

1 **Title:** Unraveling Neural Complexity: Exploring Brain Entropy to Yield Mechanistic
2 Insight in Neuromodulation Therapies for Tobacco Use Disorder

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4 **Authors:** Timothy Jordan, Ph.D.¹, Michael R. Apostol, B.A.¹, Jason Nomi, Ph.D.¹,
5 Nicole Petersen, Ph.D.^{1*}

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7 **Affiliations:** ¹Department of Psychiatry and Biobehavioral Sciences, David Geffen
8 School of Medicine, UCLA, Los Angeles CA

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10 *Corresponding author: Correspondence can be directed to Dr. Nicole Petersen, 760
11 Westwood Plaza, Los Angeles, CA 90095, npetersen@ucla.edu

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19 Abstract

20 Neuromodulation therapies, such as repetitive transcranial magnetic stimulation
21 (rTMS), have shown promise as treatments for tobacco use disorder (TUD). However,
22 the underlying mechanisms of these therapies remain unclear, which may hamper
23 optimization and personalization efforts. In this study, we investigated alteration of brain
24 entropy as a potential mechanism underlying the neural effects of noninvasive brain
25 stimulation by rTMS in people with TUD. We employed sample entropy (SampEn) to
26 quantify the complexity and predictability of brain activity measured using resting-state
27 fMRI data. Our study design included a randomized single-blind study with 42 participants
28 who underwent 2 data collection sessions. During each session, participants received
29 high-frequency (10Hz) stimulation to the dorsolateral prefrontal cortex (dlPFC) or a control
30 region (visual cortex), and resting-state fMRI scans were acquired before and after rTMS.
31 Our findings revealed that individuals who smoke exhibited higher baseline SampEn
32 throughout the brain as compared to previously-published SampEn measurements in
33 control participants. Furthermore, high-frequency rTMS to the dlPFC but not the control
34 region reduced SampEn in the insula and dlPFC, regions implicated in TUD, and also
35 reduced self-reported cigarette craving. These results suggest that brain entropy may
36 serve as a potential biomarker for effects of rTMS, and provide insight into the neural
37 mechanisms underlying rTMS effects on smoking cessation. Our study contributes to the
38 growing understanding of brain-based interventions for TUD by highlighting the relevance
39 of brain entropy in characterizing neural activity patterns associated with smoking. The
40 observed reductions in entropy following dlPFC-targeted rTMS suggest a potential
41 mechanism for the therapeutic effects of this intervention. These findings support the use
42 of neuroimaging techniques to investigate the use of neuromodulation therapies for TUD.

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44 **Keywords:** Brain Entropy; Sample Entropy; repetitive TMS; transcranial magnetic
45 stimulation; tobacco use disorder; dorsolateral prefrontal cortex

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1. Introduction

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Brain-based neuromodulation therapies, such as repetitive transcranial magnetic stimulation (rTMS), are emerging as a new class of treatments for substance use disorders. A notable milestone has been regulatory (FDA) approval of rTMS to treat tobacco use disorder (TUD). Approval was granted on the basis of a multicenter, double-blind, randomized controlled trial finding higher smoking cessation rates in individuals who received active vs. sham rTMS (Zangen et al., 2021). This important finding capitalizes on many previous studies demonstrating that excitatory rTMS to the left dorsolateral prefrontal cortex (dlPFC) increases smoking abstinence rates relative to sham (Dinur-Klein et al., 2014; X. Li et al., 2020), lowers the rates of relapse to smoking (Sheffer et al., 2018), reduces cigarette craving (X. Li et al., 2013; Pripfl et al., 2014), and reduces the number of cigarettes smoked (Abdelrahman et al., 2021; Amiaz et al., 2009; Huang et al., 2016; X. Li et al., 2020; Prikryl et al., 2014). This body of work has led to clinical recommendations advocating for the use of rTMS as a smoking cessation treatment (Young et al., 2021), and suggests that this promising new brain-based therapeutic can be informed by advances in neuroimaging that shed light on the neural circuitry alterations associated with TUD.

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Noninvasive neuromodulation treatments have been designed to capitalize on findings linking the insula to smoking cessation by attempting to stimulate the insula. The neural basis of TUD has been strongly linked to the insula via lesion studies, finding that lesions to the insula per se (Naqvi et al., 2007) and a broader network involving the insula (Joutsa et al., 2022) are associated with higher rates of smoking cessation compared to lesions involving other brain regions. Structural MRI studies also link the insula and other associated brain regions to TUD. People who smoke have smaller gray matter volumes in areas of the prefrontal cortex and anterior cingulate (Brody et al., 2004). More cigarette exposure is associated with thinner insular cortex (Morales et al., 2014), and in women, thinner insular cortex is associated with more cigarette craving (Perez Diaz et al., 2021). Both meta-analysis (Hill-Bowen et al., 2022) and mega-analysis (Mackey et al., 2019) have reported smaller amounts of gray matter in both the medial prefrontal cortex and insula in individuals with varying substance use disorders, with a smoking-specific effect (i.e., not found in individuals with other kinds of substance use disorders) of smaller volumes in the posterior cingulate cortex; Hill-Bowen et al., 2022).

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Resting-state functional connectivity studies have found that both the insula specifically, and also large-scale network dynamics involving the insula, are implicated in both acute and chronic nicotine use. People who smoke have lower overall functional connectivity in the brain (Cheng et al., 2019), which has also been shown specifically within the executive control and default mode networks (Weiland et al., 2015). Functional connectivity features can be used in machine learning to distinguish between

85 people who do and do not smoke (Wetherill et al., 2019). A triple-network model
86 describing the relationship between the salience, default mode, and executive control
87 networks (Fedota & Stein, 2015) suggests that the relationship between these three
88 networks responds dynamically to nicotine use: smoking increased coupling between
89 the left executive control network and salience network, and decreased the
90 anticorrelation between the default mode network and salience network (Lerman et al.,
91 2014).

92 Resting-state functional connectivity analyses have also specifically linked the
93 insula to cigarette craving, withdrawal, and relapse. The magnitude of withdrawal
94 correlates positively with the strength of connectivity between the right ventral anterior
95 insula and dorsal anterior cingulate cortex (Ghahremani et al., 2021), both hubs of the
96 midcingulo-insular network (also referred to as the salience, cingulo-opercular, or
97 ventral attention network; Uddin et al., 2019). Stronger connectivity between the insula
98 and cortex surrounding the central gyrus is associated with better cessation outcomes
99 (less relapse) (Addicott et al., 2015); similarly, stronger connectivity between the ventral
100 striatum and a network including the insula is associated with better cessation
101 outcomes (Sweitzer et al., 2016).

102 The insula is anatomically located underneath the cortical surface, rendering it
103 inaccessible to conventional rTMS devices, but a small proof-of-concept study (Moeller
104 et al., 2022) and electric field modeling work have suggested that deep rTMS machines
105 such as the BrainsWay® H4 coil can penetrate deeply enough to reach the insula
106 (Fiocchi et al., 2018). However, network connectivity may provide an alternate route to
107 stimulate the insula and other brain regions involved in TUD(X. Li et al., 2017) using
108 conventional rTMS devices.

109 Though stimulating left dlPFC shows promise for smoking cessation treatments,
110 the exact mechanism that it works through remains unclear. Although rTMS
111 undoubtedly produces salutary behavioral effects, and in some cases produces
112 widespread changes in functional connectivity that can extend outside the stimulated
113 network (Beynel et al., 2020), rTMS to most brain regions does not appear to change
114 BOLD signaling at the stimulation site (Rafiei & Rahnev, 2022). Therefore, the
115 mechanism by which rTMS causes changes in the stimulated region and other
116 associated regions to yield changes in behavior remains ambiguous. Developing,
117 optimizing, and personalizing these techniques may be improved by a more
118 comprehensive understanding of normal brain function, the brain dysfunction associated
119 with substance use, and the brain function that underlies responses to neuromodulation.
120 Measuring brain entropy is an emerging approach that offers the potential to extend
121 existing knowledge of brain features associated with substance use disorders.

122 Brain entropy quantifies the complexity and unpredictability of brain activity – as
123 opposed to measures such as Pearson correlations, which measure the association
124 between two brain regions, or standard deviation, which assesses variability. Sample

125 entropy (SampEn) is an approach developed in the context of information theory that
126 has recently been applied to understand the structure of neural time series data. By
127 measuring the similarity between two components (subsequences) of a time series,
128 SampEn quantifies regularities and irregularities, and thereby provides information
129 about the complexity and predictability of the time series signal. A validation study has
130 shown that SampEn can be accurately determined for fMRI data on both simulated and
131 actual datasets(Z. Wang et al., 2014). Higher SampEn values reflect time series that are
132 more complex and therefore less predictable, and conversely, lower SampEn values
133 reflect time series that are less complex and therefore more predictable. SampEn is less
134 sensitive to noise and abbreviated data sets than other forms of entropy (e.g., Shannon
135 entropy and Approximate Entropy), rendering it a good candidate for analysis of fMRI
136 time series data(Richman & Moorman, 2000; Z. Wang et al., 2014; Yentes et al., 2013).

137 Previous work has suggested that SampEn is both altered by rTMS(Song,
138 Chang, Zhang, Peng, et al., 2019) and is also different in neuropsychiatric populations
139 compared with healthy individuals, although the direction of the effect depends on the
140 population studied. Individuals with Attention Deficit Hyperactivity Disorder (ADHD)
141 have lower frontal and occipital entropy compared with controls, and symptom severity
142 correlates negatively with entropy levels(Sokunbi et al., 2013). Similarly, lower SampEn
143 measurements have been observed in patients with Alzheimer's disease(B. Wang et al.,
144 2017). Notably, machine-learning classifiers that use SampEn to distinguish patients
145 from controls outperform those relying on standard correlation-based
146 measurements(Wu et al., 2021). Likewise SampEn has been shown to correlate with
147 fractional amplitude of low-frequency fluctuation (fALFF) measurements (Song, Chang,
148 Zhang, Ge, et al., 2019; Zhang et al., 2021), network coherence frequency ranges (D. J.
149 J. Wang et al., 2018) and power spectrum measures (Bruce et al., 2009) showing that
150 changes in SampEn captures a diverse set of neural mechanisms, which is a desired
151 feature in a biomarker.

152 In contrast to the relatively lower SampEn observed in individuals with ADHD and
153 Alzheimer's Disease, higher SampEn has been observed in people who smoke(Z. Li et
154 al., 2016), and a small pilot study suggested that noninvasive neuromodulation using
155 repetitive transcranial magnetic stimulation (rTMS) can reduce both entropy and
156 cigarette craving in these individuals(Song, Chang, Zhang, Peng, et al., 2019).
157 Demonstrating that rTMS can influence entropy in people who smoke could fill this gap
158 in knowledge about rTMS mechanisms, so we sought to test the hypotheses that (1)
159 high-frequency rTMS to the dlPFC would reduce SampEn in the dlPFC and insular
160 cortex, and (2) greater reductions in SampEn in these regions would correspond with
161 greater reductions in craving.

162 2.Methods & Materials

163 2.1 Participants

164 To test the above hypotheses, data were collected from 42 participants. All
165 participants were recruited from the greater Los Angeles community. Study procedures
166 were approved by the UCLA IRB and written, informed consent was obtained from all
167 participants for being included in the study. Initial eligibility assessments were made by
168 telephone, and participants who met criteria according to their self-report were
169 scheduled for further in-person eligibility screening, which included baseline
170 neuroimaging measurements (see below).

171 To be included, participants were required to be right-handed, between the ages
172 of 18 to 45, smoking on average 5 or more cigarettes per day, and not seeking or
173 receiving treatment for smoking cessation. Participants were excluded from participation
174 if they were left-handed, met criteria for any other substance use disorder, met criteria
175 for other psychiatric conditions as assessed by the Mini International Neuropsychiatric
176 Interview version 7.0.2 (Sheehan et al., 1998); tested positive for other substances of
177 abuse by urinalysis or breathalyzer; if they reported or tested positive for pregnancy; or
178 if they were determined to have safety contraindications for rTMS or MRI, including non-
179 removable metal implants or any factor that could lower the seizure threshold. **Table 1**
180 shows the demographic characteristics of the participants included in this study.

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Demographic Table		
N		45
Years of age (mean \pm SEM)		33 \pm 7
Years of Smoking (mean \pm SD)		15.2 \pm 1.24
Sex	M	33 (73.3%)
	F	12 (26.7%)
Hours of abstinence	dIPFC	16 \pm 1
	v5	16 \pm 0.95

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201 **Table 1: Demographic Table** Study project demographics with number of participants
202 included, N, the mean age of the participants in years, the number of males and
203 females, and the average duration of abstinence prior to their test session for each
204 stimulation site.

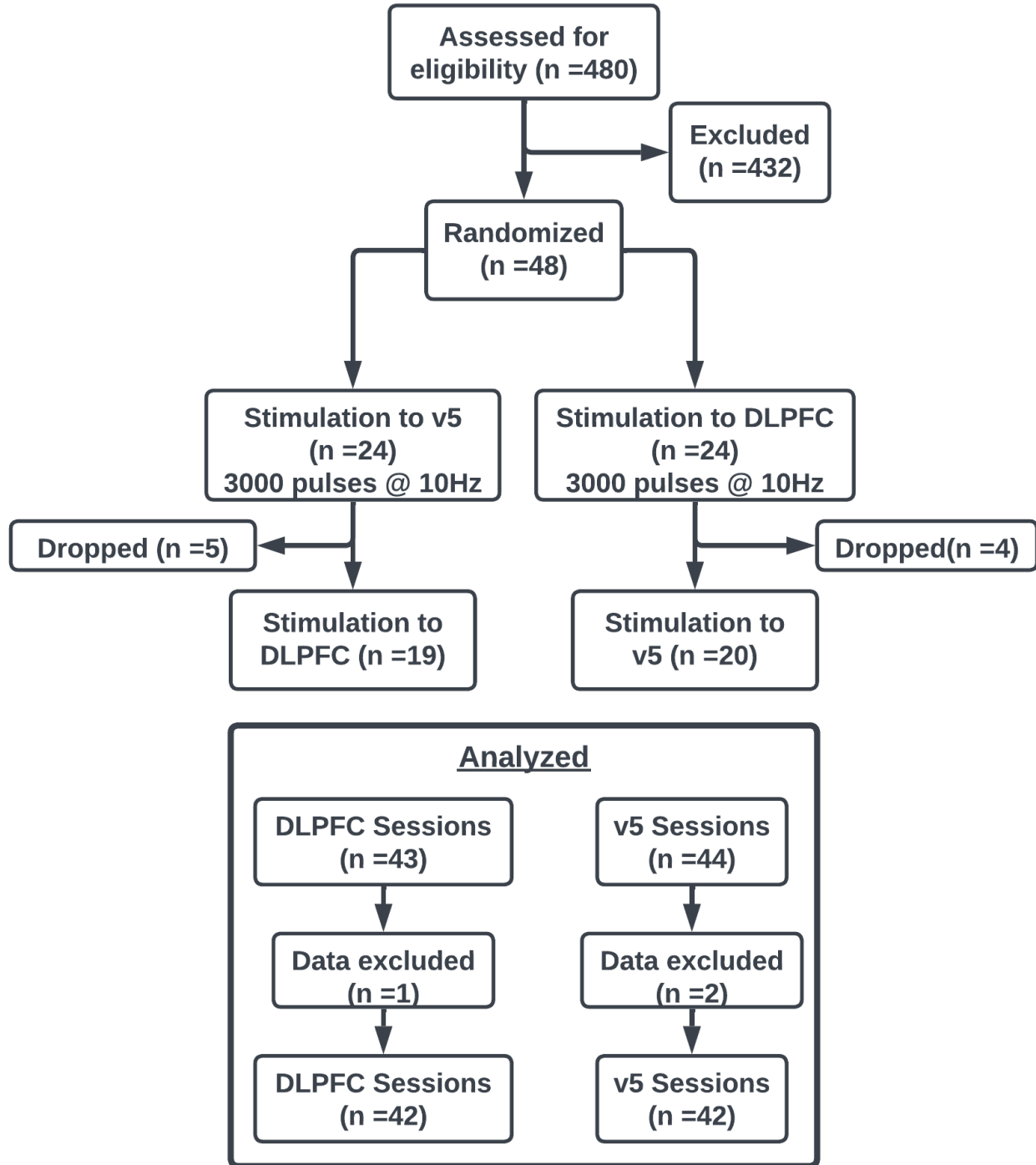
205 2. 2 Study Design

206 Participants who remained eligible after in-person assessments were scheduled
207 for data collection sessions. Each session was identical except for the region stimulated
208 (left dIPFC or visual cortex [v5]). The order of each session type was randomized and
209 counterbalanced, and participants were instructed to remain abstinent from smoking for
210 >12 hours before their data collection sessions.

211 Upon arriving in the laboratory for each data collection session, urine samples
212 were collected to confirm abstinence from illicit substances, a breathalyzer was
213 administered to confirm abstinence from alcohol, and vital signs were obtained. Expired
214 carbon monoxide was measured to confirm >12 h abstinence from cigarette smoking.

215 To assess baseline withdrawal and craving, participants completed the Shiffman-
216 Jarvik Withdrawal Questionnaire (S. M. Shiffman & Jarvik, 1976) and Urge to Smoke
217 scales (Jarvik et al., 2000) via self-report. Baseline resting-state functional images (see
218 below for sequence details) were collected. On the first stimulation day only, the
219 participant's active motor threshold was measured and recorded. On each stimulation

220 day, neuronavigation was used to position the rTMS coil. rTMS was delivered (see
221 details below), followed immediately by a post-rTMS resting-state neuroimaging scan,
222 then post-rTMS self-report of craving and withdrawal measurements. A CONSORT
223 diagram of the study can be found in the supplementary materials. **Figure 1** shows a
224 CONSORT diagram of the study.



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226 **Figure 1 CONSORT Diagram** Our study design was a randomized one-way blind

227 study. Eligible participants were randomized to either dLPFC first and v5 second, or vice

228 versa. Participant data was not excluded if they only completed one session. Three
229 sessions of data were excluded due to corrupted data or normalization errors.
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231 2.3 Behavioral Data Collection

232 Participants were required to abstain from smoking for >12 hours before each testing
233 day began to produce a state of acute withdrawal. Withdrawal is associated with a
234 range of subjective experiences, including a heightened sense of craving as well as
235 other somatic and affective symptoms. Although often linked together, withdrawal and
236 craving are separate but related components of TUD (Baker et al., 2012; S. Shiffman et
237 al., 2004). To access both variables, we used two questionnaires: Shiffman-Jarvik
238 Withdrawal Questionnaire (SJWS,(S. M. Shiffman & Jarvik, 1976)) and Urge to Smoke
239 scales (Jarvik et al., 2000). The SJWS assesses multiple domains of withdrawal,
240 including a sub-scale specific to craving. For this study, we examined the SJWS overall
241 score and the craving subscale scores in participants to capture both aspects in our
242 participants. The craving sub-scale has two scores reported, the average and total
243 scores, calculated from the questions specific to cigarette craving in the SJWS.
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245 2.4 Brain Imaging Data Collection & Preprocessing

246 Whole-brain structural and functional MR imaging was conducted on a 3 Tesla
247 Siemens Prisma Fit MRI scanner with a 32-channel head coil at the UCLA Staglin
248 Center for Cognitive Neuroscience . A single T1-weighted structural scan (TE= 2.24ms ;
249 TR= 2400ms; voxel resolution= 0.8 x 0.8 x 0.8 mm) was collected during the intake
250 session as well as a 8 minute baseline T2*-weighted multi-band sequence resting state
251 functional scan. Resting state functional scans (TE= 37ms; TR= 800ms; FoV = 208mm;
252 Slice Thickness= 2mm; Number of Slices = 72, voxel resolution= 2 x 2 x 2 mm) were
253 performed twice on test days (pre- and post-rTMS). Prior to all resting state functional
254 scans, two spin echo fieldmaps were collected in opposite directions (AP and PA).

255 FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool)
256 Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The
257 following pre-statistics processing was applied; motion correction using
258 MCFLIRT(Jenkinson et al., 2002); B0 unwarping using boundary-based registration via
259 FUGUE (Jenkinson, 2003, 2004); slice-timing correction using Fourier-space time-
260 series phase-shifting; non-brain removal using BET (Smith, 2002); spatial smoothing
261 using a Gaussian kernel of FWHM 4.0mm; grand-mean intensity normalization of the
262 entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-
263 weighted least-squares straight line fitting, with sigma=50.0s). ICA-based exploratory
264 data analysis was carried out using MELODIC (Beckmann & Smith, 2004)[Beckmann

265 2004], in order to investigate the possible presence of unexpected artifacts or activation.
266 ICA-FIX was trained on a set of 20 scans that were hand-classified into noise and non-
267 noise components, with the scans randomly selected from 5 bins sorting scans by the
268 amount of average motion present to have high and low motion data in the trained set.
269 The component classification derived from the trained data was then used in ICA-FIX to
270 classify noise and non-noise components from all subject data and non-aggressively
271 remove the noise components. After denoising, ICA-FIX applied a high-pass filter to
272 each subject's data. Registration to high resolution structural and/or standard space
273 images was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001).
274 Registration from high resolution structural to standard space was then further refined
275 using FNIRT nonlinear registration (Andersson et al., 2007b, 2007a). Lastly, average
276 time series were extracted from each subject's data based on brain nodes specified by
277 the atlas then detrended for cubic trends and finally z-score normalized.

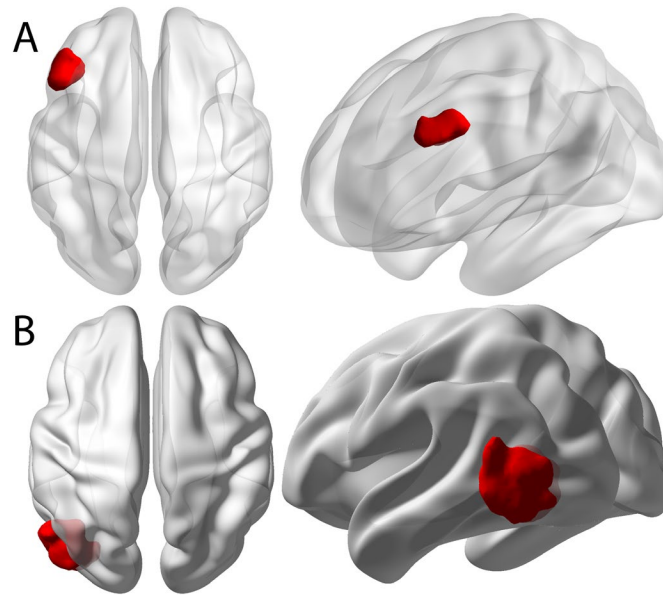
278 2.5 Brain Atlas, dIPFC and Insula

279 For this study, we used the brain parcellation proposed by Van De Ville (Van De
280 Ville et al., n.d.) to extract time series from all imaging data. Briefly, this parcellation
281 includes a Schaefer 400 brain region cortical parcellation ((Schaefer et al., 2018),
282 [https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/
283 Schaefer2018_LocalGlobal](https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal)) combined with 16 subcortical regions and 3 cerebellar
284 regions from the HCP release for a total of 419 nodes. This study focused on changes
285 in dIPFC and Insula; therefore, to determine which nodes correlated to those regions we
286 used the Harvard-Oxford probability atlas and the dIPFC ROI mask obtained from
287 Neurovault to determine which nodes were primarily in these regions. Insula was
288 determined to overlay with nodes 35, 98 to 100, and 143 in the left hemisphere and
289 nodes 234-236, 302-305 and 340 in the right hemisphere. Left dIPFC was determined to
290 overlay with nodes 137 to 142.

291 2.6 Neuromodulation

292 2.6.1 rTMS

293 TMS sessions were conducted using the Magstim Super Rapid2 Plus1
294 (MagStim, UK, <https://www.magstim.com/row-en/>) system equipped with a figure-8 coil.
295 We stimulated two regions, dIPFC and v5, during separate sessions as shown in **Figure**
296 **2**. Stimulation to dIPFC was considered the active treatment region, while v5 served as
297 a control region. Both stimulation sessions used the same stimulation sequence of 10
298 Hz stimulation for 60 trains, each train lasting 5 seconds and followed by 10 seconds of
299 no stimulation, for a total of 3000 pulses over approximately 15 minutes.



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302 **Figure 2 Stimulation Targets** A) The left dorsolateral prefrontal cortex (dlPFC) was
303 used as the target region for this project. B) Counter to dlPFC, the left visual cortex (v5)
304 was used as a control region

305 2.7 Analyses

306 2.7.1 Brain Entropy Calculations & Analysis

307 Information entropy is the measure of randomness or uncertainty of a series of
308 data without knowledge of the data series origin. One way to calculate this information
309 entropy is called Sample Entropy. Given a data series, for example a time series
310 extracted from a voxel or region of the brain, the process of Sample Entropy first divides
311 the time series up into smaller vectors of length m . Next for each of the vectors it
312 calculates the distance between the two vectors, with the requirement that they aren't
313 the same vector, i.e. $i \neq j$. If both values are less than the distance threshold (r), also
314 can be called a noise filter as it determines the possibility of the pair, then the pairing is
315 counted as a possible. The sum of all possible vector comparisons creates $B(r)$, which
316 is the probability that two sequences are similar for m points. This process is then
317 repeated for vectors of $m+1$ size to determine the number of matches and sum those
318 together and create $A(r)$, which is the probability that two sequences are similar for $m+1$
319 points. Taking the ratio of the number of matches to the number of possibles, we find
320 how much of the signal is uncertain/random. We then take the negative log of this ratio
321 since information measurements are made on the logarithmic scale. The mathematical
322 representation of this process is:

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$$\text{SampEn}(r, m) = -\log\left(\frac{A(r)}{B(r)}\right)$$

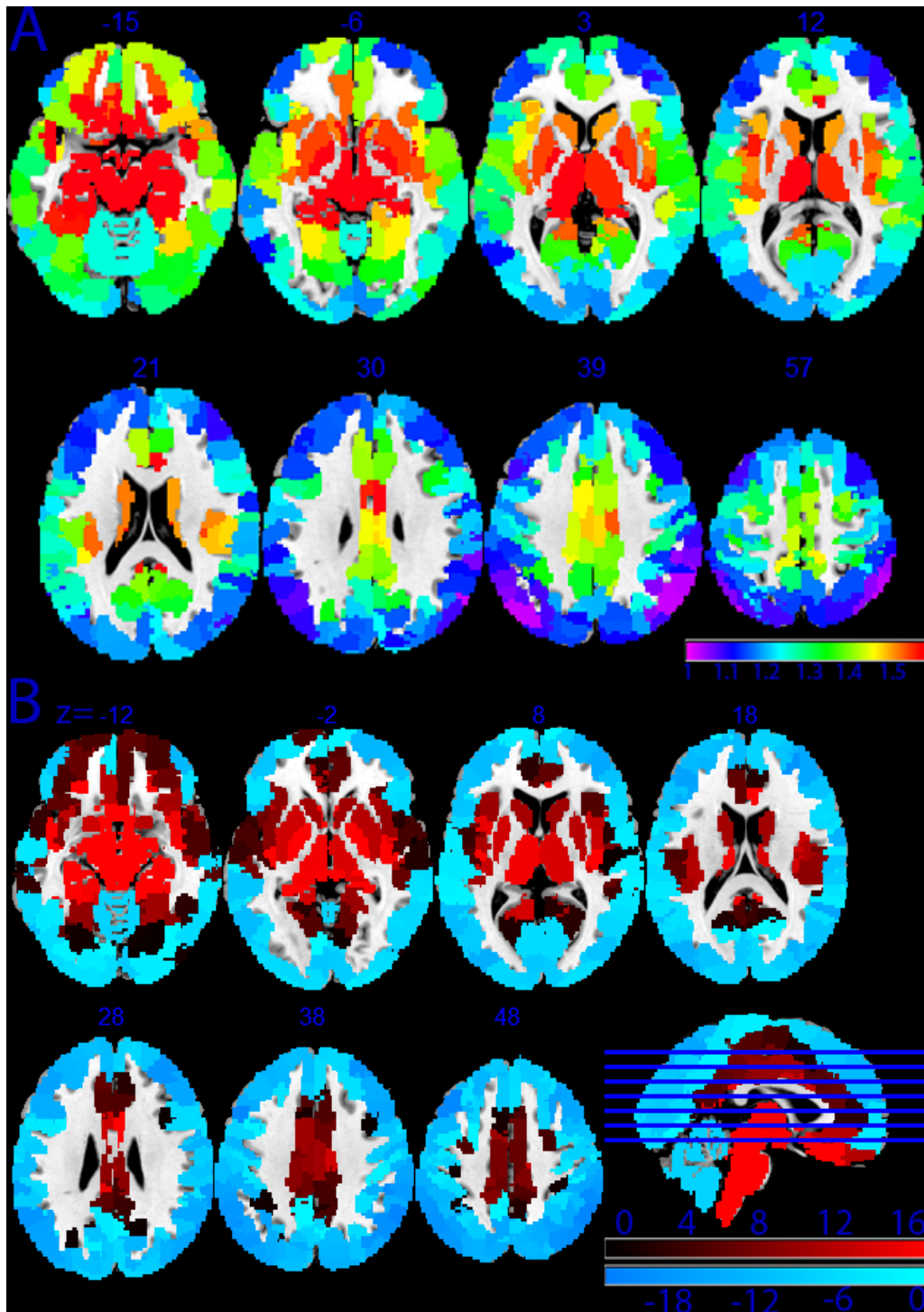
324 For this study, sample entropy of each node was calculated using the Brain
325 Entropy Mapping Toolbox (BENTbx, (Z. Wang et al., 2014)). For the parameters, we set
326 $m = 3$ and $r = 0.3$ based on a previous study examining the effects of these parameters
327 on sample entropy (Yentes et al., 2013). Extracted mean node time series were
328 organized into matrices with dimension timepoints by nodes, for the study this would
329 generate a 588x419 matrix for 419 nodes each having 588 timepoints. The BENTbx
330 would then take these matrices and calculate the entropy per node per participant.

331 3. Results

332 3.1 Brain Entropy Prior to rTMS

333 We examined the distribution of average SampEn across the brain at baseline
334 before examining changes in SampEn due to brain stimulation. Using baseline (pre-
335 stimulation) images, values for each node were collected from each participant and then
336 averaged to determine the average resting SampEn for people who smoke and are in
337 withdrawal. Likewise, all node values were averaged for each participant to determine
338 their brain's average SampEn. We then took the brain averages and compared them to
339 each node's values to determine if a region was significantly above or below the global
340 average.

341 Considering both (1) the node average SampEn and (2) node average SampEn
342 relative to brain average SampEn, we observed that gyral nodes had lower SampEn
343 than the sulci nodes and the subcortical regions. **Figure 3A** shows the contrast between
344 these areas of the brain. We also found that the majority of the outer cortical regions
345 and the cerebellum were significantly below the global average ($p_{FDR} < 0.05$), and that
346 the subcortical and orbital frontal regions were significantly above the cortex ($p_{FDR} <$
347 0.05). These observations and results complement and support previous findings by (Z.
348 Wang et al., 2014). **Figure 3B** shows the regions found to be above (red) and below
349 (blue) the average brain SampEn in people who smoke. Contrary to (Wang et al., 2014),
350 who found that the range of SampEn values across the brain spanned from 0.44 to
351 0.608, in this study, we found that SampEn ranges across the brain spanning from 1 to
352 1.75. Although we did not directly compare people who don't smoke, this finding is
353 broadly consistent with previous studies explicitly demonstrating that people who smoke
354 have a "hyper-resting brain entropy" state (Z. Li et al., 2016).

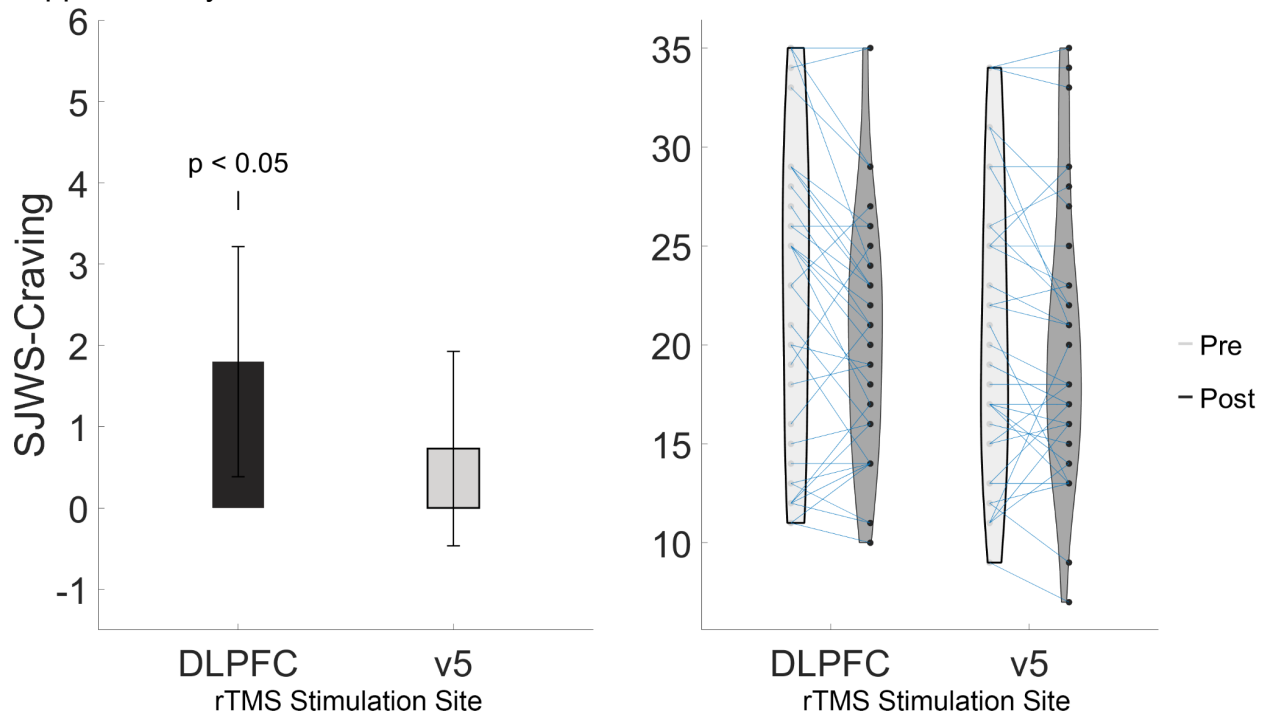


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Figure 3 Average Sample Entropy Maps A) Average sample entropy per region across the brain. Regions are defined by the Schaefer 400 parcellation and 16 sub-cortical regions & 3 cerebellum regions from the Human Connectome Project. Red indicates the highest levels of SampEn observed, and purple indicates the lowest. B) Regions with SampEn above (red) and below (blue) the average SampEn across the brain for people who smoke pre-rTMS stimulation.

362 3. 2 Changes in Craving

363 Participant self-reported craving measurements were collected before and after
364 stimulation to determine if rTMS has an immediate effect on an individual's cigarette
365 craving. Self-reported measures were compared using a paired-samples t-test and
366 corrected for multiple comparisons using the Bonferroni correction. Craving as
367 measured by the Shiffman-Jarvik Withdrawal Scale craving subscale was found to be
368 significantly different for stimulation to left dIPFC (Pre: 22 (8.25); Post: 20.45 (6.7), $t(df)$
369 = 2.36(37), $p = 0.005$, Cohen's $d = 0.31$). No significant differences were found for the
370 Urge to Smoke for stimulation to left dIPFC. No craving measures were found to be
371 significantly different for stimulation to left v5. **Figure 4 & Table 2** show the results for
372 the SJWS-Craving scores for both sessions. Results for the Urge to Smoke are in the
373 supplementary materials.



374 **Figure 4 Stimulation to left dIPFC reduced craving in participants** Left) Change
375 score for Shiffman-Jarvik Withdrawal Craving measure from Pre-rTMS minus Post-
376 rTMS values, resulting in larger positive value corresponding to larger reductions in
377 craving. Right) Violin individual point distribution plot, show each participant's individual
378 change from Pre to Post-rTMS.
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Shiffman-Jarvik Withdrawal Scale Measurements <i>Mean (SD)</i>			
		dIPFC	v5
Total Craving	Pre-rTMS	22 (8.25)	21.79 (7.74)
	Post-rTMS	20.45 (6.7)	21.07 (7.14)
Average Craving	Pre-rTMS	4.57 (1.7)	4.44 (1.57)
	Post-rTMS	4.22 (1.4)	4.26 (1.43)

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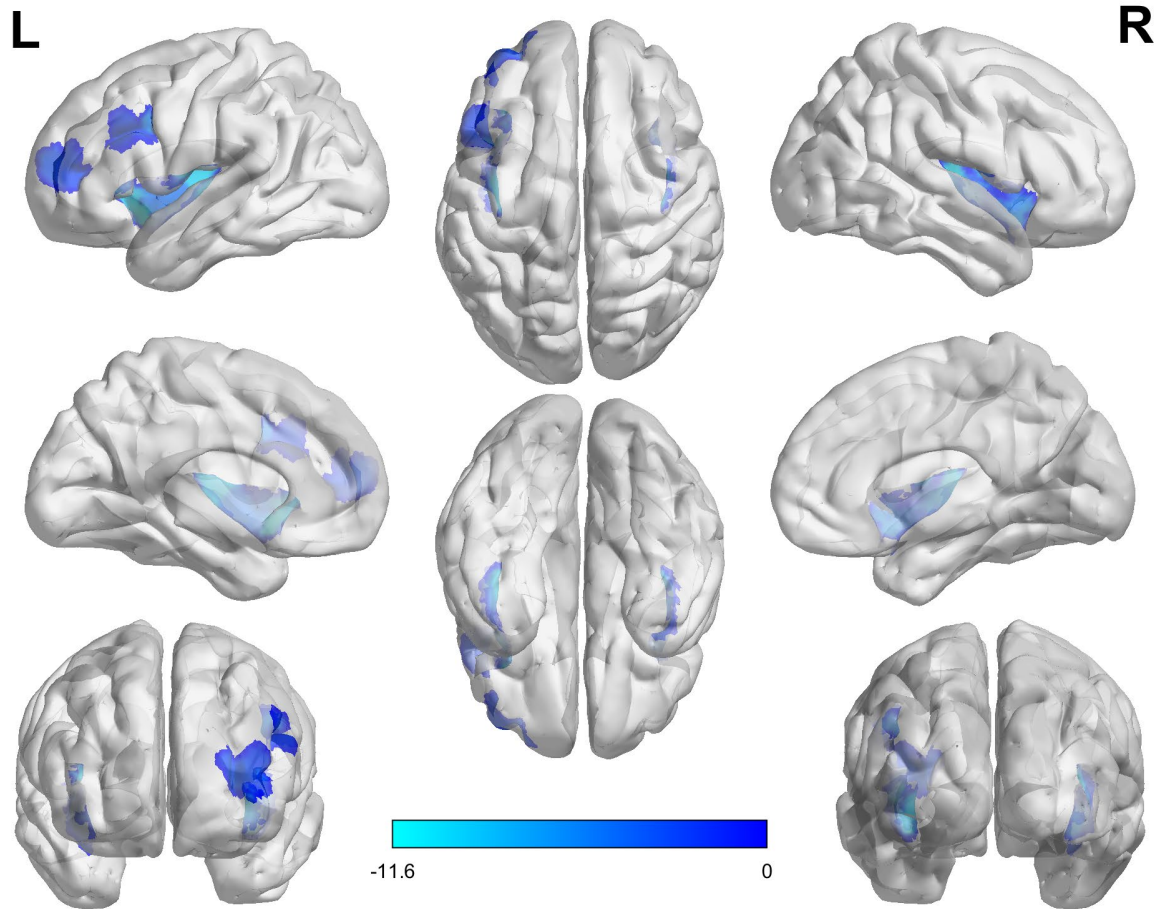
386 **Table 2 Shiffman-Jarvik Withdrawal Craving Scale Measures** Pre and Post-rTMS to
387 both targets showing both their total craving scores and average craving scores before
388 and after treatment.

389 3.3 Brain Entropy changes in left dIPFC and Insula

390 Extracted time series using the atlas previously described were normalized and
391 entered into the BENTbx to calculate each node's sample entropy. Node sample entropy
392 was compared for Pre- and Post-rTMS stimulation for all 419 regions using a paired t-
393 test. All results were corrected for multiple comparisons using the False-Discovery Rate
394 method.

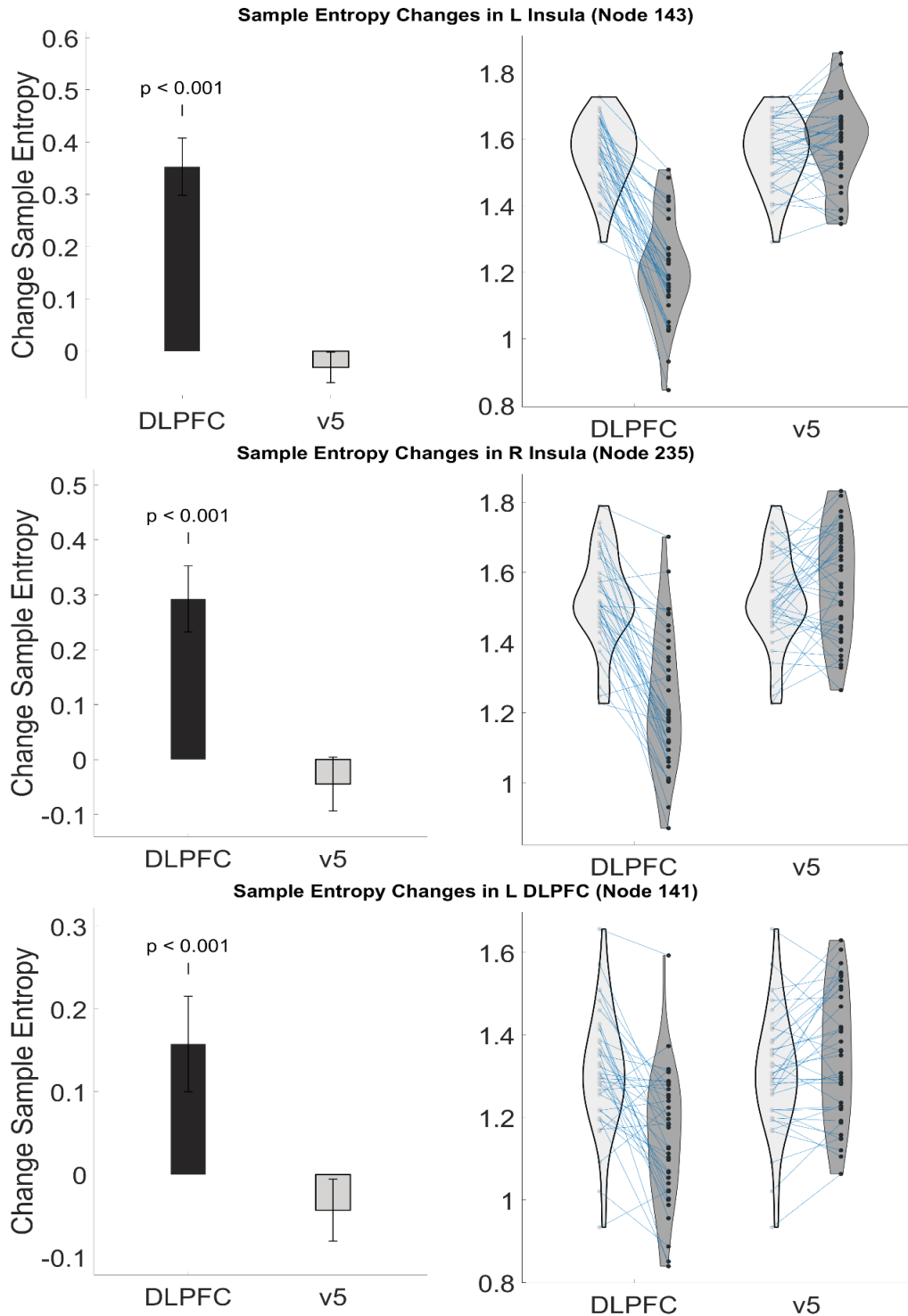
395 Examining the 19 nodes that include bilateral insula and left dIPFC, we found that
396 17 out of 19 nodes had significant changes in their SampEn measurements from pre- to
397 post-stimulation to left dIPFC. All nodes showed lower SampEn in post-stimulation
398 scans compared to pre-stimulation. **Table 3** shows the results for each node. No insula
399 or dIPFC nodes were found to change significantly after stimulation to v5. **Figures 5 & 6**
400 show the mean SampEn measurements before and after stimulation in the nodes with
401 the most significant change for each stimulation site, and a t-statistic map for those
402 nodes. Figures for all other nodes in these regions can be found in the supplementary
403 materials.

404 To determine if changes in SampEn influenced the observed changes in an
405 individual's craving, we correlated each participant's change in SampEn measurements
406 with their change in craving scores and restricted correlation values to be above $r = 0.2$.
407 No correlations were found for any of the a priori nodes.



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Figure 5 Reductions in entropy in *a priori*-selected ROIs. Regions in blue (insula and left DIPFC) were selected *a priori* as nodes that were expected to show reductions in SampEn as a result of rTMS. The *t*-statistic value for node is shown in blue, with darker values indicating a *t*-statistic closer to zero, and lighter blues showing increasingly more negative *t*-statistics as a result of stimulation to left DIPFC, indicating greater rTMS-induced decreases in SampEn.



418

419 **Figure 6 Stimulation to left dIPFC reduced sample entropy in L/R Insula and L**
420 **dIPFC nodes** Plots show change group in sample entropy (left) and individual
421 changes/distribution (right) for each node that had the lowest p-value and the region
422 that correlated with the node. Change values were calculated by subtracting Post-rTMS
423 entropy values from Pre-rTMS values.

424

Sample Entropy Statistical Results			
Schaefer Atlas Node	T-Stat (df)	p-val_FDR	Cohen's d
35 (L Insula)	-9.71(41)	5.06E-11	1.82
98 (L Insula)	-4.76(41)	4.92E-05	0.73
99 (L Insula)	-9.30(41)	1.47E-10	1.74
100 (L Insula)	-9.84(41)	3.92E-11	1.84
143 (L Insula)	-11.51(41)	1.07E-12	3.02
234 (R Insula)	-10.2(41)	1.42E-11	1.89
235 (R Insula)	-10.72(41)	4.49E-12	1.83
236 (R Insula)	-10.39(41)	9.45E-12	1.66
302 (R Insula)	-6.39(41)	4.26E-07	1.17
303 (R Insula)	-5.02(41)	2.32E-05	0.97
304 (R Insula)	-7.28(41)	3.63E-08	1.28
305 (R Insula)	-8.03(41)	4.60E-09	1.63
340 (R Insula)	-6.69(41)	1.86E-07	1.22
137 (L dIPFC)	-2.34(41)	0.03	0.41
138 (L dIPFC)	-3.06(41)	0.01	0.54
139 (L dIPFC)	-1.84(41)	0.09	0.44
140 (L dIPFC)	-2.2(41)	0.04	0.37
141 (L dIPFC)	-5.85(41)	2.16E-06	1.02
142 (L dIPFC)	-9.71(41)	5.06E-11	1.82

425 **Table 3 Sample Entropy T-test Results for Pre vs Post T-stat, FDR-corrected p-**
 426 **value, and cohen's d for all a-priori nodes.**

427

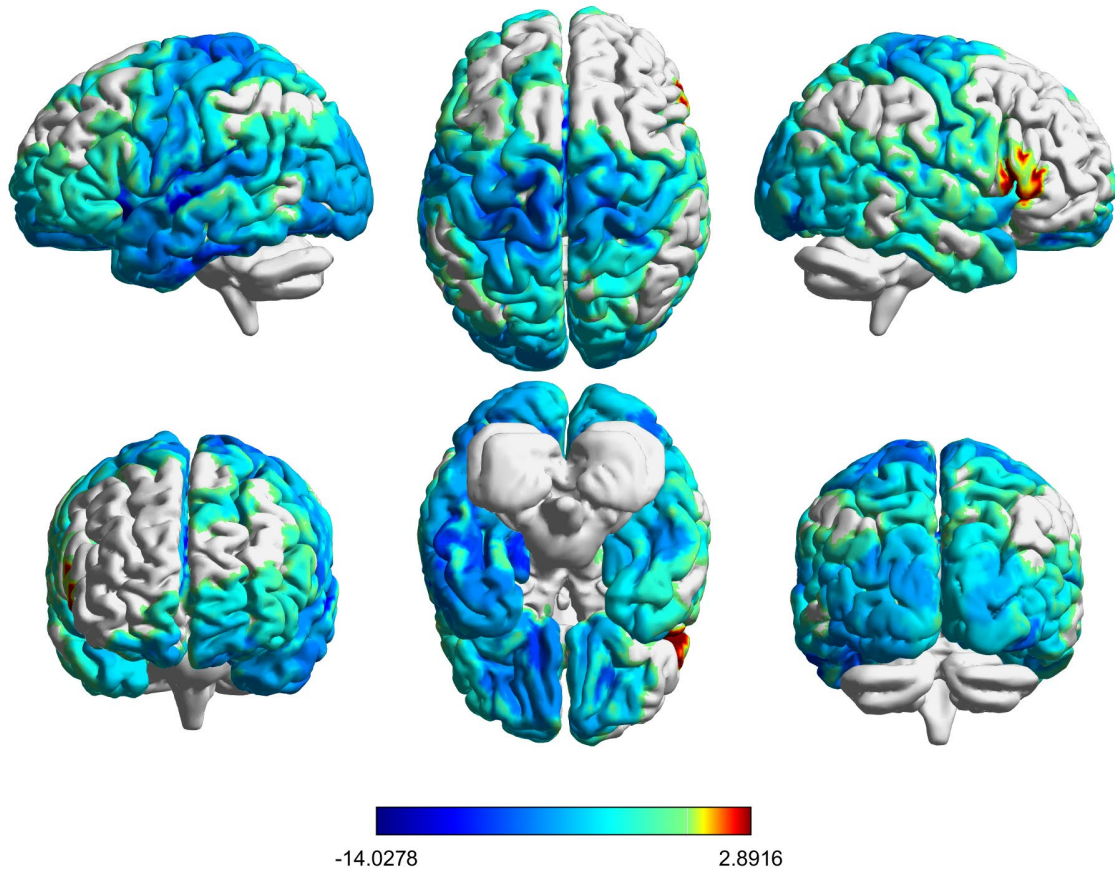
428 3.4 Potential confounding variables

429 To determine whether other participant characteristics may have influenced
430 SampEn analyses, five variables (sex, ethnicity, age, years of smoking and education)
431 were examined for relationships with SampEn. Pre-rTMS SampEn and change in
432 SampEn were compared between male and female participants using an independent-
433 samples t-test. Pre-rTMS SampEn was compared between all 8 ethnicity categories
434 using a one-way ANOVA. For sex differences, nodes 99, 100, 303, and 304 were found
435 to have differences between male and female participants with females having higher
436 entropy in all nodes. These differences did not survive multiple comparison corrections,
437 but warrant exploration in future studies. No significant differences were found between
438 ethnicity groups. Supplementary Table S4 showing the average SampEn per node for
439 each ethnic group can be found in the supplementary materials. Pearson correlations
440 were calculated for Age/Years of Smoking/Education level vs. Pre-rTMS SampEn to
441 determine if any of the variables influenced the entropy measurement in our participant
442 population. No significant correlations ($p > 0.05$) were found between age, years of
443 smoking or education level and Pre-rTMS SampEn in left dIPFC, left or right Insula. A
444 table of non-significant correlation values with each variable and the corresponding p-
445 values can be found in the supplementary materials.

446

447 3.5 Exploratory Findings

448 After the above *a priori* ROI results were obtained and determined to have no
449 correlation with observed changes in craving, we decided to examine other nodes for
450 significant changes and correlation with behavior. We observed that for left dIPFC
451 stimulation, entropy changed significantly across the majority of the brain. **Figure 7**
452 shows a t-statistic map showing the t-statistic associated with the comparison of each
453 region's SampEn before and after stimulation. Three nodes (133, 314, and 318) were
454 found to have significant changes in SampEn (Cohen's $d = 0.56, 1.06, 0.58$; $p_{FDR} =$
455 $0.0016, 2 \cdot 10^{-4}, 6.1 \cdot 10^{-6}$, respectively) and have a moderate correlation with craving.
456 In node 133, which overlaps with the inferior temporal gyrus, changes in SampEn
457 correlated with the changes in SJWS-Craving ($r(df) = 0.36(40)$). Nodes 314 and 318,
458 both in the right superior frontal gyrus (SFG), had moderate correlations between their
459 changes in SampEn and changes in UTS ($r(df) = 0.39(34)$ and $r(df) = 0.43(34)$,
460 respectively). All tables and figures for these results are in the supplementary materials.



461
462 **Figure 7 Brainwide changes in SampEn as a result of rTMS to dIPFC show**
463 **widespread reductions in entropy.** Changes in SampEn from pre- to post-dIPFC
464 stimulation are shown here as t-statistics. Red indicates increased entropy following
465 rTMS, gray indicates no change, and increasingly darker blues indicate increasingly
466 greater reductions in entropy as a result of dIPFC stimulation. These reductions in
467 entropy can be observed throughout the brain, with only a few small regions of
468 increased entropy.
469

470 4. Discussion & Conclusion

471 4.1 dIPFC & Insula

472 In this study we used excitatory rTMS to the left dIPFC to reduce cigarette
473 craving and sample entropy in the bilateral insula and left dIPFC. Although no
474 correlation was found between the magnitude of SampEn changes in these regions and
475 the magnitude of craving changes, these data suggest that one mechanism by which

476 neuromodulation produces craving relief may include reducing regional brain entropy.
477 This is strengthened by our exploratory results showing that changes in regional
478 SampEn for SFG and ITG did have moderate correlations with craving changes.

479 This investigation builds on ample previous work strongly relating left dIPFC
480 stimulation to reductions in cigarette craving, consumption, and ultimately, cessation.
481 Although the evidence base for this treatment is mounting, the mechanism by which
482 dIPFC stimulation produces its effects are not well-understood. One small (N = 10)
483 investigation showed that dIPFC stimulation reduces fractional amplitude of low-
484 frequency fluctuations in the insula, and also reduced connectivity between the
485 stimulation site and medial prefrontal cortex (X. Li et al., 2017), suggesting that
486 modulation of insula activity by dIPFC stimulation may be the mechanism by which
487 rTMS alleviates craving.

488 Our finding that dIPFC stimulation reduces entropy in the insula is consistent with
489 previous evidence suggesting that rTMS to the dIPFC produces its salutary effects.
490 However, based on the current findings, the insula's link to the observed rTMS induced
491 reductions in craving still remains to be seen. One explanation for this may be that
492 stimulation of the left dIPFC doesn't cause enough of a reduction in withdrawal and
493 craving to allow for a link to be seen, which may be a result of the relatively small dose
494 of rTMS we delivered in this experiment. Because the magnitude of craving reduction
495 corresponds to the magnitude of entropy reduction in the SFG, even though the
496 difference between pre and post Urge to Smoke scores was minimal and inconsistent in
497 participants, these findings suggest that rTMS to the dIPFC may be a viable target, but
498 not the most effective. Direct stimulation to SFG may prove to be more effective.

499 The superior frontal gyrus has been linked to smoking through a previous brain
500 stimulation study. (Rose et al., 2011) showed in a small study of 15 participants that
501 excitatory stimulation to SFG resulted in immediate reductions in self-reported craving
502 and reductions in craving due to neutral cues. Two previous studies showed that in
503 people who smoke, SFG demonstrated higher levels of spontaneous activity (Niu et al.,
504 2023) and lower resting functional connectivity (Zhou et al., 2017) relative to controls.
505 These findings could be broadly consistent with our observations of entropy reductions,
506 as rTMS may reduce entropy in SFG, thus causing the region to stabilize its activity and
507 thereby reduce craving.

508 4.2 Limitations

509 This investigation delivered only single-session rTMS, and therefore conclusions
510 about long-term effects cannot be drawn. Notably, however, in a pivotal multi-center trial
511 of rTMS for smoking cessation, acute (single-session) reductions in craving did predict
512 successful smoking cessation (Zangen et al., 2021). Additionally, our control condition
513 in this investigation involved stimulation to a different brain site that was delivered to our
514 test population of people with TUD. The lack of a control group (people who do not

515 smoke) prevents any conclusions about entropy in people with and without TUD from
516 being drawn from this data; however, previous work has performed this comparison and
517 found higher brain entropy in people who smoke compared to controls (Z. Li et al.,
518 2016).

519 Brain entropy was calculated in this study using fMRI collected data, which has a
520 lower temporal resolution than other methods of neuroimaging, such as
521 electroencephalography. This restriction on temporal resolution potentially limits the
522 results determined here and should be validated using a neuroimaging method with
523 higher resolution so that more accurate measures of entropy can be determined due to
524 finer time scales. Likewise, although extensive denoising of data was carried out,
525 residual noise could remain in the data and therefore influence the results.

526 4.3 Conclusion

527 In this study, we were able to replicate previous findings that rTMS can reduce
528 sample entropy in the brain, and extended these findings in people who smoke,
529 showing that the effect of rTMS on sample entropy is consistent across different
530 populations. We also replicated previous observations about the distribution of brain
531 entropy across the brain and observed evidence of potentially increased resting entropy
532 in people who smoke. Although changes to insula and left DLPFC SampEn did not
533 correlate with changes in behavior, we did find that post-TMS reductions in entropy in
534 two other regions, the SFG and ITG, correlated with rTMS-induced reductions in
535 craving. This result provides additional (although indirect) evidence that entropy is
536 higher in people who smoke than people who do not, and suggests that by reducing
537 entropy in specific regions associated with smoking, we can reduce cigarette craving.
538 This work shows that sample entropy may be a potential biomarker for measuring
539 efficacy of rTMS-based smoking cessation treatments.

540 4.4 Future Directions

541 Future studies should examine this effect in larger populations using more
542 substantial doses of rTMS. Moreover, future investigations may test the effect of using
543 baseline entropy in regions associated with smoking, specifically insula and SFG, to
544 adjust individual treatments. Next, we will also need to explore the functional
545 connectivity changes in these participants to see if the regions found with significant
546 changes in SampEn also have changes in functional connectivity and compare them
547 separately and together as predictors of behavior changes. Expanding upon this work,
548 further investigations into brain complexity should be examined outside of just regional
549 complexity. These should include measures of complexity of functional connections
550 using functional entropy (Yao et al., 2013), entropy states and directional influences of
551 entropy (Varley et al., 2023), and community mapping entropy (Betz et al., 2019). By

552 developing our understanding of how these measures of entropy change due to TMS,
553 entropy can be better applied as a biomarker for treatments.

554

555 **Data and Code availability**

556 The data and code that support the results of this study are available on Github
557 (<https://github.com/humanbrainzappingatucla>). Any additional information required to
558 reanalyze the data used in this paper is available upon request and use agreement with
559 the corresponding author

560

561 **Author Contributions**

562 Conceptualization, T.J. and N.P.; Methodology, T.J. and J.N.; Software, T.J.; Formal
563 Analysis, T.J.; Investigation, M.A., T.J., and N.P.; Data Curation, T.J.; Writing - Original
564 Draft, T.J. and N.P.; Writing - Review & Editing, T.J. M.A. J.N., and N.P.; Visualization,
565 T.J.; Supervision, T.J. and N.P.; Project Administration, M.A. and N.P.; Funding
566 Acquisition, N.P.

567

568

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572

573 **Declaration of Competing Interests**

574 The authors declare no competing interests.

575

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582

583 **Supplemental Materials**

584 Supplemental figures and tables can be found here: (link to be generated)

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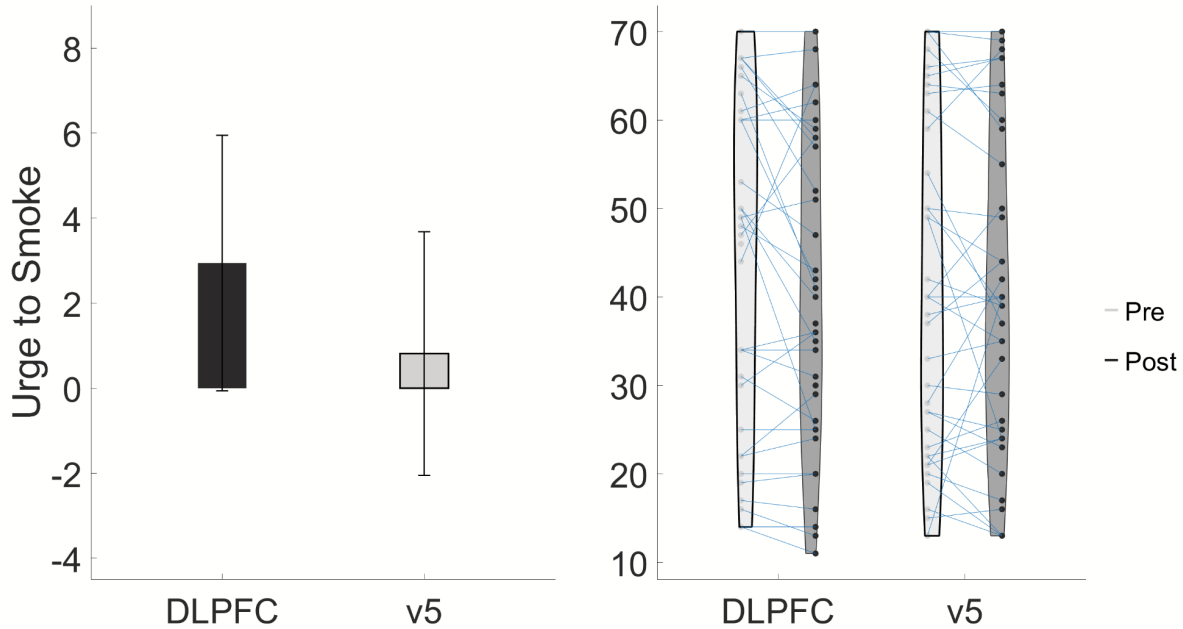
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1 Supplemental Materials

2

3 Urge to Smoke Results



4

5

6 **Figure S1 Changes in Urge to Smoke (related to Figure 3)** No significant changes in
 7 Urge to Smoking were found for stimulation to left dIPFC.

Urge to Smoke Measurements			
		dIPFC	v5
UTS	Pre-rTMS	43.74 (20.05)	43.4 (19.54)
	Post-rTMS	41.1 (19.1)	41.7 (18.26)

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9 **Table S1 Urge to Smoke measurements (related to Table 1)** Pre and Post-rTMS to
 10 both targets showing both their urge to smoke scores before and after treatment.

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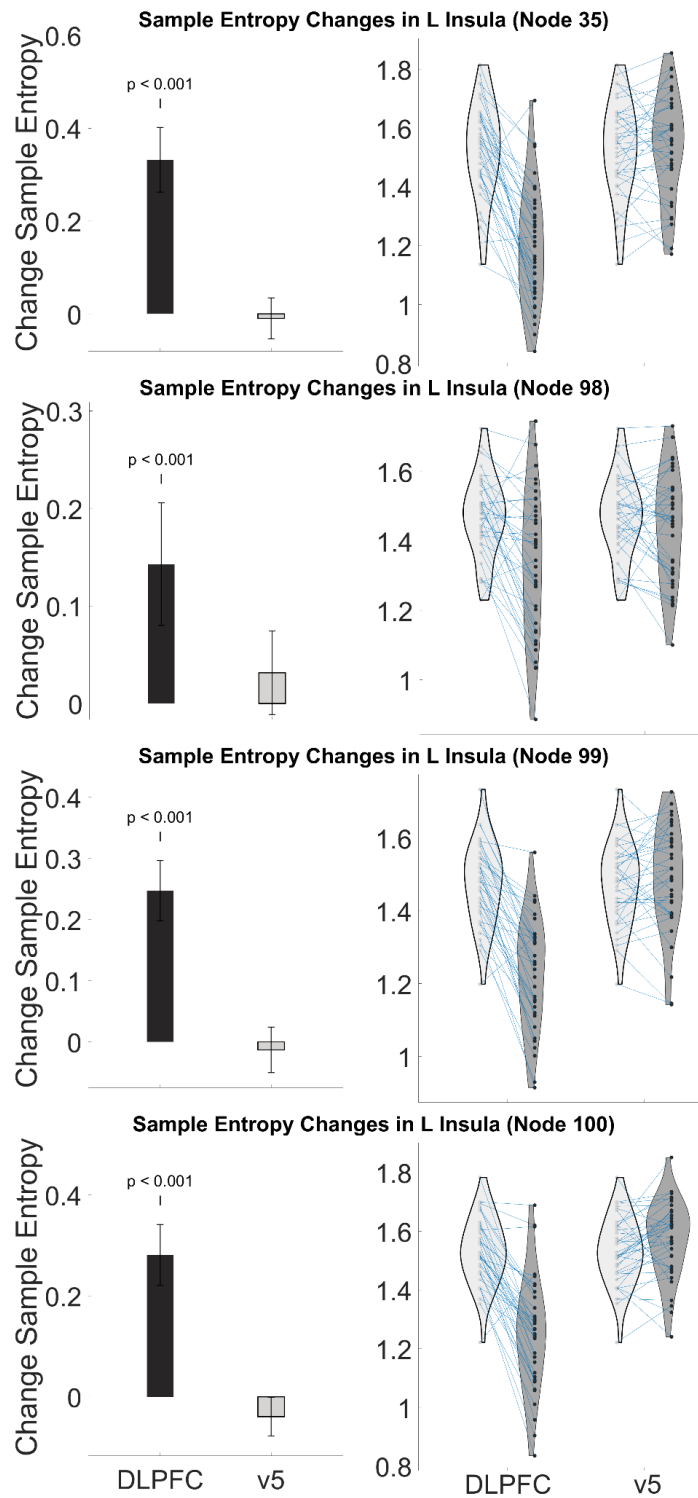
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Sample Entropy of L/R Insula and left dIPFC nodes

Sample Entropy Pre-rTMS & Post-rTMS			
Schaefer Atlas Node	Time	dIPFC entropy, mean (SD)	V5 entropy, mean (SD)
35 (L Insula)	Pre-rTMS	1.516 (0.159)	1.528 (0.156)
	Post-rTMS	1.191 (0.193)	1.539 (0.17)
98 (L Insula)	Pre-rTMS	1.463 (0.114)	1.466 (0.123)
	Post-rTMS	1.324 (0.199)	1.442 (0.147)
99 (L Insula)	Pre-rTMS	1.464 (0.128)	1.481 (0.109)
	Post-rTMS	1.233 (0.162)	1.493 (0.143)
100 (L Insula)	Pre-rTMS	1.522 (0.119)	1.529 (0.111)
	Post-rTMS	1.246 (0.182)	1.567 (0.127)
143 (L Insula)	Pre-rTMS	1.533 (0.134)	1.553 (0.111)
	Post-rTMS	1.208 (0.141)	1.586 (0.139)
234 (R Insula)	Pre-rTMS	1.563 (0.135)	1.578 (0.12)
	Post-rTMS	1.26 (0.184)	1.586 (0.137)
235 (R Insula)	Pre-rTMS	1.515 (0.13)	1.528 (0.137)
	Post-rTMS	1.22 (0.186)	1.563 (0.151)
236 (R Insula)	Pre-rTMS	1.546 (0.14)	1.564 (0.14)
	Post-rTMS	1.245 (0.197)	1.596 (0.208)
302 (R Insula)	Pre-rTMS	1.596 (0.112)	1.59 (0.119)
	Post-rTMS	1.429 (0.182)	1.617 (0.131)

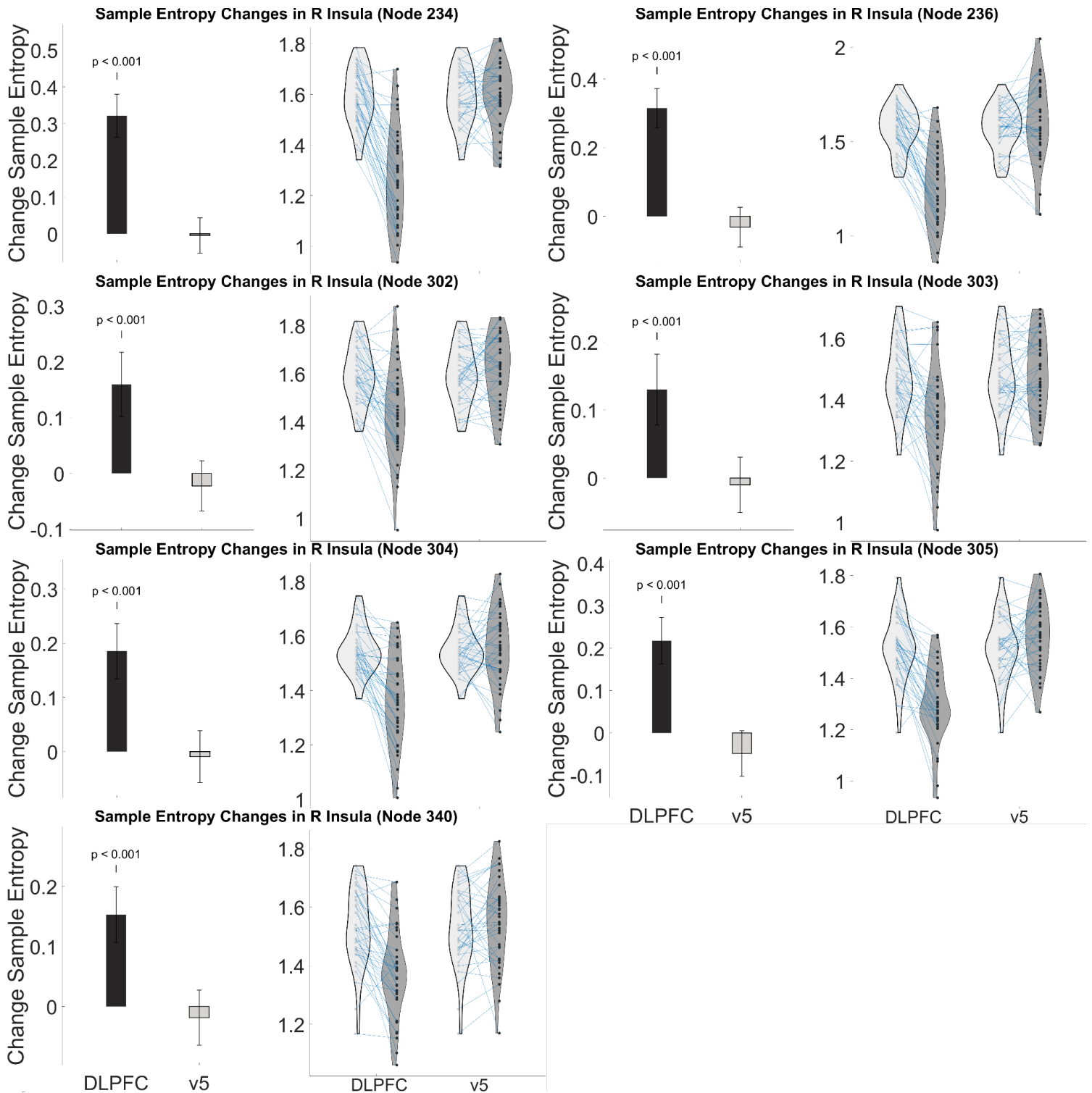
303 (R Insula)	Pre-rTMS	1.467 (0.113)	1.484 (0.112)
	Post-rTMS	1.347 (0.155)	1.484 (0.121)
304 (R Insula)	Pre-rTMS	1.537 (0.095)	1.544 (0.095)
	Post-rTMS	1.357 (0.158)	1.552 (0.13)
305 (R Insula)	Pre-rTMS	1.517 (0.129)	1.522 (0.129)
	Post-rTMS	1.308 (0.166)	1.567 (0.123)
340 (R Insula)	Pre-rTMS	1.527 (0.137)	1.525 (0.128)
	Post-rTMS	1.379 (0.144)	1.548 (0.141)
137 (L dlPFC)	Pre-rTMS	1.138 (0.129)	1.149 (0.114)
	Post-rTMS	1.083 (0.138)	1.13 (0.147)
138 (L dlPFC)	Pre-rTMS	1.167 (0.142)	1.17 (0.131)
	Post-rTMS	1.097 (0.147)	1.15 (0.134)
139 (L dlPFC)	Pre-rTMS	1.121 (0.105)	1.127 (0.1)
	Post-rTMS	1.088 (0.137)	1.119 (0.127)
140 (L dlPFC)	Pre-rTMS	1.142 (0.134)	1.158 (0.124)
	Post-rTMS	1.094 (0.134)	1.16 (0.119)
141 (L dlPFC)	Pre-rTMS	1.306 (0.146)	1.308 (0.14)
	Post-rTMS	1.152 (0.151)	1.348 (0.155)
142 (L dlPFC)	Pre-rTMS	1.15 (0.153)	1.153 (0.141)
	Post-rTMS	1.11 (0.135)	1.155 (0.124)

24
 25 **Table S2 Sample Entropy of each node Pre and Post-rTMS (related to Figure 5)** Sample
 26 entropy measures for each node found to have significant changes in sample entropy post-
 27 rTMS to DLPFC. All measures are given as mean measures with standard deviation.

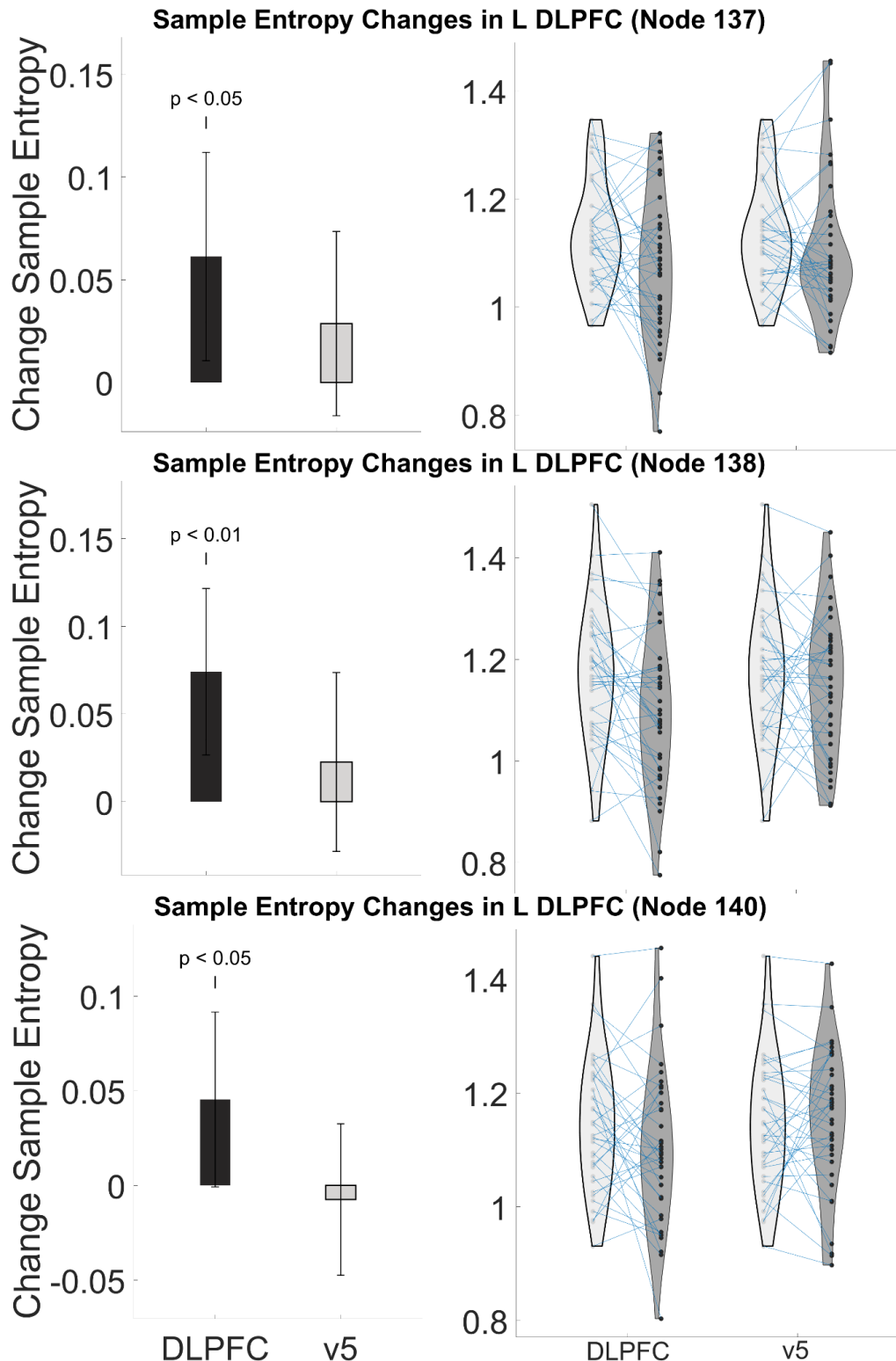


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Figure S2 Stimulation to left dIPFC reduced sample entropy in left Insula (related to Figure 5) Plots show change group in sample entropy (left) and individual changes/distribution (right) for each left Insula node. Change values were calculated by subtracting Post-rTMS entropy values from Pre-rTMS values.



35 **Figure S3 Stimulation to left dIPFC reduced sample entropy in right Insula**
36 **(related to Figure 5)** Plots show change group in sample entropy (left) and individual
37 changes/distribution (right) for each right Insula node. Change values were calculated
38 by subtracting Post-rTMS entropy values from Pre-rTMS values.
39



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41 **Figure S4 Stimulation to left dIPFC reduced sample entropy in left Insula (related**

42 **to Figure 5) Plots show change group in sample entropy (left) and individual**

43 **changes/distribution (right) for each left dIPFC node. Change values were calculated by**

44 **subtracting Post-rTMS entropy values from Pre-rTMS values.**

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Confounding Variable Correlations

Sample Entropy across Ethnicity						
Node	Asian (N=5)	Native Hawaiian/ Pacific Islander (N=1)	Black / African American (N=11)	White (N=19)	Hispanic (N=4)	More than One Race (N=2)
35	1.6(0.2)	1.4(0)	1.5(0.2)	1.5(0.2)	1.5(0.1)	1.5(0.1)
98	1.5(0.1)	1.4(0)	1.5(0.1)	1.4(0.1)	1.5(0.1)	1.5(0.1)
99	1.5(0.1)	1.5(0)	1.5(0.1)	1.4(0.1)	1.6(0.1)	1.4(0)
100	1.6(0.1)	1.5(0)	1.5(0.1)	1.5(0.1)	1.5(0.1)	1.5(0)
143	1.6(0.1)	1.6(0)	1.5(0.2)	1.5(0.1)	1.5(0.1)	1.6(0.1)
234	1.6(0.2)	1.5(0)	1.5(0.2)	1.5(0.1)	1.6(0.1)	1.6(0)
235	1.5(0)	1.4(0)	1.5(0.2)	1.5(0.1)	1.5(0)	1.5(0)
236	1.6(0.1)	1.6(0)	1.5(0.1)	1.5(0.2)	1.6(0.1)	1.5(0.1)
302	1.7(0.1)	1.4(0)	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.5(0)
303	1.5(0.1)	1.4(0)	1.5(0.1)	1.4(0.1)	1.5(0.1)	1.5(0.2)
304	1.6(0.1)	1.5(0)	1.5(0.1)	1.5(0.1)	1.6(0.1)	1.5(0)
305	1.6(0.1)	1.4(0)	1.5(0.2)	1.5(0.1)	1.5(0)	1.5(0)
340	1.6(0.1)	1.5(0)	1.5(0.1)	1.5(0.1)	1.6(0.1)	1.6(0.1)
137	1.2(0.2)	1.1(0)	1.1(0.2)	1.1(0.1)	1.1(0)	1.1(0.1)
138	1.3(0.1)	1.3(0)	1.1(0.2)	1.1(0.1)	1.2(0.1)	1.2(0)
139	1.1(0.1)	1.1(0)	1.1(0.1)	1.1(0.1)	1.1(0)	1.1(0)
140	1.2(0.1)	1.1(0)	1.2(0.2)	1.1(0.1)	1.2(0.1)	1.1(0.1)
141	1.4(0.1)	1.4(0)	1.3(0.2)	1.2(0.1)	1.4(0.1)	1.3(0.1)

142	1.3(0.1)	1.2(0)	1.1(0.2)	1.1(0.1)	1.3(0.1)	1.1(0.1)
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48 **Table S3 No significant differences in Pre-rTMS entropy between ethnicities**
 49 Ethnic groups were compared for Pre-rTMS sample entropy measures to determine if
 50 there were significant differences. No significant differences were found for any of the
 51 nodes. This table shows how many participants in each ethnic group were included in
 52 this study and their group's mean sample entropy with standard deviation for each
 53 node.

54

Node	Age		Years of Smoking		Education Level	
	r	p	r	p	r	p
35	0.03	0.83	0.03	0.84	0.00	0.98
98	0.18	0.26	0.18	0.27	-0.22	0.16
99	0.05	0.76	0.12	0.45	0.05	0.74
100	0.15	0.34	0.14	0.36	0.05	0.77
143	0.15	0.36	0.13	0.40	0.17	0.28
234	-0.01	0.95	-0.01	0.97	-0.07	0.66
235	0.03	0.87	0.02	0.88	-0.06	0.70
236	0.00	0.99	0.00	0.98	0.07	0.64
302	-0.07	0.67	-0.13	0.42	0.25	0.11
303	0.03	0.85	0.12	0.45	-0.19	0.22
304	0.18	0.26	0.24	0.13	0.07	0.65
305	-0.06	0.72	-0.05	0.77	-0.29	0.06
340	0.23	0.14	0.16	0.31	0.03	0.84
137	0.12	0.46	0.09	0.59	-0.16	0.32
138	0.08	0.60	0.08	0.62	-0.16	0.30
139	0.16	0.30	0.20	0.21	-0.25	0.10
140	-0.01	0.95	-0.03	0.87	-0.19	0.24
141	0.13	0.39	0.21	0.19	0.17	0.27

142	0.21	0.19	0.09	0.55	0.05	0.77
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55 **Table S4 No significant correlations between Pre-rTMS entropy and confounding**
 56 **variables** Pearson correlations for three confounding variables (age, years of smoking,
 57 and education) were calculation for Pre-rTMS sample entropy measures to determine if
 58 there were significant correlations. No correlations were found for any of the nodes for
 59 any of the variables. This table shows the pearson correlation coefficient (r) and the p-
 60 value of each coefficient for each variable with pre-rTMS sample entropy measures.

61

62 Exploratory Findings Entropy Results

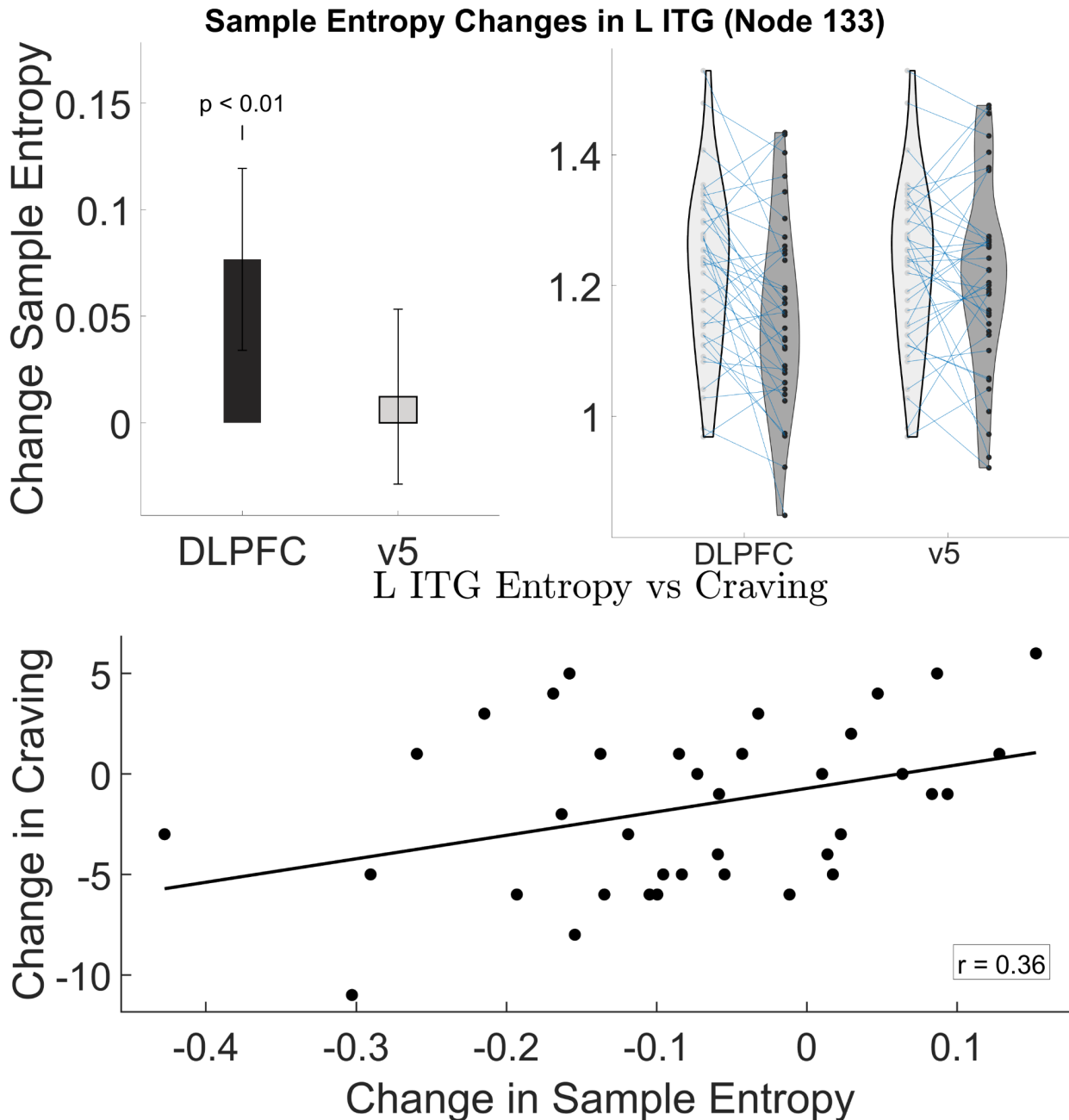
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Sample Entropy Pre-rTMS & Post-rTMS			
Schaefer Atlas Node	Time	dIPFC entropy, mean (SD)	V5 entropy, mean (SD)
133 (L ITG)	Pre-rTMS	1.21 (0.14)	1.23 (0.13)
	Post-rTMS	1.14 (0.14)	1.22 (0.14)
314 (R SFG)	Pre-rTMS	1.36 (0.14)	1.37 (0.14)
	Post-rTMS	1.21 (0.17)	1.4 (0.16)
318 R SFG)	Pre-rTMS	1.32 (0.17)	1.32 (0.17)
	Post-rTMS	1.22 (0.18)	1.31 (0.17)

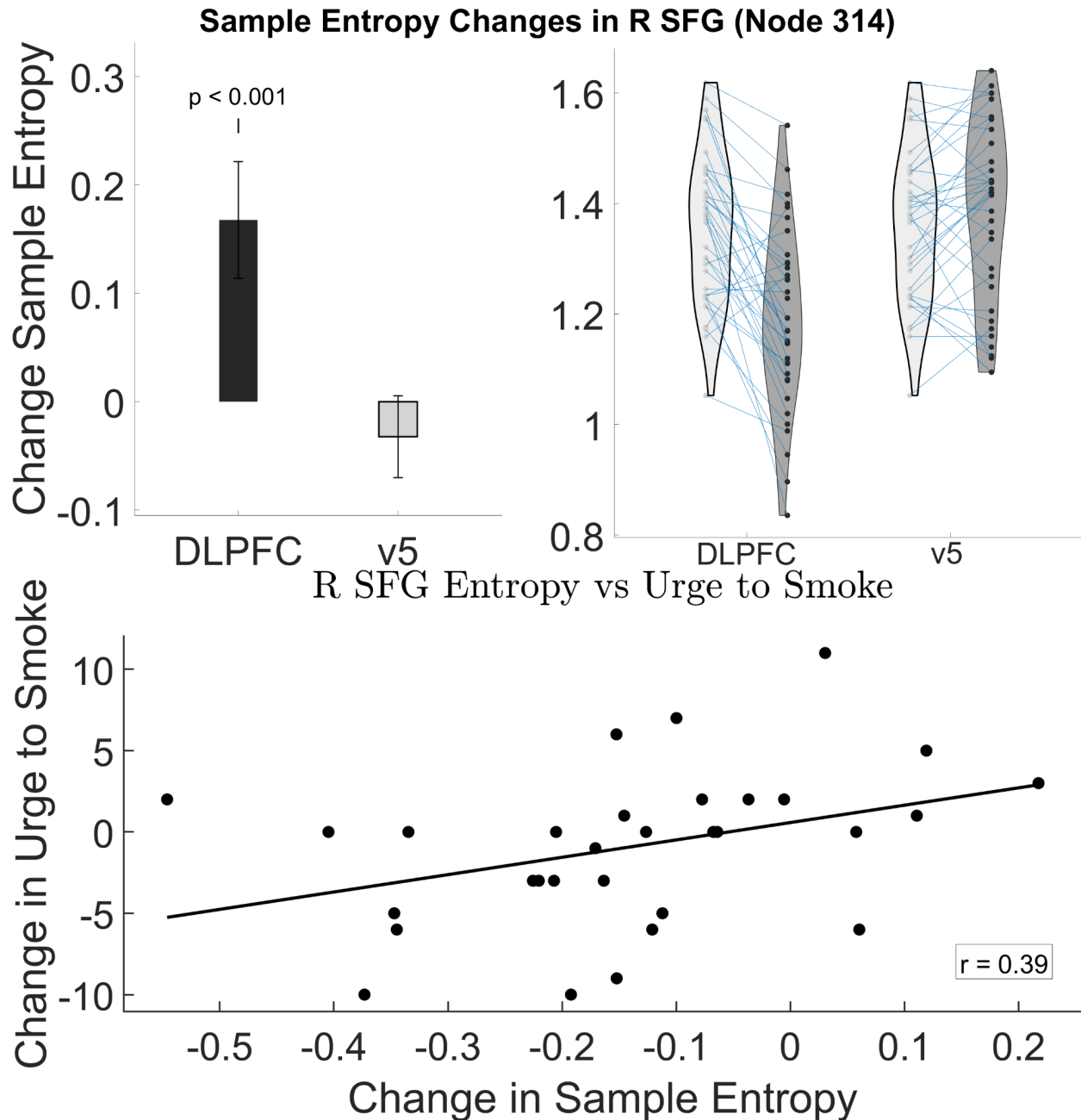
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65 **Table S5 Sample Entropy of each exploratory node Pre and Post-rTMS (related to Figure**
 66 **7)** Sample entropy measures for each node found to have significant changes in sample
 67 entropy post-rTMS to DLPFC. All measures are given as mean measures with standard
 68 deviation.

69



71 **Figure S5 Stimulation to left dIPFC reduced sample entropy in left Inferior**
72 **Temporal Gyrus (ITG) (related to Figure 7) Top:** Plots show change group in sample
73 entropy (left) and individual changes/distribution (right) for this node and the region that
74 correlated with the node. Change values were calculated by subtracting Post-rTMS
75 entropy values from Pre-rTMS values. **Bottom:** Correlation plot between changes in
76 sample entropy in left ITG and craving ($r=0.36$, $p= 0.027$) as measured by the Shiffman-
77 Jarvik Withdrawal Scale (SJWS) subscale for craving.
78



79

80 **Figure S6 Stimulation to left dIPFC reduced sample entropy in right superior**

81 **frontal gyrus (SFG)Top:** Plots show change group in sample entropy (left) and

82 individual changes/distribution (right) for this node and the region that correlated with

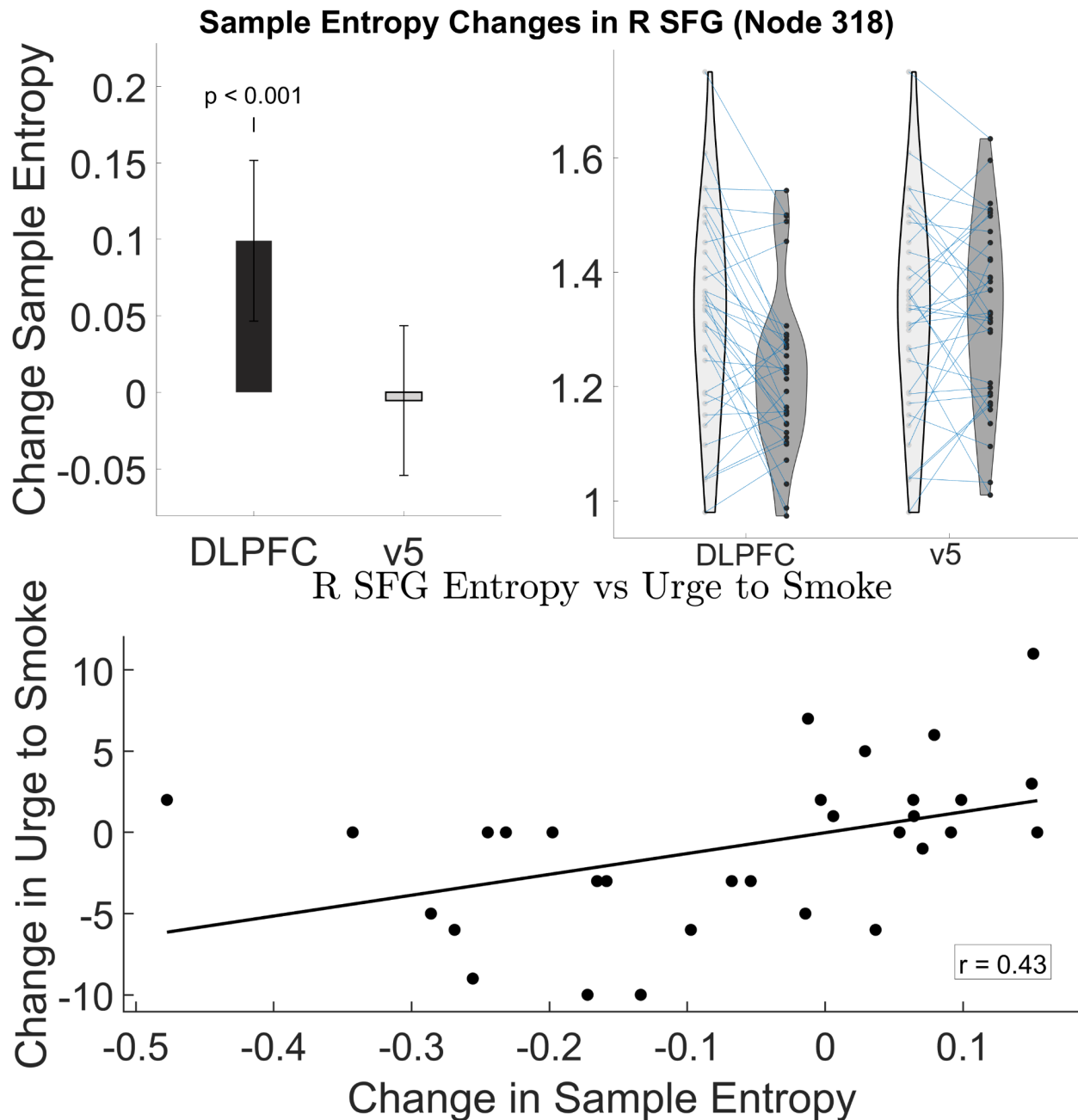
83 the node. Change values were calculated by subtracting Post-rTMS entropy values from

84 Pre-rTMS values. **Bottom:** Correlation plot between changes in sample entropy in right

85 SFG and craving ($r=0.39$, $p= 0.025$) as measured by the Shiffman-Jarvik Withdrawal

86 Scale (SJWS) subscale for craving.

87



88

89 **Figure S7 Stimulation to left dIPFC reduced sample entropy in right superior**
90 **frontal gyrus (SFG) Top:** Plots show change group in sample entropy (left) and
91 individual changes/distribution (right) for this node and the region that correlated with
92 the node. Change values were calculated by subtracting Post-rTMS entropy values from
93 Pre-rTMS values. **Bottom:** Correlation plot between changes in sample entropy in right
94 SFG and craving ($r=0.43$, $p= 0.016$) as measured by the Shiffman-Jarvik Withdrawal
95 Scale (SJWS) subscale for craving.