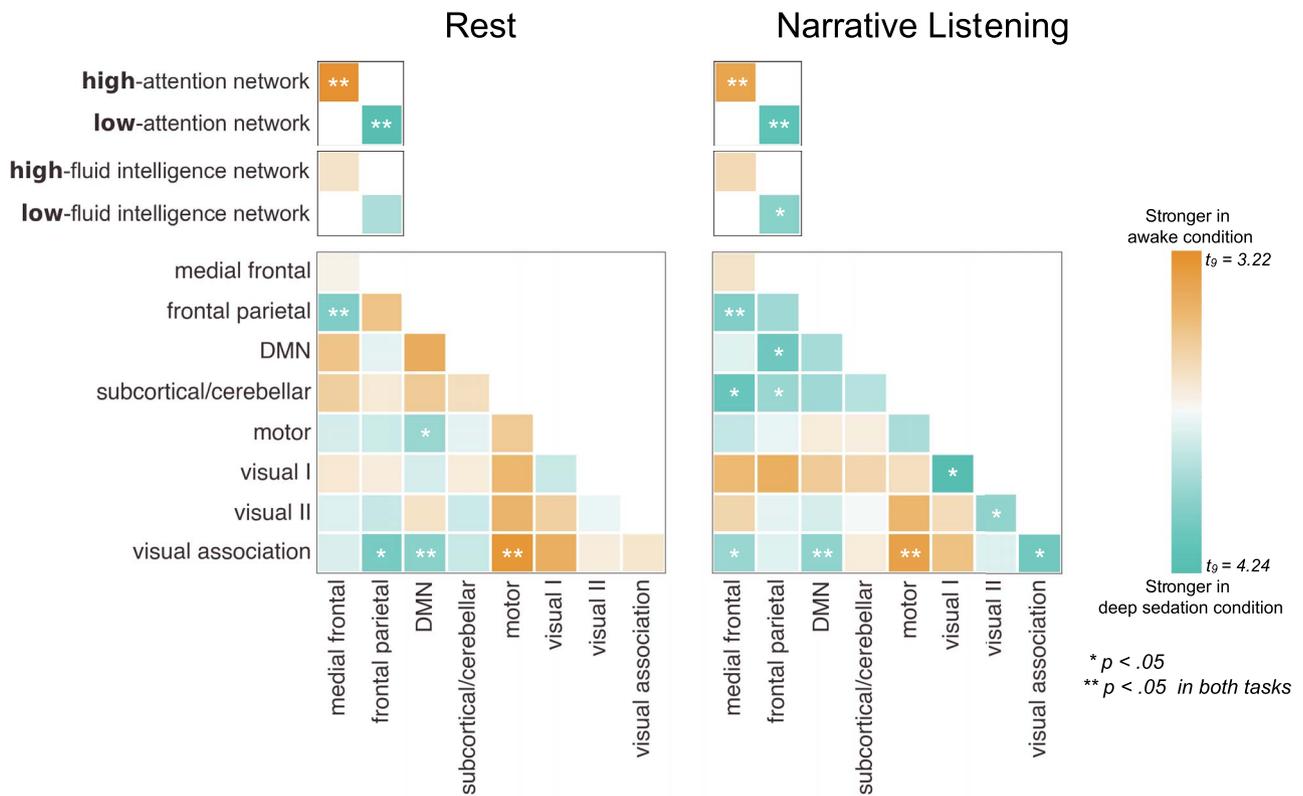


Fig. 2. Effects of propofol on functional network strength. Differences in within-network and between-network strengths (averaged functional connectivity) during the “awake” and “deep-sedation” conditions. Propofol’s effect on the sustained attention networks was greater than the effect on both the fluid intelligence networks and the majority of canonical network pairs.

SE = 0.18, $F[3, 94.5] = 0.47$, $P = 0.70$; low-fluid intelligence: $b = 0.56$, SE = 0.18, $F[3, 92.5] = 4.53$, $P = 0.005$). There was no main effect of task or interaction of sedation condition and task on high-fluid intelligence or low-fluid intelligence network strength.

We performed paired t-tests comparing the percent change in overall sustained attention and fluid intelligence network strength from “awake” to “deep sedation” during both task conditions. Overall network strength was calculated as the difference between strength in the network predicting higher behavioral scores and the network predicting lower behavioral scores. Results revealed greater percent change in sustained attention than fluid intelligence network strength during both rest and narrative listening (rest: $t_9 = 2.75$, $P = 0.022$, narrative listening: $t_9 = 2.87$, $P = 0.018$). Thus, propofol has a greater effect on the sustained attention networks than networks predicting fluid intelligence. We did not test for a 3-way interaction between functional network, task, and sedation condition with mixed effects models as only 9 participants were included in this analysis.

Propofol modulates sustained attention networks more than canonical resting-state networks

Although networks defined to predict fluid intelligence were not as sensitive to sedation as the sustained

attention networks, this does not preclude the possibility that other functional networks are affected by propofol sedation—perhaps even more so than the sustained attention networks. To test this possibility, we assessed the effect of sedation on functional connectivity in 8 canonical resting-state networks as well as the pairwise connections between these networks (36 network pairs in total) (Fig. 2). Providing further evidence for the selectivity of the effect on the sustained attention CPM, propofol’s effect on the high-attention network was numerically greater than the positive effects for any of the 36 pairs of canonical resting-state networks during both tasks. The effect of propofol on the low-attention network was greater than any negative effect for all pairs of canonical resting-state networks during rest and all but one network during narrative listening (connections within primary visual network).

Finally, we compared differences in sustained attention network strength between the “awake” and “deep sedation” conditions (assessed with a paired t-test) to differences in the strength of in 10,000 same-size random networks. During rest, the effect in the high-attention network was >96.71% of same-sized random networks, and the effect in the low-attention network was >98.79% of same-sized random networks. During narrative listening, the effect in the high-attention network was >99.79% of same-sized random networks, and the effect in the

low-attention network was >100% of same-sized random networks. In sum, this replication demonstrates the robustness of the finding that the sustained attention CPM is uniquely sensitive to propofol sedation.

Beyond the sustained attention networks, effects of propofol on functional connectivity on canonical networks are consistent with those reported previously (Rosenberg et al. 2020). This prior work, performed in an independent dataset, found that 7 of the 36 canonical network pairs were significantly modulated by propofol administration. Of those 7 pairs, 6 overlap with the 7 network pairs showing the greatest effect in the present study during rest ($P < 0.07$, 1. frontoparietal-visual association, 2. motor-visual association, 3. frontoparietal-medial frontal, 4. default-visual association, 5. motor-default, 6. default-default, and 7. visual I-visual association). None of the effects in the canonical networks in the present study survived Bonferroni correction for 36 tests (Fig. 2).

Propofol sedation networks overlap with the sustained attention networks

The sustained attention networks are modulated by propofol sedation, but to what extent do the functional connections that change most with propofol sedation overlap with the connections in the sustained attention networks? To investigate, we examined the overlap between both the “Awake” networks (i.e., the networks stronger during wakefulness) and the “Deep Sedation” networks (i.e. the networks stronger during deep sedation) and the high- and low-attention networks. We predicted that the high-attention network would share significant overlap with the Awake networks, while the low-attention network would share significant overlap with the Deep Sedation networks.

To this end, we used the network-based statistic to identify functional networks most affected by propofol sedation. We did this at three different edge-selection thresholds, retaining edges that significantly differed between “Awake” and “Deep Sedation” scans at $P = 0.05$, 0.01, 0.001, respectively. We detected significant “Awake” networks (network significance defined as $P < 0.05$) for all 3 edge-selection threshold levels for the rest condition, and 1 out of 3 (0.01) edge-selection threshold levels for the narrative-listening condition (Figs 3 and 4). We detected significant “Deep Sedation” networks for all three edge-selection threshold levels tested and for both task conditions. In general, “Awake” networks consisted of nodes in the occipital, prefrontal, and temporal lobes, while “Deep Sedation” networks were dominated by nodes in the prefrontal, limbic, and temporal lobes.

As expected, there was significant overlap between “Awake” networks and the high-attention network but not the low-attention network (Fig. 4). Furthermore, there was significant overlap between “Deep Sedation” networks and the low-attention network but not the high-attention network.

Looking at the rest condition and the 0.01-threshold “Awake” network, 37 edges overlapped with the high-attention network, making up 4.9% of the high-attention network ($P = 1.25 \times 10^{-7}$). The reverse pattern held true for the “Deep Sedation” network, with 36 edges in common between the 0.01-threshold “Deep Sedation” network and the low-attention network, making up 5.7% of the low-attention network ($P = 6.45 \times 10^{-9}$). This result replicated in the narrative-listening condition (high-attention “Awake” overlap: 34 edges, 4.5% of network, $P = 1.11 \times 10^{-9}$; low-attention “Deep Sedation” overlap: 57 edges, 9.0% of network, $P = 9.44 \times 10^{-15}$). Consequently, the functional networks that differ between sedation and wakefulness overlap with those that differ between states of better and worse sustained attention.

We expected the propofol networks to show less overlap with the fluid intelligence networks than the sustained attention networks, in line with the hypothesis that the sustained attention networks are more sensitive to cognitive and attentional state changes. We observed significant overlap between “Awake” networks and the high-fluid intelligence network but not the low-fluid intelligence network. For the 0.01-threshold “Awake” rest network, there were 23 edges overlapping with the high-fluid intelligence network, making up 3.4% of the high-fluid intelligence network ($P = 0.007$). The “Deep Sedation” network presented the opposite pattern, showing significant overlap with the low-fluid intelligence but not the high-fluid intelligence network. For the 0.01-threshold “Deep Sedation” rest network, there were 27 edges shared with the low-fluid intelligence network, making up 4.2% of the low-fluid intelligence network ($P = 9.4 \times 10^{-5}$). These patterns replicated in the narrative-listening condition (high-fluid intelligence “Awake” overlap: 21 edges, 3.1% of network, $P = 2.37 \times 10^{-4}$; low-fluid intelligence “Deep Sedation” overlap: 31 edges, 4.8% of network, $P = 9.44 \times 10^{-15}$).

Supporting our prediction, comparisons of network overlap revealed that the sustained attention network showed significantly greater overlap with the propofol networks in eight of the 10 comparisons (2 propofol networks [“Awake,” “Deep Sedation”] \times 3 edge selection thresholds [$P < 0.05$, 0.01, 0.001] \times 2 task conditions [rest, narrative listening] minus 2 instances where no significant propofol network was found = 10 comparisons) and numerically greater overlap for all comparisons except overlap with the 0.001-threshold “Awake” rest network. This difference is not merely driven by a difference in the overall size of the sustained attention and fluid intelligence networks: The networks are of comparable sizes (sustained attention networks = 1,387 edges, fluid intelligence networks = 1,333 edges), and this difference persists when comparing overlap as a percentage of network size. These results suggest that the functional networks most strongly modulated by propofol share a more similar architecture to the functional networks underlying sustained attention function than to those associated with fluid intelligence.

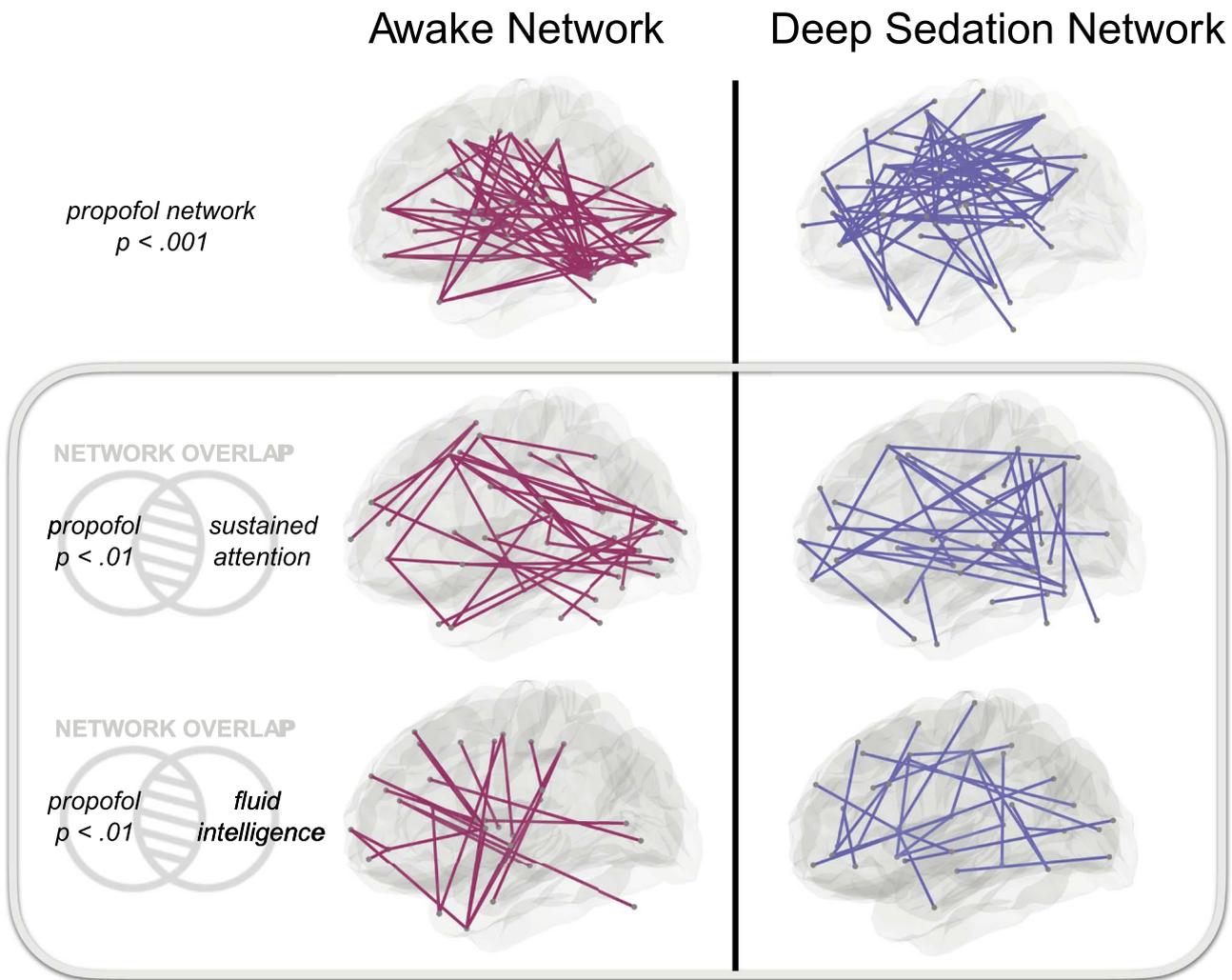


Fig. 3. The “Awake” network shows significant overlap with the high-attention and high-fluid intelligence networks, whereas the “Deep Sedation” network shows significant overlap with the low-attention and low-fluid intelligence networks. The propofol networks illustrated (top row) were created with an edge-selection threshold of $p < .001$. For the Overlap illustrations (bottom two rows), propofol networks were created with an edge-selection threshold of $p < .01$ were utilized.

Propofol and task condition modulate within- and between-subject functional connectome similarity

In addition to gauging propofol’s effect on neural signatures of sustained attention, we assessed how sedation affects functional connectivity patterns more broadly. To this end, we examined the between-subject connectome similarity while participants were awake vs. sedated. A paired *t*-test comparing similarity values during “awake” resting-state scans to those of “deep sedation” resting-state scans demonstrated that participants are more similar to one another when awake than when under sedation ($t_9 = 6.73$, $P = 8.52 \times 10^{-5}$). Furthermore, this result replicated in the narrative-listening condition ($t_9 = 5.20$, $P = 5.65 \times 10^{-4}$). Interestingly, this result suggests that propofol sedation does not simply mute individual differences in functional connectivity patterns and causes all participants to show a connectivity pattern common across the population. Instead, participants’ functional connectivity patterns look more similar to each other when they are awake.

In addition to assessing the effect of sedation on similarity, we also examined the effect of task. Paired *t*-test revealed, surprisingly, greater similarity during resting-state scans than during narrative-listening scans, and this result replicated in 3 of the 4 sedation conditions (awake: $t_{15} = 9.92$, $P = 5.57 \times 10^{-8}$; mild: $t_{12} = 1.15$, $P = 0.27$; deep: $t_7 = 6.64$, $P = 0.001$; recovery: $t_{14} = 5.50$, $P = 7.82 \times 10^{-5}$). This finding is somewhat counterintuitive, given extensive work showing that individuals shown the same movie or played the same audio narrative in the scanner demonstrate higher levels of intersubject correlation compared to rest (Hasson et al. 2004; Kandeepan et al. 2020). In these data, Kandeepan et al. (2020) observed significant intersubject correlation at all levels of sedation but not during rest. Furthermore, it has been demonstrated previously in a separate dataset that functional connectome similarity is increased both within and across participants during movie-watching compared to rest (Vanderwal et al. 2017). This analysis suggests that greater BOLD time course similarity may not necessarily translate

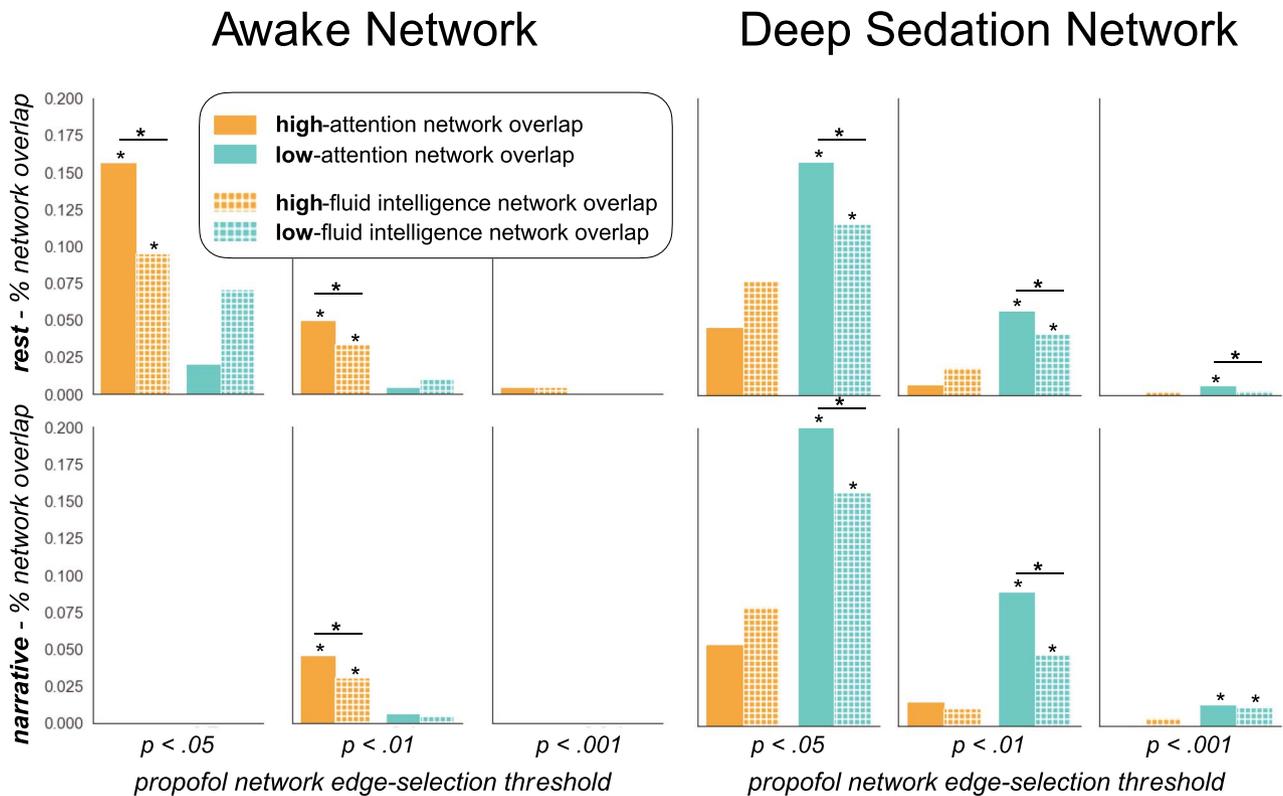


Fig. 4. The sustained attention networks show significantly greater overlap with the propofol networks than do the fluid intelligence networks. *P*-values in the x-axis indicate the threshold at which edges were selected when defining the propofol networks. Stars indicate the significance of the percent overlap ($P < 0.05$, Bonferroni-corrected for 4 comparisons, *P*-values computed using hypergeometric cumulative density function). Stars above black lines indicate a significant difference in percent overlap between networks ($P < 0.05$, *P*-values computed using permutation testing).

to greater functional connectome similarity between individuals.

To further explore the influence of individual, task, and sedation level on functional connectome similarity, we limited our sample to only those with acceptable motion in all eight conditions (2 task \times 4 sedation conditions). This resulted in $n = 6$ participants, and for each scan for each of these participants, we calculated pairwise connectome similarity (defined as the Spearman correlation) to that of every other scan (Fig. 5). Our sample in this analysis was limited by our relatively conservative motion exclusion threshold (excluding scans with $>0.50\%$ of frames censored for head motion; see Supplementary Fig. 1). To see the same figure with all 17 participants, see Supplementary Fig. 3. Our results conceptually replicate those of Gratton et al. (2018), which found a relatively high contribution of subject-related variation on overall variation in network boundaries (compared to task- and session-level variations), although, here, we examine functional connectivity similarity between group-defined nodes rather than investigating network boundaries. Specifically, subject-dependent effects are readily apparent, with higher similarity between different runs from the same individual (mean $r = 0.436$) and lower similarity across individuals (mean $r = 0.214$). Furthermore, consistent with the paired *t*-tests described above, visual inspection reveals greater connectome similarity during rest than

narrative listening both within and between individuals and greater similarity between individuals at lower than higher levels of sedation.

Discussion

To what extent does an individual's functional connectome reflect stable individual traits vs. varying mental states? Work demonstrates that individual differences can be discerned from functional connectivity patterns, with successful prediction of between-subject variation in personality (Hsu et al. 2018; Cai et al. 2020), working memory performance (Galeano Weber et al. 2017; Yamashita et al. 2018; Avery et al. 2019), and reading recall (Jangraw et al. 2018), among other behaviors. But what about intra-individual differences? Here, we add support for the existence of state-selective variation in functional connectome by testing if a predefined network predicting sustained attention is sensitive to pharmacological intervention with propofol. Using an independent dataset, we replicate the effect of propofol on the sustained attention CPM. We find that, as predicted in our preregistration, greater propofol sedation is associated with neural signatures of worse-sustained attention function, suggesting that behaviorally relevant aspects of the functional connectome vary with short-term, pharmacologically induced changes in cognitive and attentional states. Further demonstrating

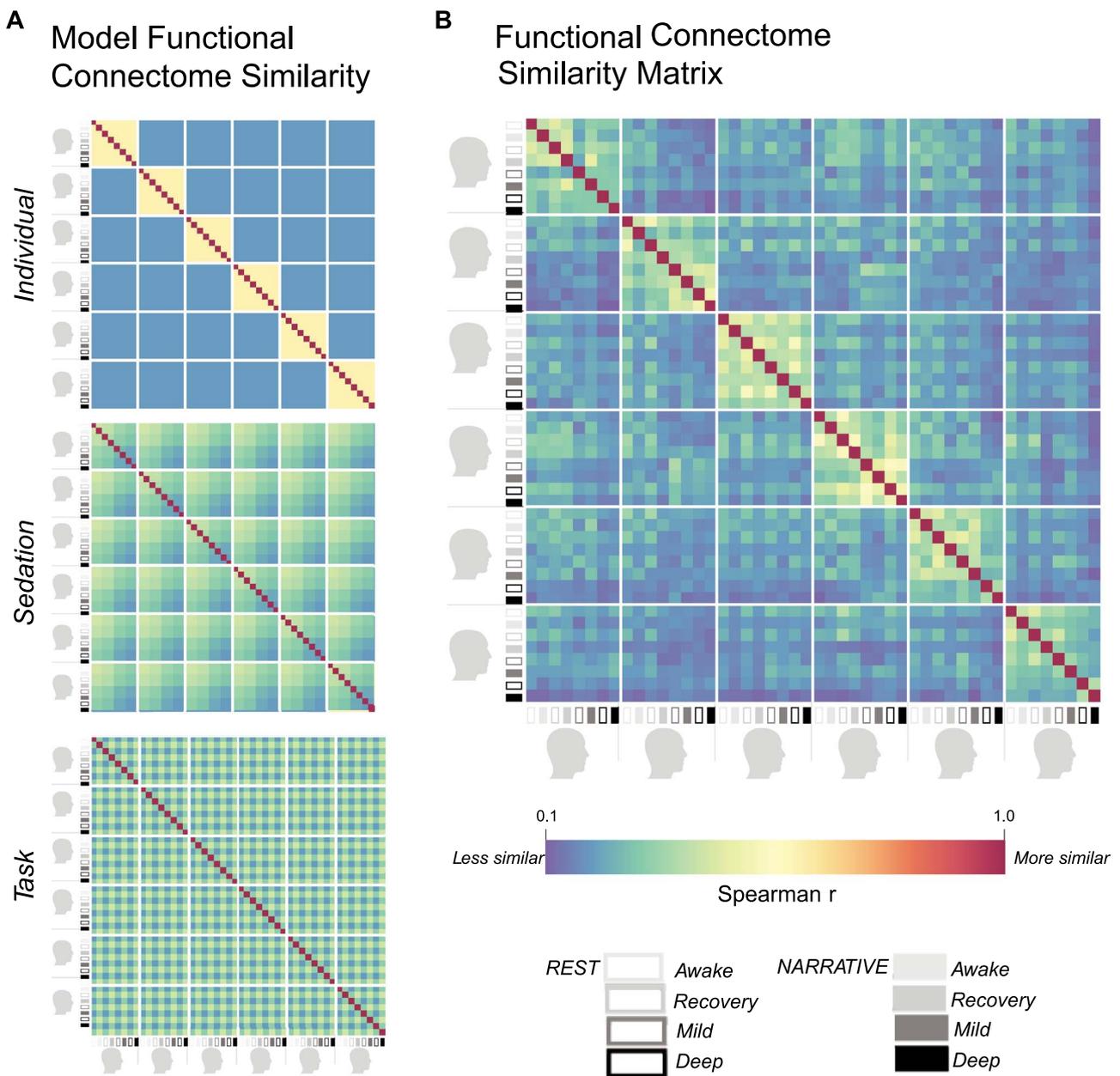


Fig. 5. A) Model functional connectome similarity matrices. Model matrices represent hypothetical effects of individual, sedation level, and task on connectome similarity. Comparing the observed connectome similarity matrix B) to the “Individual” model, higher similarity along the diagonal suggests a strong effect of individual variation on similarity. Comparing the connectome similarity matrix to the “Sedation” model, we see evidence of higher similarity values for lower sedation levels. Finally, the grid-like pattern visible in connectome similarity matrix confirms an effect of task as predicted by the “Task” model. However, this pattern is in the opposite direction than predicted, with higher similarity for rest than the narrative-listening task. B) Functional connectome similarity matrix. Pairwise functional connectivity similarity for all eight conditions (2 task \times 4 sedation) for 6 participants with usable data in all 8 conditions. Each cell represents the Spearman correlation between two functional connectomes.

robustness, this finding replicated in a novel narrative-listening condition. This work illustrates the feasibility of assessing the external validity of brain-based predictive models using fully preregistered hypotheses and analyses.

The utility of a connectome-based model of cognitive function relies on it being both generalizable and selective. Generalizing across datasets, for instance, provides evidence that a model characterizes the measure of interest rather than merely picking up on idiosyncrasies in a given participant sample from a single fMRI scanner.

In the present study, we demonstrate cross-dataset generalizability by replicating the effects of propofol on the sustained attention networks in data from a novel set of participants collected at an independent scanning site. Just as cross-dataset generalizability is important, cross-measure generalizability is also key. A model is less useful if it only predicts a specific behavioral measure (such as psychological task performance) rather than other measures of the same underlying cognitive or attentional function (such as ADHD symptomatology for models of sustained attention) (Rosenberg, Finn, et al. 2016). An

emphasis on generalizability both across datasets and related measures, among other practices such as preregistration, is crucial for tackling the reproducibility crisis in psychology and neuroscience.

Though perhaps less frequently discussed, the selectivity of a model is as important as its generalizability. If a model generalizes in a way such that it cannot be distinguished from other models (here, predefined predictive networks), it is also less useful if one aims to disentangle various cognitive functions from one another. For instance, suppose one wishes to characterize the functional networks associated with mathematical ability. If a predictive model performs equally well in predicting individual's math and reading scores, it is hard to argue that this model informs our understanding of the neural underpinnings of mathematical aptitude *per se*. Critically, in the current work, we also add evidence to the “selectivity” criteria, as we demonstrate that not all behaviorally predictive brain networks are equally sensitive to propofol-induced state changes. Rather, our results suggest that canonical resting-state networks as well as a previously defined model of fluid intelligence are less sensitive than the sustained attention network to the effects of propofol sedation. This suggests that perhaps the model of fluid intelligence captures less state-like variability and more trait-like variability compared to the sustained attention CPM, which is in line with research demonstrating that fluid intelligence is relatively stable within individuals' over time (Kazlauskaitė and Lynn 2002; Schaie et al. 2004). Furthermore, after defining “propofol” networks, based on the networks differing most between deep and awake conditions, we found that the propofol network had greater overlap, on average, with the sustained attention networks than the fluid intelligence networks. These results suggest that the functional networks underlying attention function, compared to those associated with fluid intelligence, may share a more similar architecture to the functional networks most strongly modulated by sedation with propofol.

Future work will reveal the extent to which networks defined to predict individual differences in other processes are sensitive to within-subject state change. Although a growing body of work has found evidence that the connectome-based model of individual differences in sustained attention function also successfully differentiates between within-subject state change, this may not be the case for all behavioral traits. For instance, 3,4-methyl enedioxy methamphetamine (MDMA) influences social function, increasing subjective sociability and feelings of closeness with others (Bedi et al. 2009). Would a functional network defined to predict trait extraversion (Hsu et al. 2018) be sensitive to within subject state change induced by administration of MDMA? Perhaps the neural basis of individual differences in social function is orthogonal to the neural basis of change in social behavior within one person. More broadly, pharmacological studies provide unique opportunity

to test the generalizability and selectivity of predictive models.

The current study differs somewhat with respect to prior findings regarding sedation's effect on functional connectivity patterns. For instance, past work found a decrease in within-DMN connectivity with propofol sedation (Boveroux et al. 2010; Tang and Ramani 2016; Guldenmund et al. 2017; Qiu et al. 2017). However, results here suggest that DMN connectivity with other networks is differentially affected by propofol sedation. Specifically, within-DMN connectivity decreased during rest but not during narrative-listening scans, whereas DMN-visual association network connectivity increased during both tasks. This difference in findings can perhaps be attributed to the fact that lower levels of sedation have been associated with no change in DMN connectivity (Stamatakis et al. 2010). The present study defines “deep” sedation as a lower level of sedation (Ramsay level 5) compared to the sedation condition in some prior work (Ramsay levels 5–6 in Boveroux et al., for instance, or “deep sedation” as defined by the American Society of Anesthesiologists in Qiu et al. 2017) reporting decreases in DMN connectivity. Results in the present study also contrast with prior work showing that sedation decreases frontoparietal connectivity (Boveroux et al. 2010; Amico et al. 2014). Data here suggest increased frontoparietal connectivity during sedation, specifically frontoparietal-medial frontal connectivity, as well as frontoparietal-visual association connectivity. Observed changes in functional connectivity in visual regions, however, are consistent with past work, where sedation was associated either with no change, or an increase in connectivity (Martuzzi et al. 2010; Qiu et al. 2017). Here, we report significant increases in within-network connectivity in V1, V2, and visual association networks in the narrative-listening condition and no significant changes in visual network connectivity during rest. Additional work may resolve how parameters, such as sedation level, scan length, preprocessing approach, and task, mediate the effect of propofol sedation on functional connectivity. While the present findings are not wholly consistent with all prior work, propofol's effect on functional connectivity patterns is consistent across tasks within the current dataset (rest and narrative listening) and with the findings reported in an independent dataset analyzed with a similar preprocessing pipeline and data exclusion criteria (see “Propofol modulates sustained attention networks more than canonical resting-state networks”) (Rosenberg et al. 2020).

In addition to investigating the effect of propofol on connectome-based models of behavior and canonical resting-state networks, we characterized how sedation and task manipulation affected the similarity of individuals' overall functional connectivity patterns. With regard to the effect of sedation on similarity, we began with two plausible competing hypotheses: (i) Sedation decreases ongoing thoughts, feelings, etc., that

may differ across individuals and drive differences in functional connectivity patterns, thereby resulting in more similar connectivity patterns across individuals. (ii) Any kind of cognitive processing (even if the content differs to across individuals) acts as a constraint on functional connectivity, resulting in connectome patterns that are more similar in the absence of sedation. We found evidence for the latter hypothesis, observing greater similarity when participants were awake compared to when they were sedated. In addition to examining the effect of task on between-subject similarity, our analyses explored the extent to which task condition affects between-subject similarity. We found that rest was associated with greater across-subject connectome similarity compared to narrative listening. This finding is surprising, given past work that demonstrates that, in development, movie-watching raises between-subject connectome similarity relative to rest (Vanderwal et al. 2017). Lack of visual input in the present study may help explain this difference in results. In Vanderwal et al. (2017), participants watched and listened to a film, whereas here, participants only listened to audio for the “narrative” condition. Synchronous visual input may drive between-subject similarity higher in the “narrative” condition relative to rest. Furthermore, in Vanderwal et al. (2017), the resting-state scan was collected while participants stared at a fixation cross, while in the present study, participants were instructed to keep their eyes closed. Past work has found significant differences between functional connectivity for eyes open vs. eyes closed resting-state scans and perhaps this helps explain the divergence of the present findings from prior work (Costumero et al. 2020). The current work furthers our understanding of how disparate factors modulate connectome similarity within and across individuals by simultaneously examining the impact of individual, sedation level, and task.

One limitation of the present study is a relatively small sample size (total $n=17$; $n=6$ with usable data from all scan conditions). However, our use of pre-registration to detail predicted effects in advance as well as the use of an independent dataset to replicate a previous finding are intended to act as safeguards against false-positive results that may arise with small samples. Second, although an effort was made to titrate the level of propofol administration such that individuals were equally sedated (Naci et al. 2018; Kandeepan et al. 2020), there were likely remaining individual differences in level of sedation achieved, which could ultimately impact connectome similarity across sedation levels. Thus, additional work can help determine the ways in which tasks and pharmacological interventions modulate connectome similarity between participants. Finally, additional work may benefit from defining functional connectivity in a more fine-grained manner, as opposed to the coarser region-by-region approach used here (Guntupalli et al. 2018). In the

current study, we use a whole-brain atlas with relatively large nodes (a 268-node parcellation, Shen et al. 2013). However, recent advances have revealed greater power for predicting fluid intelligence when using a fine-grained approach, specifically using voxel-wise functional connectivity after performing hyperalignment (Feilong et al. 2021). These results motivate the use of fine-grained functional connectivity in future work employing predictive models of fluid intelligence and other cognitive traits, particularly in the context of pharmacological intervention, as the effects of pharmacological intervention on hyperaligned fine-grained functional connectivity have not yet been examined. Additionally, while here we use a single group-level atlas to examine network strength across conditions, recent work demonstrates that functional networks reconfigure substantially across task states (Salehi et al. 2020) and vary significantly person to person (Bijsterbosch et al. 2018; Kong et al. 2019). Future work may benefit from considering variation not only in network strength defined with a group-level atlas, but variation in node boundaries across individuals and sedation conditions.

Conclusion

In sum, we replicate the effect of propofol on the sustained attention CPM. In addition to this replication, we provide novel evidence that the magnitude of this effect is selective to the sustained attention network. Finally, we demonstrate that task and sedation manipulations in this dataset have significant and unexpected effects on connectome similarity. Ultimately, we add greater support for the idea that within-subject attentional state changes are encoded in within-subject differences in functional connectivity and offer grounds for further exploration of the way functional connectivity models of different cognitive functions may differ in their sensitivity to state- vs. trait-like differences.

Acknowledgements

We thank Abigail Greene for sharing the CPMs of fluid intelligence. Additionally, we thank Sivayini Kandeepan, Lorina Naci, and Emily Nichols for sharing these data and answering questions regarding OpenNeuro dataset ds003171.

Supplementary material

Supplementary material is available at *Cerebral Cortex Journal* online.

Funding

This work was supported by National Science Foundation BCS-2043740 (M.D.R.) and resources provided by the University of Chicago Research Computing Center.

Conflict of Interest statement. None declared.

Data availability

Code is available at <https://github.com/tchamberlain/propofol>. The data underlying this article are available on OpenNeuro at <https://openneuro.org/datasets/ds003171/>, and can be accessed with identifier ds003171.

References

- Amico E, Gomez F, Di Perri C, Vanhaudenhuyse A, Lesenfants D, Boveroux P, Bonhomme V, Bricchant JF, Marinazzo D, Laureys S. Posterior cingulate cortex-related co-activation patterns: a resting state fMRI study in propofol-induced loss of consciousness. *PLoS One*. 2014;9(6):e100012. <https://doi.org/10.1371/journal.pone.0100012>.
- Avery EW, Yoo K, Rosenberg MD, Greene AS, Gao S, Na DL, Scheinost D, Constable TR, Chun MM. Distributed patterns of functional connectivity predict working memory performance in novel healthy and memory-impaired individuals. MIT Press. 2020;32(2): 241–255. https://doi.org/10.1162/jocn_a_01487.
- Bates D, Mächler M, Bolker BM, Walker SC. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1):1–48. <https://doi.org/10.18637/jss.v067.i01>.
- Bedi G, Phan KL, Angstadt M, De Wit H. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology (Berl)*. 2009;207(1):73–83. <https://doi.org/10.1007/s00213-009-1635-z>.
- Bijsterbosch JD, Woolrich MW, Glasser MF, Robinson EC, Beckmann CF, Van Essen DC, Harrison SJ, Smith SM. The relationship between spatial configuration and functional connectivity of brain regions. *Elife*. 2018;7:e32992. <https://doi.org/10.7554/eLife.32992>.
- Boveroux P, Vanhaudenhuyse A, Bruno M-A, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. *Anesthesiology*. 2010; 113(5):1038–1053. <https://doi.org/10.1097/ALN.0B013E3181F697F5>.
- Cai H, Zhu J, Yu Y. Robust prediction of individual personality from brain functional connectome. *Soc Cogn Affect Neurosci*. 2020;15(3): 359–369. <https://doi.org/10.1093/SCAN/NSAA044>.
- Costumero V, Bueichékú E, Adrián-Ventura J, Ávila C. Opening or closing eyes at rest modulates the functional connectivity of V1 with default and salience networks. *Sci Rep*. 2020;10(1):9137. <https://doi.org/10.1038/s41598-020-66100-y>.
- Feilong M, Guntupalli JS, Haxby JV. The neural basis of intelligence in fine-grained cortical topographies. *Elife*. 2021;10:e64058. <https://doi.org/10.7554/eLife.64058>.
- Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, Papademetris X, Constable RT. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci*. 2015;18(11):1664–1671. <https://doi.org/10.1038/nn.4135>.
- Galeano Weber EM, Hahn T, Hilger K, Fiebach CJ. Distributed patterns of occipito-parietal functional connectivity predict the precision of visual working memory. *Neuroimage*. 2017;146:404–418. <https://doi.org/10.1016/j.neuroimage.2016.10.006>.
- Gratton C, Laumann TO, Nielsen AN, Greene DJ, Gordon EM, Gilmore AW, Nelson SM, Coalson RS, Snyder AZ, Schlaggar BL, et al. Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. *Neuron*. 2018; 98(2):439–452.e5. <https://doi.org/10.1016/j.neuron.2018.03.035>.
- Greene AS, Gao S, Scheinost D, Constable RT. Task-induced brain state manipulation improves prediction of individual traits. *Nat Commun*. 2018;9(1):2807. <https://doi.org/10.1038/s41467-018-04920-3>.
- Guldenmund P, Vanhaudenhuyse A, Sanders RD, Sleight J, Bruno MA, Demertzi A, Bahri MA, Jaquet O, Sanfilippo J, Baquero K, et al. Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep. *Br J Anaesth*. 2017;119(4):674–684. <https://doi.org/10.1093/BJA/AEX257>.
- Guntupalli JS, Feilong M, Haxby JV. A computational model of shared fine-scale structure in the human connectome. *PLoS Comput Biol*. 2018;14(4):e1006120. <https://doi.org/10.1371/journal.pcbi.1006120>.
- Hasson U, Nir Y, Levy I, Fuhrmann G, Malach R. Intersubject synchronization of cortical activity during natural vision. *Science*. 2004; 303(5664):1634–1640. <https://doi.org/10.1126/science.1089506>.
- Hsu WT, Rosenberg MD, Scheinost D, Constable RT, Chun MM. Resting-state functional connectivity predicts neuroticism and extraversion in novel individuals. *Soc Cogn Affect Neurosci*. 2018;13(2):224–232. <https://doi.org/10.1093/scan/nsy002>.
- Jangraw DC, Gonzalez-Castillo J, Handwerker DA, Ghane M, Rosenberg MD, Panwar P, Bandettini PA. A functional connectivity-based neuromarker of sustained attention generalizes to predict recall in a reading task. *Neuroimage*. 2018;166:99–109. <https://doi.org/10.1016/j.neuroimage.2017.10.019>.
- Kandeepan S, Rudas J, Gomez F, Stojanoski B, Valluri S, Owen AM, Naci L, Nichols ES, Soddu A. Modeling an auditory stimulated brain under altered states of consciousness using the generalized ising model. *Neuroimage*. 2020;223:117367. <https://doi.org/10.1016/j.neuroimage.2020.117367>.
- Kazlauskaitė V, Lynn R. Two-year test-retest reliability of the colored progressive matrices. *Percept Mot Skills*. 2002;95(2):354. <https://doi.org/10.2466/pms.2002.95.2.354>.
- Kong R, Li J, Orban C, Sabuncu MR, Liu H, Schaefer A, Sun N, Zuo X-N, Holmes AJ, Eickhoff SB, et al. Spatial topography of individual-specific cortical networks predicts human cognition, personality, and emotion. *Cereb Cortex*. 2019;29(6):2533–2551. <https://doi.org/10.1093/cercor/bhy123>.
- Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E, Oosterlaan J. Does methylphenidate improve academic performance? A systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;28(2):155–164. <https://doi.org/10.1007/S00787-018-1106-3>.
- Kucyi A, Esterman M, Capella J, Green A, Uchida M, Biederman J, Gabrieli JDE, Valera EM, Whitfield-Gabrieli S. Prediction of stimulus-independent and task-unrelated thought from functional brain networks. *Nat Commun*. 2021;12(1):1793. <https://doi.org/10.1038/s41467-021-22027-0>.
- Martuzzi R, Ramani R, Qiu M, Rajeevan N, Constable RT. Functional connectivity and alterations in baseline brain state in humans. *Neuroimage*. 2010;49(1):823–834. <https://doi.org/10.1016/j.neuroimage.2009.07.028>.
- Naci L, Haug A, MacDonald A, Anello M, Houldin E, Naqshbandi S, Gonzalez-Lara LE, Arango M, Harle C, Cusack R, et al. Functional diversity of brain networks supports consciousness and verbal intelligence. *Sci Rep*. 2018;8(1):13259. <https://doi.org/10.1038/s41598-018-31525-z>.
- Qiu M, Scheinost D, Ramani R, Constable RT. Multi-modal analysis of functional connectivity and cerebral blood flow reveals

- shared and unique effects of propofol in large-scale brain networks. *Neuroimage*. 2017;148:130–140. <https://doi.org/10.1016/j.NEUROIMAGE.2016.12.080>.
- Rosenberg MD, Finn ES, Scheinost D, Papademetris X, Shen X, Constable RT, Chun MM. A neuromarker of sustained attention from whole-brain functional connectivity. *Nat Neurosci*. 2016;19(1):165. <https://doi.org/10.1038/NN.4179>.
- Rosenberg MD, Zhang S, Hsu WT, Scheinost D, Finn ES, Shen X, Constable RT, Li CSR, Chun MM. Methylphenidate modulates functional network connectivity to enhance attention. *J Neurosci*. 2016;36(37):9547–9557. <https://doi.org/10.1523/JNEUROSCI.1746-16.2016>.
- Rosenberg MD, Scheinost D, Greene AS, Avery EW, Kwon YH, Finn ES, Ramani R, Qiu M, Constable RT, Chun MM. Functional connectivity predicts changes in attention observed across minutes, days, and months. *Proc Natl Acad Sci*. 2020;117(7):3797–3807. <https://doi.org/10.1073/pnas.1912226117>.
- Salehi M, Greene AS, Karbasi A, Shen X, Scheinost D, Constable RT. There is no single functional atlas even for a single individual: functional parcel definitions change with task. *Neuroimage*. 2020;208:116366. <https://doi.org/10.1016/j.neuroimage.2019.116366>.
- Schaefer KW, Willis SL, Caskie GIL. The Seattle longitudinal study: relationship between personality and cognition. *Aging Neuropsychol Cogn*. 2004;11(2–3):304–324. <https://doi.org/10.1080/13825580490511134>.
- Shen X, Tokoglu F, Papademetris X, Constable RT. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *Neuroimage*. 2013;82:403–415. <https://doi.org/10.1016/j.neuroimage.2013.05.081>.
- Stamatakis EA, Adapa RM, Absalom AR, Menon DK. Changes in resting neural connectivity during propofol sedation. *PLoS One*. 2010;5(12):e14224. <https://doi.org/10.1371/JOURNAL.PONE.0014224>.
- Tang CY, Ramani R. Functional connectivity and anesthesia. *Int Anesthesiol Clin*. 2016;54(1):143–155. <https://doi.org/10.1097/AIA.0000000000000083>.
- Vanderwal T, Eilbott J, Finn ES, Craddock RC, Turnbull A, Castellanos FX. Individual differences in functional connectivity during naturalistic viewing conditions. *Neuroimage*. 2017;157:521–530. <https://doi.org/10.1016/j.neuroimage.2017.06.027>.
- Yamashita M, Yoshihara Y, Hashimoto R, Yahata N, Ichikawa N, Sakai Y, Yamada T, Matsukawa N, Okada G, Tanaka SC, et al. A prediction model of working memory across health and psychiatric disease using whole-brain functional connectivity. *Elife*. 2018;7:e38844. <https://doi.org/10.7554/ELIFE.38844>.
- Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage*. 2010;53(4):1197–1207. <https://doi.org/10.1016/j.NEUROIMAGE.2010.06.041>.