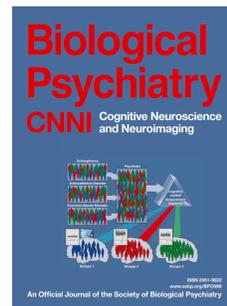


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Time varying functional connectivity decreases as a function of acute nicotine abstinence

John R. Fedota^{1, *}, Thomas J. Ross^{1, *}, Juan Castillo¹, Michael R. McKenna^{1,2}, Allison L. Matous^{1,3},
Betty Jo Salmeron¹, Vinod Menon⁴, & Elliot A. Stein¹

¹ Neuroimaging Research Branch, National Institute on Drug Abuse-Intramural Research Program, NIH, Baltimore, MD; ² Ohio State University, Columbus, OH; ³ Geisel School of Medicine at Dartmouth, Hanover, NH; ⁴ Stanford University School of Medicine, Stanford, CA
* equal contribution

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Corresponding author:

John Fedota & Elliot A. Stein, Neuroimaging Research Branch, National Institute on Drug Abuse-Intramural Research Program, NIH, 251 Bayview Blvd, Baltimore, MD 21224
(john.fedota@nih.gov; Estein@nih.gov)

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ABSTRACT

Background:

The Nicotine Withdrawal Syndrome (NWS) includes affective and cognitive disruptions whose incidence and severity vary across time during acute abstinence. However, most network-level neuroimaging employs static measures of resting state functional connectivity (rsFC), assume time-invariance, and are thus unable to capture dynamic brain-behavior relationships. Recent advances in rsFC signal processing allow characterization of “time varying functional connectivity” (TVFC), which characterizes network communication between networks that reconfigure over the course of data collection. As such, TVFC may more fully describe network dysfunction related to the NWS.

Methods:

To isolate alterations in the frequency and diversity of communication across network boundaries during acute nicotine abstinence we scanned n=25 cigarette smokers in the nicotine sated and abstinent states and applied a previously-validated method to characterize TVFC at a network and nodal level within the brain.

Results:

During abstinence, we found brain wide decreases in the frequency of interactions between network nodes in different modular communities (i.e. temporal flexibility; TF). In addition, within a subset of the networks examined the variability of these interactions across community boundaries (i.e. spatiotemporal diversity; STD) also decreased. Finally, within two of these networks the decrease in STD was significantly related to NWS clinical symptoms.

Conclusions:

Employing multiple measures of TVFC in a within subjects’ design, we characterized a novel set of changes in network communication and link these changes to specific behavioral symptoms of the NWS. These reductions in TVFC provide a meso-scale network description of the relative inflexibility of specific large-scale brain networks during acute abstinence.

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Introduction

Acute nicotine abstinence is a key early hurdle to smoking cessation as most cessation attempts fail within a week of their target quit day(1). These poor treatment outcomes are due, in part, to components of the Nicotine Withdrawal Syndrome (NWS) precipitated by acute smoking abstinence. The aversive symptoms of the NWS both dissuade smokers from attempting to quit(2) and promote relapse via negative reinforcement—the relief of the withdrawal state(3–5).

The clinical presentation of the NWS includes increased negative affect(6,7), lapses of attention(8–11), and punctate craving for nicotine(6). Critically, across both subjective and objective measures of NWS symptoms, variability in onset, time course, and phenomenology is consistently observed(12–17). For example, craving increases early and again late in the day(15), and negative affect spikes intermittently following cessation(17). Symptoms are more variable in withdrawn smokers after quitting than before, suggesting that smoking may buffer or constrain aversive symptoms, which are then “unleashed” by cessation(18). The incidence of these NWS symptoms increases with increased acute psychosocial stress(19–22). The volatility in affective disruptions may also interact with the oft-reported cognitive disruptions such that periodic lapses in attention—caused by subjective feelings of distress(23,24) and nicotine craving(14)—drive abstinence-related cognitive decrements(8).

As substance use disorder (SUD) is considered a brain circuit- and network-level disease(25,26), the variability in the presentation of NWS clinical symptoms should be linked to dynamic, time dependent changes in brain network communication and configuration. To this point, characterization of large-scale network communication in SUD populations generally

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show *increases* in resting state functional connectivity (rsFC) as a function of abstinence across a variety of circuits and brain networks(27,28). However, considering the variability in clinical NWS symptom presentation, it is notable that the extant literature almost exclusively employed static rsFC methods that assume unchanging network structure over time. This assumption limits the temporal resolution of the network communication described to the total data acquisition period and likely underspecifies the nature of the brain-based disruptions associated with the NWS.

Recent advances in fMRI time series signal processing allow characterization of “time varying functional connectivity” (TVFC)(29–33), which characterizes communication between networks that reconfigure over the course of data collection. Such characterizations of TVFC are of particular relevance to the study of SUD, as ongoing, spontaneous (i.e. dynamic) brain activity has been related to the maintenance of brain circuit homeostasis(34,35) via adaptive physiological response to external and internal perturbation. These homeostatic processes are impaired across a variety of SUDs, including nicotine dependence(36). Specifically, these less adaptive compensatory responses to homeostatic challenges in SUD(37), which manifest as time variant clinical symptoms during abstinence, may be better indexed by measures of TVFC as opposed to static functional connectivity.

To date, most TVFC studies have interrogated data from healthy individuals, and generally demonstrate reductions in TVFC associated with poorer behavioral performance(31,38–40) and increased negative affect(41). Consistent with these affective and behavioral disruptions is a small but growing literature on SUD-related change in dynamic TVFC (42–45). Across a variety of methods used to characterize TVFC, these studies consistently

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report a *reduction* in TVFC associated with SUD, including a study from our lab reporting a *decrease* in the frequency of transitions between brain network states as a function of acute nicotine abstinence(45).

Here, we employ a TVFC method initially developed and validated in healthy individuals(46) that allows for a more focused characterization of TVFC at both a brain network and nodal level. The observed changes in TVFC are then related to changes in subjective measures of NWS symptom severity and objective performance on a modified version of the Eriksen flanker task to assess attentional control in a within-subjects design. Based on previous evidence linking reductions in TVFC with negative affect and poor cognitive performance in healthy populations(31,38–41) and to SUD more generally (42–45), we predicted that the external perturbations of and stress induced by acute abstinence in SUD will be associated with reduced TVFC. We hypothesize that acute nicotine abstinence will lead to decreased TVFC in a set of brain networks and nodes previously associated with attentional processing and the NWS (i.e. Salience Network (SN), Frontoparietal Control Network (FPC), Default Mode Network (DMN))(26,45) as well as those associated with emotional processing (insula-amygdala, anterior cingulate cortex, and ventral medial orbitofrontal cortex)(47). Further, we hypothesize that decreased TVFC will be associated with increased NWS symptom severity.

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Methods

Participants

36 participants completed all experimental procedures. Results from 20 of these 36 participants (55%), including reductions in a distinct measure of TVFC during abstinence, have been previously reported(45) (see Supplemental Materials for participant inclusion criteria). 11 of 36 participants were excluded from analysis for excessive head motion (average framewise displacement (FD) >0.2 mm(48)) in either of their two scans, resulting in data analyzed from n=25 participants (Table 1). Written informed consent was obtained in accordance with the National Institute on Drug Abuse (NIDA)-Intramural Research Program Institutional Review Board.

---Table 1---

Experimental Design

The experiment followed a longitudinal, within-subjects design where each participant completed two MRI scanning sessions: one during *ad lib* sated smoking followed by an acute abstinence scan, with the last cigarette ~48 hours before scan. During both MRI scanning sessions participants completed an 8 minute, eyes open resting scan directly followed by a 25-minute version of the parametric flanker task (PFT). (Fig 1). The data presented here are part of a larger smoking cessation protocol. Thus, for 28/36 participants, the abstinence scan marked the start of a quit attempt and the order of the two scans was fixed, with sated preceding abstinence scan by an average of 60.5 days (median=22.1 days). For all participants, a stable smoking pattern between sated scan and 48 hours prior to abstinence scan was verified by self-

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report and urine cotinine. All participants had equivalent cigarettes/day and no quit attempts between the stated and abstinence scans.

Clinical NWS Instruments

Subjective ratings and analyses

Immediately prior to each scanning session, subjective ratings of withdrawal (Wisconsin Smoking Withdrawal Scale (WSWS))(49), affect (Positive and Negative Affect Schedule (PANAS))(50), perceived stress (Perceived Stress Scale (PSS))(51), and craving (Tobacco Craving Questionnaire (TCQ))(52) were assessed using previously-validated clinical instruments.

Subjective clinical instrument scores for each scan session were assessed. STATE (abstinence [-] sated) effects were calculated via paired t-test for total score of WSWS, and PSS as well as factor scores for TCQ. Subscale scores for PANAS were submitted to a SUBSCALE*STATE repeated measures ANOVA.

Behavioral performance and analyses

The parametric flanker task was used as an assay of attentional processing. This task is a modified version of the classic Eriksen flanker task designed to represent varying levels of demand for cognitive control driven by response conflict on a trial-by-trial basis. The procedural details of the task implementation in smokers have been described previously(53) and are included in the supplemental materials. Behavioral performance on the task was quantified via correct reaction time (RT) and correct RT coefficient of variation (RTCV) (i.e. standard deviation of RT/mean RT). Counts of error type (Errors of Commission, Errors of Omission) were

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evaluated to assess selective attention as a function of nicotine abstinence. For errors of omission, STATE effects were quantified by paired t-test. For all other behavioral measures, values were submitted to a STATE (sated-abstinent) * DEMAND for cognitive control (high/medium/low) repeated measures ANOVA.

---Figure 1: Experimental Design---

MRI data acquisition and analyses

We followed the processing pipeline, including the analysis code, from the Chen et al. TVFC study(54). (Fig 2) Raw data were minimally preprocessed using fmriprep (v0.4.5)(55), with the first 10 frames discarded to account for scanner equilibrium. (See supplemental materials for full acquisition and preprocessing details)

The brain was parcellated into 264 nodes based on the canonical Power et al. scheme(56), including supraordinate organization into 14 large-scale networks; 5mm spheres were placed at the center coordinates for each of the 264 ROIs. Based on the group EPI mask, any node with <50% voxel coverage was excluded, resulting in 240 nodes included in the current analysis (see Supplemental Materials, Fig S1, and Table S2 for excluded regions). For each scan, mean signals within the 240 nodes were extracted and high-pass filtered ($f > .008$ Hz) using a least-squares FIR filter (MATLAB function `firls`).

Functional connectivity matrix (FCM)

At the individual subject and session levels, both a static and a dynamic FCM were created.

Static FCM (240x240) were created using Pearson correlation on the entire 230-point timeseries

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and Fischer z-transformed. Dynamic FCM were created using a 40s sliding window, a 1 TR step, and exponentially decaying weights(57). The weights were set to

$$w_t = w_0 e^{(t-T)/\tau}, t = 1, 2, \dots, T,$$

where w_0 is set such that the coefficients sum to one and τ is set to 1/3 of the window length.

The weighed Pearson correlations were Fisher transformed, resulting in 210 (240x240) dynamic FCM per individual in each session.

Community detection

Community detection was implemented using the Louvain algorithm implemented in the Brain Connectivity Toolbox (v2017_04_05)(58), resulting in a community structure based on an optimal Q^* parameter that maximizes intramodular connectivity while minimizing intermodular connectivity(59). For each application, community detection was randomly initialized 100 times and the iteration with the largest Q^* was retained. This community structure is thus data-driven and is not restricted by the *a priori* network membership imposed by the Power et al., parcellation(60). Community detection was performed on group average and session average static FCM and, at the individual level, on the FCM from each of the 210 dynamic windows. The community structure derived from the group average static FCM pooled across both scanning sessions—herein called the reference community—was applied in the calculation of TVFC metrics as described below. We intentionally chose a reference static FCM pooled across both

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sessions to keep the comparisons on equal footing, and to avoid any bias by choosing only one session.

TVFC metrics

Within each dynamic window an adjacency matrix was computed. In the adjacency matrix, if nodes i and j are in the same community, then cell (i,j) is 1 (or 0 if their communities differ). The adjacency matrices were averaged across the 210 dynamic windows to create a temporal co-occurrence matrix C . Thus, cell C_{ij} quantified the proportion of time that nodes i and j spent in the same community, even as the overall community structure changed over time. Temporal co-occurrence matrices were computed for each individual in each session. The temporal co-occurrence matrix and group static FCM were then combined to derive two nodal-level measures of TVFC as follows:

Temporal flexibility (TF) quantifies the degree to which a given node interacts outside of its reference community. For nodes i and j , participant k and session l , TF is:

$$tf_{ikl} = \frac{\sum_{j, u_j \neq u_i} C_{ijkl}}{\sum_{j \neq i} C_{ijkl}},$$

where u_i is the community of node i from the group static FCM pooled across sessions. Thus, TF represents the frequency of interactions a given node has outside of its static reference community divided by the total interactions a given node has with all other nodes.

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Spatiotemporal Diversity (STD) quantifies the variability in a node's interaction outside of its reference community. It is the normalized connection diversity(61), using the temporal co-occurrence matrix instead of the FCM, and is inspired by Shannon entropy. For node i , participant k and session l , the STD is:

$$std_{ikl} = -\frac{1}{\log(m)} \sum_{u \in M} p_{ikl}(u) \log(p_{ikl}(u)),$$

where M is the set of communities (numbering m), $p_{ikl}(u) = s_{ikl}(u)/s_{ikl}$, s_{ikl} is the sum of the temporal co-occurrence matrix for node i , participant k and session l and all communities and, similarly, $s_{ikl}(u)$ is the sum for community u . The $\log(m)$ term normalizes std to $[0,1]$. While TF and STD both measure similar constructs, they do differ. For example, a node can frequently interact with a single node outside its community (high TF, low STD) or interact frequently with a variety of nodes from other communities (high TF, high STD).

Network and Community values for TF and STD were calculated by averaging the nodal scores within each of the 14 *a priori* networks based on the Power et al. parcellation(60) or the 4 detected communities (see Results) in the group static FC matrix, respectively to assess the robustness of the results to alternative network definitions.

TVFC session effects

Changes in TF and STD calculated at the network or community level were assessed via repeated measures ANOVA with factors NETWORK and STATE (sated/abstinent) or

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COMMUNITY and STATE, with change in framewise displacement (FD) included as a covariate.

Main effects of STATE or interactions (e.g. NETWORK*STATE) in the absence of an FD interaction (i.e. NETWORK*STATE*FD) were characterized with post-hoc comparisons, Bonferroni corrected for multiple comparisons at $\alpha < 0.05$.

Regression analyses

To relate changes in subjective withdrawal symptoms and/or behavior to changes in TVFC (at the network, community, or node levels), statistical models were built via robust linear regression using the `lmrob` function from R package *robustbase*(62). Based on the variability inherent in subjective reports, robust regression was employed to provide statistical estimates less sensitive to the presence of outliers in the data. As with the TVFC session effects, change in FD was included in the regression model ($\Delta \text{behavior} \sim \Delta \text{brain} + \Delta \text{FD}$) to control for relationships confounded by residual changes in head motion across scan sessions.

---Figure 2: Time varying connectivity analysis pipeline---

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RESULTS

Abstinence and clinical NWS assessments

Physiological assessment

Consistent with self-reports of ~48 hours of full nicotine abstinence (50.2±9.7 hrs), expired CO (ppm) was significantly reduced during abstinence (sated scan (22.8±1.6); abstinent scan (2.5±0.2); $F(1,24)=186.8$ $p<.0001$).

Clinical Instruments

Subjective ratings of stress, affect and withdrawal were all modulated by acute nicotine abstinence; subjective ratings of craving, however, were not. PSS showed a STATE effect ($F(1,24)=4.50$, $p<.05$) such that perceived stress was greater during abstinence. PANAS showed a STATE*SUBSCALE (positive/negative affect) interaction ($F(1,24)=18.92$, $p<.001$). Follow-up tests showed positive affect decreased during abstinence ($F(1,24)=21.02$, $p<.0001$) while negative affect was unchanged ($F(1,24)=2.42$, $p=.13$). WSWs total score showed a strong trend level STATE effect ($F(1,24)=4.10$, $p=.054$) with increased ratings of withdrawal during abstinence. None of the four TCQ factors showed a STATE effect (all F 's < 0.95). (Figs 3A, S2)

Behavioral performance

In the Parametric Flanker Task, Errors of Omission, showed a main effect of STATE such that omissions increased during abstinence (sated scan (6.08±7.88); abstinent scan (12.1±15.9); ($F(1,24)=8.62$, $p<.01$). No other measure of behavioral performance (RT, RTCV, Errors of Commission) showed an effect of STATE (all F 's < 2.20) or a STATE*DEMAND interaction (all F 's < 0.94) (Figs 3B, S3)

---Figure 3: Abstinence induced change in clinical measures of the Nicotine Withdrawal-Syndrome--

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Neuroimaging results

Even with the removal of 11 subjects due to excessive head movement ($FD > 0.2$ mm), residual FD showed an effect of STATE ($t(24)=3.79$, $p < .001$) such that average FD was greater during the abstinence (0.14 mm) than the sated (0.11 mm) scan. Although these FD levels fall well below the floor effect previously described(48), change in FD was added as a covariate to all subsequent neuroimaging analyses of STATE effects.

Temporal Flexibility (TF) and Spatiotemporal Diversity (STD): a priori network analyses

When nodal TVFC values were averaged across the *a priori* networks(60), TF showed a main effect of STATE ($F(1, 23)= 8.81$, $p < .01$) such that TF was reduced in abstinence vs. sated condition, while STD showed a STATE * NETWORK interaction ($F(3.71, 85.24)=2.60$, $p < .05$). Subsequent post hoc tests, corrected for multiple comparisons across the 14 networks, showed reductions in STD for the Cingulo-opercular Control network (COC) ($F(1,23)=17.45$, $p < .005$), Default Mode Network (DMN) ($F(1,23)=16.84$, $p < .01$) and the “uncategorized” network (UNC) ($F(1,23)=14.58$, $p < .05$); there was a strong trend level effect for the Salience Network (SN) ($F(1,23)= 9.88$, $p = .05$). In each case, network STD was reduced between abstinence vs. sated (Fig 4, S4, S5).

TF and STD: data-driven reference community analyses

When nodal TVFC values were averaged across detected community membership, TF showed a main effect of STATE ($F(1,23)=12.92$, $p < .005$) such that TF was reduced during abstinence. Additionally, STD showed a STATE*COMMUNITY interaction ($F(2.24, 51.54)=6.73$, $p < .005$) such

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that only one of the four identified communities showed a reduction in STD as a simple main effect of STATE ($F(1,23)=18.00$, $p<.005$) (Fig S6).

--Figure 4: Time varying connectivity change as a function of abstinence--

Correlations between behavioral measures and clinical reports with neuroimaging data

Subjective measures of withdrawal: Perceived Stress Scale (PSS)

Of the networks that showed a STATE effect (i.e. [abstinence (-) satiety]) on STD, change in “uncategorized” network STD was positively related with change in PSS ($p<.004$) (Fig 5A).

Behavioral measures of withdrawal: Errors of Omission

Of the networks that showed a STATE effect on STD, change in STD within the DMN and “uncategorized” networks were negatively related with change in Errors of Omission (DMN, $p<.02$; UNC, $p<.03$) (Fig 5B).

-- Figure 5: Correlations between abstinence-induced changes in Spatiotemporal Diversity and clinical Nicotine Withdrawal Syndrome symptoms--

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Discussion

We examined alterations in whole brain resting state TVFC as a function of acute nicotine abstinence vs. satiety. We identified reductions in the frequency and variability of interactions between nodes within larger networks across the brain that point to an abstinence-precipitated allostatic alteration in brain dynamics. Brain wide *decreases* in the frequency of interactions between network nodes in different modular communities (i.e. TF) were observed following 48 hours of smoking abstinence. In addition, within a subset of the 14 *a priori* large-scale networks examined—Cingulo-opercular Control (COC), Default Mode (DMN), Salience (SN), and “Uncategorized” (UNC)—the variability of these interactions (i.e. STD) across community boundaries was also *decreased*. Critically, within two of these networks (DMN and UNC), the decrease in STD was significantly related to NWS clinical symptoms. Thus, reductions in TVFC during early abstinence, when most treatment failures are seen, appear to characterize a systems-level dysfunction that may be a key mechanistic component of the NWS. These observed decreases in TVFC were directionally consistent with our previous results showing a decrease in network state transitions within a circumscribed set of networks(45) in a subset of the same participants.

Temporal Flexibility (TF)

The frequency of a given network’s interaction with nodes outside of its reference community, defined as TF, demonstrated a brain-wide reduction in inter-community participation across both *a priori* networks and *data driven* community parcellations during abstinence. This suggests a maladaptive increase in segregation of individual networks and commensurate

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reductions in communication efficiency across the brain. In healthy populations, such increased network segregation is associated with a) specialized processing and a lack of adaptability(63–65); b) performance of less demanding or automatic tasks(66–68); and c) the promotion of learned associations at the expense of flexible exploratory behavior(38,64,69,70). In the case of SUD, acute abstinence enhances such segregation by reducing the frequency of communication across subnetwork boundaries.

This observed reduction in TF during abstinence can be interpreted within the allostatic overload framework(71,72). During allostatic overload, repeated exposure to stress precipitates a dysregulated physiological response in an effort to restore homeostatic stability. However, this maladaptive response reduces stability and flexibility of the regulatory response(37,73). As TVFC is a measure of the modulation of the complex dynamic whole brain network(38,74,75), a reduction in the flexibility of connections over time is consistent with allostatic load. That is, the stress of acute abstinence is associated with a pervasive, brain-wide decrease in periodic communication between otherwise segregated network communities.

A putative mechanism for the observed decrease in TF is a reduction in synaptic plasticity during acute nicotine abstinence. Normally functioning synapses use metaplasticity to titrate levels of long-term potentiation and depression within a homeostatic dynamic range, thus avoiding run away strengthening or weakening of connections(76). In contrast, SUD is associated with reduced synaptic plasticity, reduced dynamic response to stressors, and more rigid synaptic connections(77,78). Thus, in SUD—especially during withdrawal—the brain is in a potentiated state and appears unable to reconfigure in response to environmental demands. Related clinical evidence illustrates an inability to induce synaptic plasticity in motor circuits via

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non-invasive brain stimulation during nicotine abstinence(79,80). While these prior results describe reductions in plasticity of specific circuits, the current findings provide a meso-scale description of a similar phenomenon.

Spatiotemporal Diversity (STD)

In contrast to the broad reduction in TF, a focused reduction in STD—the variability of interactions between a given set of nodes and the rest of the brain(46,81)—was observed in a subset of the networks or communities tested. Only four networks (COC, DMN, SN, and UNC) displayed a limited repertoire of interactions with other brain areas, and these interactions were less frequent during abstinence. Three of the 4 networks that display reduced STD during abstinence have been previously implicated in cognitive control (SN and COC)(82,83), tonic alertness (COC and DMN)(84,85) and abstinence-related dysfunction in SUD (SN and DMN)(26,86,87). Further, the observed focal decreases in STD coincide with the sites of highest nicotinic acetylcholine receptor expression in the human brain (COC and SN)(88), implicating disrupted nicotinic signaling dynamics in the reduction of STD during abstinence.

Beyond an overlap with the expression of nicotinic receptors, the networks displaying reduced STD during abstinence are canonical members of the “rich club” architecture of the brain(89). The rich club consists of a group of densely interconnected nodes that have been shown to coordinate the integration of information processed locally throughout the brain(90–92) and provide a stable scaffold upon which dynamic reconfigurations in the brain’s network structure can occur in response to task demands or arousal(64,74,75,93). Indeed, hubs within the rich club have been identified in the SN, COC, and DMN(89,91,92); additional nodes in the orbitofrontal cortex (OFC; part of the UNC network in the current parcellation) are part of the

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dynamical workspace of binding nodes(94) that serve to integrate disparate processing across the brain as a compliment to the rich club.

During acute abstinence, the integration of locally processed information is disrupted as the networks associated with the rich club do not interact as broadly with other nodes across the brain. This decrease in cross-network interaction is indexed by the reduction in STD for the four networks identified. The co-occurrence of reductions in the frequency (TF) and variability (STD) of communication in only these networks may have an outsized impact in promoting segregation at the cost of integration during abstinence, leading to the affective and attentional disruptions of NWS.

Strengthening this interpretation and the importance of network hubs displaying varied interactions with the rest of the brain, a subset of these observed reductions in STD were directly correlated with the clinical presentation of the NWS. Decreases in STD within both the DMN and “uncategorized” networks were negatively correlated with Errors of Omission in an attentional control task. That is, the greater the STD decrease in the DMN or “uncategorized” network, the larger the increase in the number of Errors of Omission.

The focus of these effects in the DMN suggests a bias towards internally constructed as opposed to externally derived information(95), while the focus on the “uncategorized” network—a collection of nodes not strongly associated with any of the other a priori networks(83) but including nodes in the OFC—potentially suggest impairments in assigning value to various targets of attention(96,97). That said, these suggestions remain speculative and require further validation, although they are consistent with disruptions in vigilance reported during abstinence(8,11). Further, in healthy populations, optimal task performance is

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associated with integration across otherwise segregated networks in the brain(98) and sparse connectivity across networks/communities has been previously related to self-reported fatigue(99). Thus, the lapses in attention seen in abstinence and related to decreased communication across the brain fits with these normative findings.

In contrast to the intuitive relationship between decreased STD and increased attentional disruption, the relationship between decreased STD and affective symptoms of NWS is less clear. The positive correlation between abstinence induced changes within UNC network STD and perceived stress shows that as STD decreases, perceived stress also decreases. SUD is strongly associated with impairments in interoceptive processing(100–103), including decreased activation to interoceptive cues in the OFC—a constituent node of the UNC network(104). These findings plus the well-characterized dissociation between physiological arousal and self-report in smokers(13,105) (i.e. Nesbitt’s Paradox(106)) suggest that the subjective point estimates of NWS employed in the current study may have been suboptimal in characterizing changes in the intensity (not to mention the frequency) of affective disruptions associated with changes in TVFC.

The current results should be viewed within several limitations. Specifically, the nature and significance of TVFC to brain function is an area of active research(29) where the literature includes both results consistent with the findings herein as well as results calling into question the ability to accurately quantify TVFC in 8 minutes of resting data(107). In this study, we employed a previously-validated TVFC methodology(46), and the reductions TVFC observed were consistent with evidence employing this method in cocaine dependence(44) and previous work from our lab employing an alternative measure of TVFC(45). That said, replication of

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these reductions across multiple TVFC metrics in independent samples is an important direction of further study.

An additional open question in the TVFC literature is how to match the timescales of behavioral and neurobiological measures. While NWS clinical symptoms present on the order of days, hours or minutes, the presumptive neurobiological events responsible for these observable behaviors occur on the order of milliseconds (synaptic plasticity) or seconds (sliding window functional connectivity measures as employed in the current study). While progress has been made relating measures across scales(31,41), an important next step is to relate changes in TVFC to continuous task performance or ecologic momentary assessments of subjective affect in SUD and NWS(15,16,108,109). Such efforts would better characterize the volatility of these subjective symptoms during abstinence and relate them to the described decreases in TVFC.

Finally, several methodological considerations are important to discuss. First, any method that uses clustering algorithms for community detection (e.g. the Louvain algorithm employed here and in the original paper(54)) is influenced by the selection of a priori parameters(59). Future work refining these methods should more fully explore the parameter space to identify optimal a priori values for a given dataset. Second, no consensus exists for appropriate filtering cutoffs to guard against spurious temporal correlations in sliding window correlation methods. While it has been suggested that a high pass filter value of $(1/\text{sliding window length})$ is necessary during preprocessing to remove spurious fluctuations in TVFC(110), a contemporaneous discussion suggests that shorter windows and lower high pass filter values can be employed provided careful statistical testing ensuring that the signal is not

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stationary is employed(111). Finally, physiological noise may impact the calculation of TVFC metrics and the BOLD signal(112,113). In the current study physiological noise was not directly measured or accounted for in the analysis. Though, it should be noted both white matter and CSF regressors were included in our analysis. These signals have been shown to help mitigate the effects of physiological noise(114,115).

Taken together, the current study describes both broad and focused reductions in TVFC during acute nicotine abstinence depending on the measure employed. These decreases are in contrast to the mostly consistent increases in static rsFC previously reported(27,28), and identify specific networks whose function is impaired by abstinence. Further, these reductions in TVFC create a meso-scale network description, linking prior evidence of reductions in synaptic plasticity with large-scale theories of allostatic load and relative inflexibility of network response to the acute stress of abstinence. By employing multiple measures of TVFC in a within subjects' design, we characterize a novel description of changes in network communication and link these changes to specific behavioral symptoms of the NWS. Moving forward, interventions to mitigate the effects of the observed network stasis on attentional processes during abstinence may be of interest.

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Table 1: Participant Demographics

	N=25
Gender (M/F)	15 / 10
Age	37.76 ± 2.05
Race (AA/C/MR)	11 / 13 / 1
Education (years)	13.2 ± 0.41
IQ (WASI)	103.56 ± 2.62
FTND	4.72 ± 0.35
Cigarettes per day	13.96 ± 1
Age of Smoking Initiation	15.88 ± 0.76
Years smoked	18.4 ± 2

Values are n/n or mean +/- SE.

AA=African American; C=Caucasian; MR=Multiple Races;

WASI= Wechsler Abbreviated Scale of Intelligence;

FTND=Fagerström Test of Nicotine Dependence

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Figure Legends

Figure 1: Experimental Design: Longitudinal within-subjects design. Session 1=Sated smoking (last cigarette immediately prior to subjective clinical NWS instruments and ~45min prior to MRI scan). Session 2=acute nicotine abstinence (~48 hours of biologically-verified abstinence prior to subjective clinical NWS instruments and MRI scan).

Figure 2: Time varying connectivity analysis pipeline. Average time courses were extracted from a 240 node parcellation (5mm radius spheres based on(60) (see figure S1 for spatial distribution)) . Static connectivity matrices from the entire time courses were combined to form a group connectivity matrix, and from this, a community structure was derived using network theory. In our case, 4 communities were found, and nodal community membership is indicated by the colors in the bar adjacent to the group matrix. Separately, dynamic connectivity matrices were formed from 40 s windows of the time courses, their community structure calculated, and temporal co-occurrence matrices created consisting of the fraction of time that 2 nodes spend in the same community. These co-occurrence matrices were combined with the group community structure to form two measures of time-varying connectivity. The highlighted boxes give example calculations of these 2 measures for a hypothetical node belonging to community 2 (in this example colored blue in the group community structure).

Figure 3: Abstinence induced change in clinical measures of the Nicotine Withdrawal Syndrome. A) subjective (WSWS, PSS, PANAS Positive) and B) behavioral (Errors of Omission) STATE ([abstinence-sated]) effects. See Supplemental Materials for all clinical measure results. Dots represent individual subject data in each session. WSWS=Wisconsin Smoking Withdrawal Scale; PSS= Perceived Stress Scale; PANAS=Positive and Negative Affect Schedule; Session 1=smoking satiety, Session 2= smoking abstinence
^o = $p < .055$; * = $p < .05$; ** = $p < .01$; **** = $p < .0001$

Figure 4: Time varying connectivity change as a function of abstinence. A) Nodal results. Each circle represents a single node (240 total) from the whole brain parcellation. Color of the circle indicates a priori network membership (56). Vectors indicate the magnitude of change in Temporal Flexibility (TF) and Spatiotemporal Diversity (STD) as a function of nicotine abstinence. B) Network results. Average STD value across nodes constituting each of the four a priori networks showing a decrease as a function of abstinence. C) Whole brain results. Average TF value across all 14 networks decreased as a function of abstinence. Network abbreviations: AUD=Auditory; CBL= Cerebellar; COC=Cingulo-Opercular Control; DAN=Dorsal Attention; DMN=Default Mode; FPC=Fronto-Parietal Control; MRN=Memory Retrieval; SMH=Somatomotor Hand; SMM=Somatomotor Mouth; SN= Saliency; SUB=Subcortical; UNC=Uncategorized; VAN=Ventral Attention; VIS=Visual
 * = $p < .05$; ** = $p < .01$; *** = $p < .005$

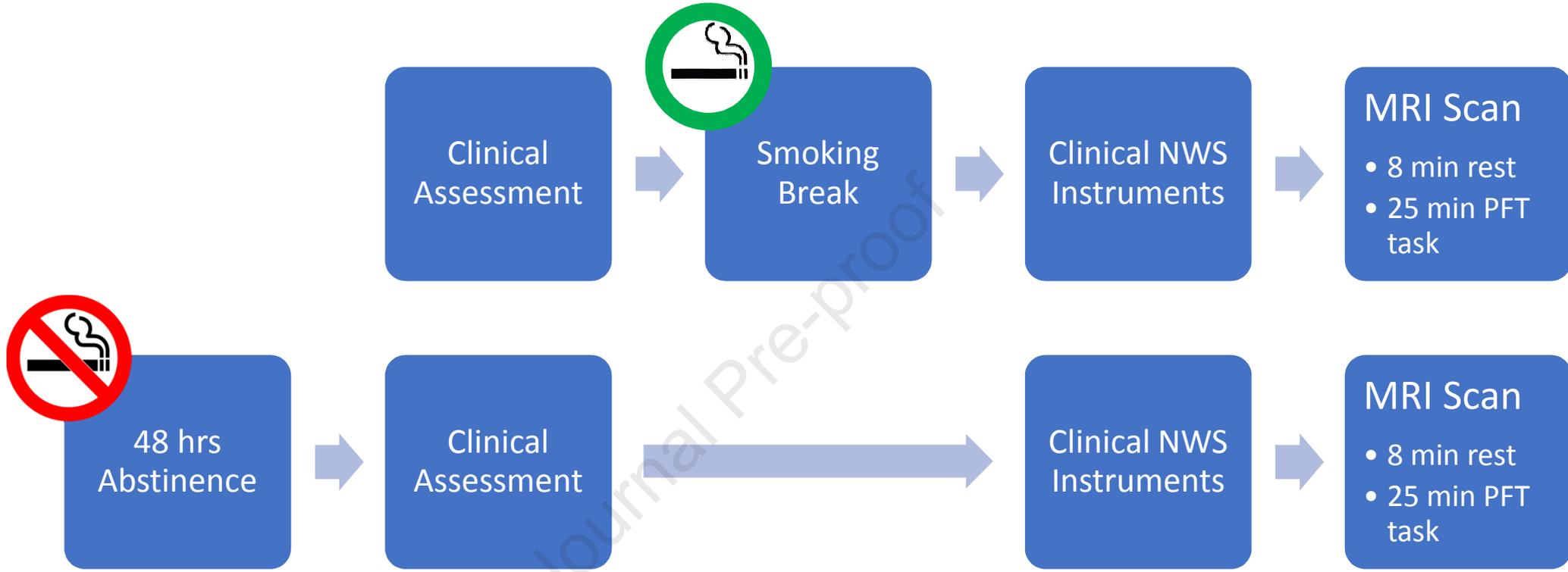
Figure 5: Correlations between abstinence-induced changes ([abstinent-sated]) in Spatiotemporal Diversity (STD) and clinical Nicotine Withdrawal Syndrome symptoms. A) Relationship with subjective report. A decrease in STD in the “Uncategorized” network is significantly related to a decrease in Perceived Stress Scale. B) Relationship with behavior. Decreases in STD in the Default Mode and “Uncategorized” networks are significantly related to an increase in errors of omission in the Parametric Flanker Task.

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DMN=Default Mode; UNC= Uncategorized; PSS=Perceived Stress Scale

Journal Pre-proof

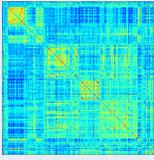
Session 2 Session 1



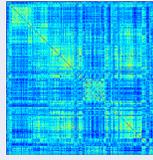
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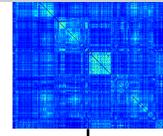
Session 1



Session 2



Group static connectivity map



Group community structure



Static connectivity maps made from entire timecourses

Average timecourse data from a 240 node parcellation

40 Second windowed data extracted

Connectivity matrices derived from the windowed data

Community structure derived from windowed connectivity matrices

Temporal co-occurrence matrices (proportion of time 2 nodes spend in the same community)

Temporal Flexibility (TF) Example

Node (i) belonging to community (u) 2 (blue)

Sum of temporal co-occurrence (C) of other (non-blue) communities (shaded in gray) divided by sum of entire row (i.e. across all communities)

$$tf_i = \frac{\sum_{j, u_j \neq 2} C_{ij}}{\sum_j C_{ij}}$$

First measure of Time Varying Connectivity (TVC)

Note that TF is a measure of how much a node interacts outside its community

Spatiotemporal Diversity (STD) Example

Node (i) belonging to community (u) 2 (blue)

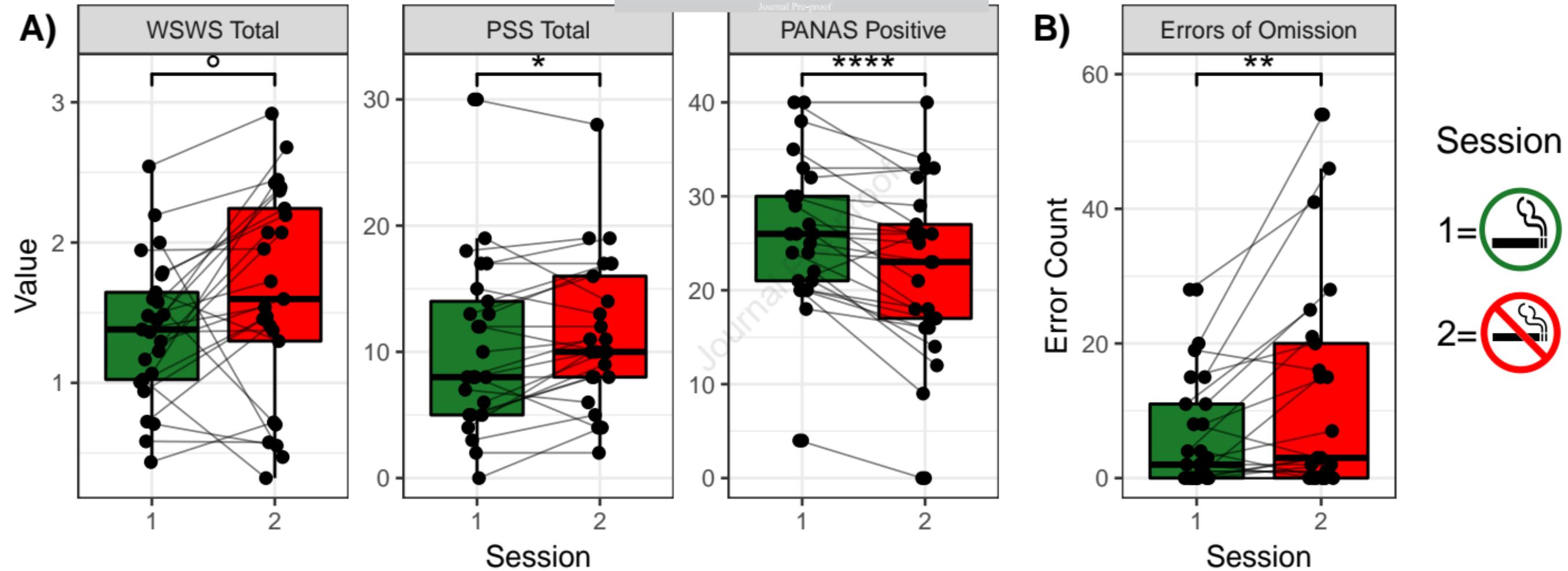
For the 4 communities, compute p (similar to TF above)

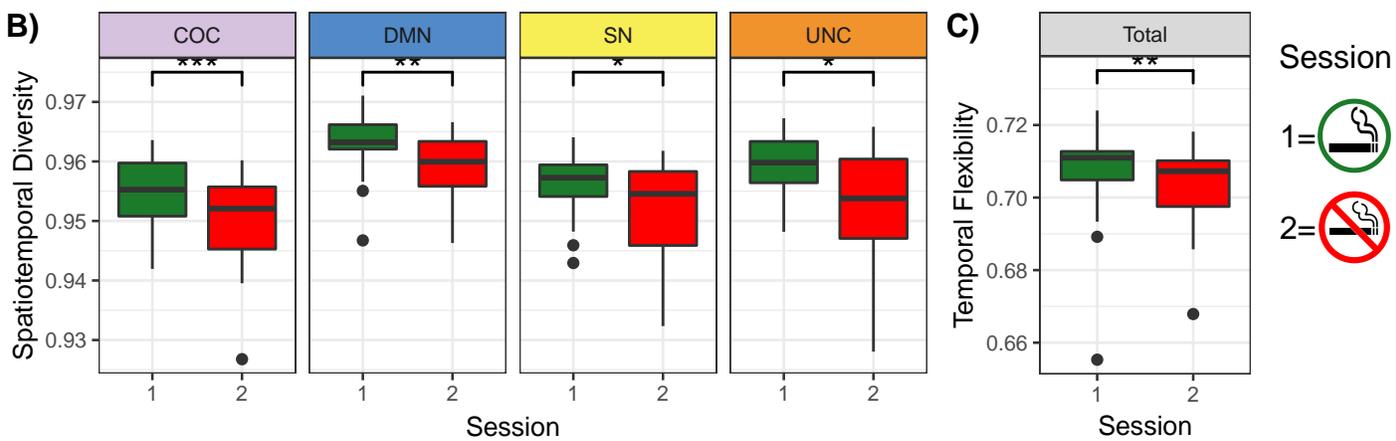
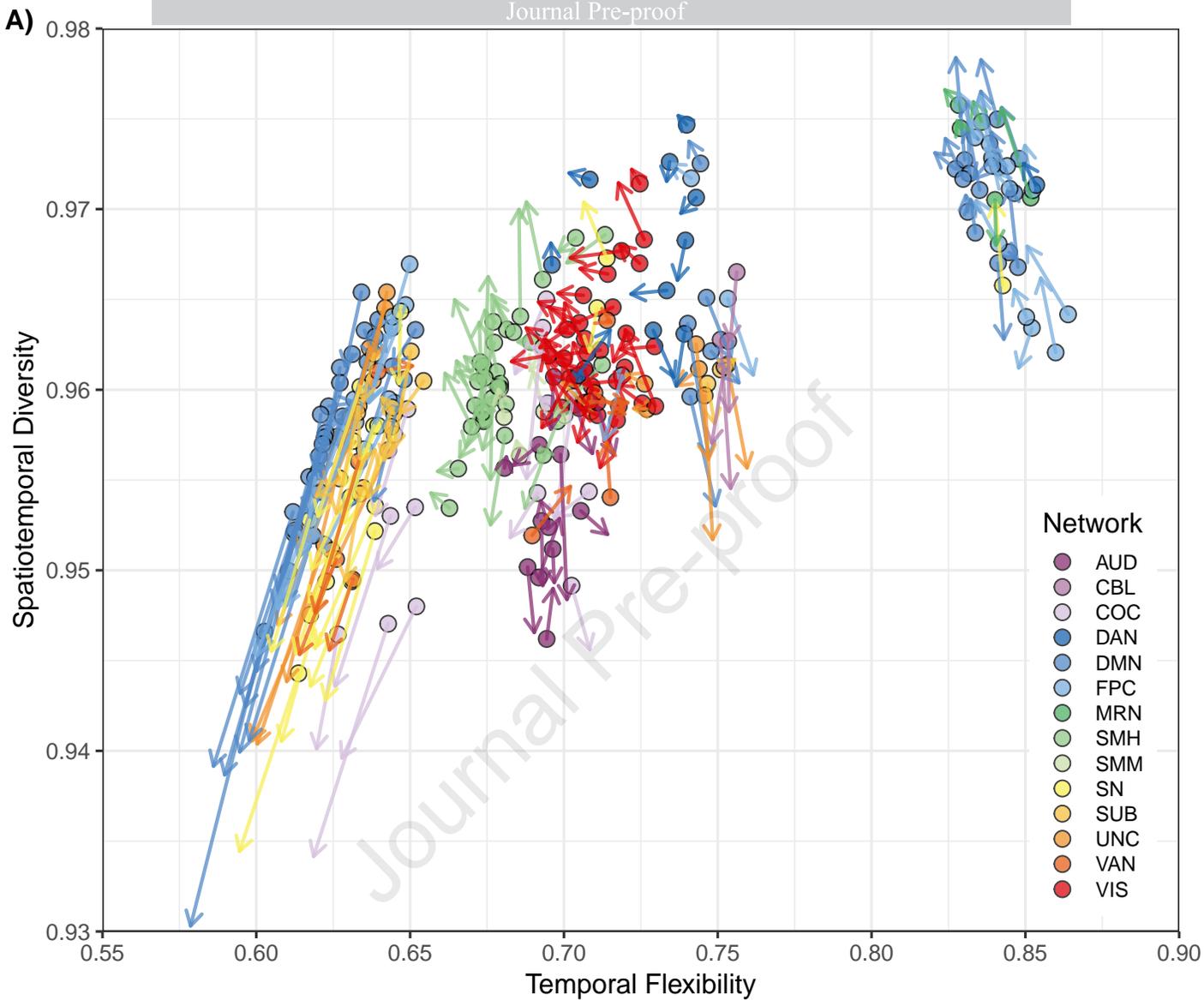
E.g., for community 1 (maroon)

$$p_{i1} = \frac{\sum_{j, u_j \in 1} C_{ij}}{\sum_j C_{ij}} \quad std_i = \frac{1}{\log(4)} \sum_{u=1}^4 p_{iu} \log(p_{iu})$$

Second measure of Time Varying Connectivity (TVC)

Note that STD is maximal for a node that interacts equally with all communities (including its own) and minimal for insular and promiscuous nodes





Perceived Stress Scale

Errors of Omission

