Anxious/depressed individuals exhibit disrupted frontotemporal synchrony during cognitive conflict encoding

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Abstract

Anxiety and depressive disorders are associated with cognitive control deficits, yet their underlying neural mechanisms remain poorly understood. Here, we used high-resolution stereotactic EEG (sEEG) to determine how anxiety and/or depression modulates neural and behavioral responses when cognitive control is engaged in individuals with medically refractory epilepsy undergoing sEEG monitoring for surgical evaluation.

We analyzed sEEG data recorded from frontotemporal regions of 29 participants (age range: 19-55, mean age: 35.5, female: 16/29) while they performed a Multi-Source Interference Task (MSIT) designed to elicit cognitive conflict. Neurobehavioral interviews, symptom rating scales, and clinical documentation were used to categorize participants as demonstrating anxiety and/or depression symptoms (A/D, n=13) or as epilepsy controls (EC, n=16). Generalized linear mixed-effects (GLME) models were used to analyze behavioral and neural data. Models of oscillatory power were used to identify brain regions within conflict-encoding networks in which coherence and phase locking values (PLV) were examined in A/D and EC.

A/D participants demonstrated a greater conflict effect (response time slowing with higher cognitive load), without impairment in response time (RT) or accuracy compared to EC. A/D participants also showed significantly enhanced conflict-evoked theta (4-8Hz) and alpha (8-15Hz) power in the dorsolateral prefrontal cortex (dlPFC) and amygdala as well as widespread broadband activity in the lateral temporal lobe (LTL) compared to EC. Additionally, theta coherence and PLV between dlPFC-LTL and dlPFC-amygdala were reduced by conflict in A/D.

Our findings suggest individuals with anxiety/depression symptoms exhibit heightened frontotemporal oscillatory activity and disrupted frontotemporal synchrony during cognitive conflict encoding, which may indicate a greater need for cognitive resources due to ineffective cognitive processing. These results highlight a potential role of frontotemporal circuits in

conflict encoding that are altered in anxiety/depression, and may further inform future therapeutic interventions aimed at enhancing cognitive control in these populations.

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Introduction

Anxiety and depressive disorders are a leading cause of disability and socioeconomic burden.[1,2] In the United States, 8.5% of adults experienced a major depressive episode in 2022, and 15.6% of adults experienced symptoms of anxiety in 2019.[3,4] Existing pharmacotherapies have moderate efficacy,[5] which is partly due to lack of specificity for dysfunctional brain circuits.[6,7] Electrical brain stimulation can provide a targeted approach for treating these disorders, but has yielded mixed results.[8-10] One reason for these challenges is the high comorbidity between anxiety and depressive disorders, which reduces therapeutic efficacy.[11,12] Another is that anxiety and depression are assessed by rating scales which do not account for individual heterogeneity, and can be subject to self-report and recall biases.[13,14] A more adaptable approach is to target functional deficits defined in the Research Domain Criteria (RDoC),[15] which can be reliably measured using established behavioral paradigms, and are associated with compromised neural circuitry.

A core functional domain frequently compromised in anxiety/depressive disorders is cognitive control, which is the ability to flexibly adapt thoughts and actions to align with longitudinal goals.[16-18] Cognitive control recruits attention, working memory, perception, and response inhibition processes to suppress prepotent thoughts/responses in favor of task-relevant ones.[19,20] Impaired response inhibition in anxiety/depressive disorders can be reflected as maladaptive, cyclical negative thoughts and behaviors.[21-23] Therefore, cognitive control may provide a clinically relevant and robust target for therapeutic intervention.

Response inhibition during cognitive control can be assessed by behavioral tasks such as a Stroop test,[24] which introduces (cognitive) conflict between task-relevant and task-irrelevant information. Conflict evokes theta (4-8Hz) and high gamma (70-110Hz) oscillations in the prefrontal cortex (PFC) and the dorsal anterior cingulate cortex (dACC), which are thought to play key roles in conflict detection and subsequent response inhibition.[25-30] Recently, stereotactic EEG (sEEG) has enabled examination of these oscillatory signatures with greater spatial resolution. Studies using a multi-source interference task (MSIT) that elicits robust neural responses to conflict[31-35] have observed conflict encoding in distributed frontotemporal regions including the orbitofrontal cortex (OFC), lateral temporal lobe (LTL), amygdala, and hippocampus, in addition to the PFC and dACC.[35-38] Of note is the LTL, which facilitates semantic memory, speech, emotion, and sensory processes[39-45] engaged during cognitive tasks.[46-48] However, the LTL and its interactions with the PFC and dACC during conflict encoding has not been well-characterized. Given that patients with temporal lobe epilepsy in sEEG studies frequently exhibit executive dysfunction[49] and comorbid anxiety and depression,[50-52] the role of frontotemporal circuits in cognitive control warrants further investigation.

Extant literature implicates that aberrant PFC and dACC activity during conflict, rather than overt behavioral impairment, underlies cognitive control deficits in anxiety/depressive disorders.[22,53-56] Heightened activity in PFC and dACC of anxious/depressed individuals during conflict is thought to reflect inefficient cognitive processing,[53-56] or a functional overlap between cognitive control and avoidance behaviors.[22] However, some studies found anxious/depressed individuals demonstrate PFC and/or dACC hypoactivity and impaired behavioral performance during conflict.[57,58] Taken together, anxiety and depression may lead to deleterious and/or compensatory changes in cognitive control circuitry, but the extent of these deficits remains unclear. Moreover, dysregulated conflict encoding in individuals with anxiety/depression symptoms has yet to be examined with sEEG, which may better capture large-scale neural interactions.

We previously showed conflict enhances prefrontal theta power on sEEG during the MSIT.[35] However, we did not consider neuropsychiatric effects on conflict-encoding oscillations. Here, we examined conflict-encoding frontotemporal networks in participants with epilepsy and comorbid anxiety and/or depression symptoms (A/D), and in epilepsy controls (EC), to identify potential targets for future therapeutic intervention. The goals of this study were to (1) determine whether A/D and EC exhibit behavioral and/or neural differences during conflict encoding, and (2) whether functional connectivity in frontotemporal conflict-encoding networks is altered in A/D (Fig. 1A). Given that anxious/depressed individuals often perform similarly to comparators on cognitive control tasks,[17] we hypothesized that (1) A/D would exhibit enhanced frontotemporal oscillations during conflict encoding, and (2) aberrant frontotemporal connectivity across distributed conflict-encoding networks while maintaining task performance.

Materials and methods

Participants

The present study includes data from 29 participants with intractable epilepsy undergoing invasive sEEG monitoring for seizure localization (Fig. 1B, Supplementary Table 1). Eighteen participants (age range: 19-55, mean age: 34.6, female: 10/18, left-handed: 5/18) were previously recruited at Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH).[35] Eleven participants (age range: 27-47, mean age: 36.9, female: 6/11, left-handed: none) were recruited at the University of Cincinnati Medical Center (UCMC) during the study period. MGH/BWH and UCMC participants did not significantly differ in age ($t(28)=0.662$, $P=0.514$), sex ($\chi^2=0.003$, $P=0.958$), or handedness (Fisher exact test: $P=0.125$), and were pooled for all analyses.

Study procedures occurred in the epilepsy monitoring unit (EMU) at least two days following implantation. Implantation procedures were performed for clinical indications with no research consideration. Participants were informed that study involvement would not influence or alter their medical care. All participants provided written informed consent obtained according to the Declaration of Helsinki, and study procedures were approved by MGH/BWH and UCMC Institutional Review Boards.

Categorization of A/D and EC

Psychiatric histories of participants were obtained from neurobehavioral interviews with a clinical neuropsychologist prior to or during the monitoring period, and/or from chart reviews of UCMC participants. Nineteen participants completed one or more of the following self-reported assessments of anxiety or depression severity: Beck Anxiety Inventory (BAI),[59] Generalized Anxiety Disorder-7 (GAD-7),[60] Beck Depression Inventory-II (BDI-II),[61] or Patient Health Questionnaire-9 (PHQ-9).[62] Participants were categorized as A/D if they met one or more of the following criteria: 1) assessed by the interviewing neuropsychologist as having current or prior anxiety and/or depression symptoms, 2) history of treatment for a diagnosed anxiety disorder and/or unipolar depression, or 3) endorsed moderate or greater anxiety and/or depression on the BAI (≥16), GAD-7 (≥10), BDI-II (≥20) or PHQ-9 (≥10). Participants who did not meet A/D criteria and had no history of any psychiatric disorder were designated as epilepsy controls (EC).

Multi-Source Interference Task (MSIT)

Participants performed a version of the MSIT[31,63] (Fig. 1C) on a computer monitor using Presentation or Psychophysics toolbox[64-66] (MGH/BWH), or on laptop computer using Honeycomb (https://github.com/neuromotion/task-msit) (UCMC). During MSIT trials, participants were presented with three numbers ranging from 0-3, one of which is unique. Participants were instructed to press the number key (1, 2, or 3) on a computer keyboard corresponding to the identity, but not position, of the unique number. For low conflict (congruent) trials, the identity of the unique number corresponded to its position on the keyboard and flanking stimuli were "0", which was not a valid response. For high conflict (incongruent) trials, the identity of the unique number differed from its position on the keyboard to engage inhibitory control (Simon effect), and flanking stimuli were valid responses (Flanker effect). Stimuli were presented for up to 2s, after which an inter-trial fixation cross was presented with random jitter between 2-4s. Participants were instructed to keep the fingers of their dominant hand on the response keys throughout the task while responding as quickly and accurately as possible. Each participant completed a training block, then 2-8 blocks of 48 or 64 trials with unlimited break time provided between blocks. Response times and accuracy (correct, incorrect, or omitted response) were recorded during the task. Data from training blocks were excluded from behavioral and neural analyses.

sEEG acquisition and electrode localization

sEEG data were recorded from stereotactic depth electrodes (Ad-Tech Medical, Racine, WI, USA, or PMT, Chanhassen, MN, USA) that were 0.8-1.0mm in diameter with 8-16 platinum/iridium contacts 1-2.4mm in length. Recordings at MGH/BWH were acquired with a sampling rate of 2kHz (Neural Signal Processor, Blackrock Microsystems Inc., Salt Lake City, UT, USA), and at UCMC with a sampling rate of 512Hz (Natus Quantum, Natus Medical Inc., Middleton, WI, USA). At the time of acquisition, depth recordings were referenced to an EEG electrode placed on the skin at either cervical vertebra 2 or Cz. Image onset times were synchronized with sEEG data using a transistor-transistor logic (TTL) trigger generated by a PCI parallel port output from MATLAB (MGH/BWH), or a photodiode placed on the bottom-right of the laptop screen (UCMC). For the latter, when a response was made, a bright circle undetectable to the participant would appear on the laptop screen at the photodiode's position. Analog photodiode voltages and TTL signals during the task were recorded by the EEG acquisition system.

Electrode localization was performed using a modular FreeSurfer-based pipeline.[67,68] Preoperative T1-weighted MRI scans were manually registered in FreeSurfer to postoperative CT scans of implanted electrodes, which were then mapped to the DKT40 atlas[69] using an automated probabilistic labeling algorithm.[70] For this study, we considered sampled regions with sufficient representation in each group (≥5 participants). Using these criteria, we selected electrodes localized to the following regions defined from atlas labels (Supplementary Table 2): left and right dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), ventrolateral prefrontal cortex (vlPFC), OFC, LTL, dACC, amygdala, and hippocampus. Channels localized outside of selected regions were excluded from neural analyses.

sEEG pre-processing

sEEG recordings were pre-processed using Fieldtrip[71] and custom MATLAB scripts. Channel data were aligned with stimulus onset times and epoched to 5s stimulus-locked trials from -2 to +3s with respect to stimulus onset. We included 1s of buffer data at the ends of each trial to account for edge effects induced by Morlet wavelet transformation. Channel data were then bipolar re-referenced, high-pass filtered at 0.5Hz (5^{th}-order Butterworth filter) if low-frequency artifacts were visually observed, notch-filtered between 55-65Hz (4^{th}-order Butterworth filter) to remove line noise, and then down-sampled to 512Hz to account for differences in sampling rate. Inter-ictal spike activity and amplifier saturation artifacts were

labeled by a z-score threshold set for each participant and manually inspected. Trials with labeled artifacts were excluded from neural analyses.

Canonical time-frequency analyses

We estimated stimulus-locked time-frequency power in theta (4-8Hz), alpha (8-15Hz), beta (15-30Hz), gamma (30-55Hz), and high gamma (70-110Hz) bands using Fieldtrip and custom MATLAB scripts. Morlet wavelet transformation was applied to channel data to estimate single-trial spectral power from -1 to +2s with respect to stimulus onset. Wavelets were set to 7 cycles and a width of 3 SD, and spectral decomposition was performed with time resolution of 23.4ms and frequency resolution of 1Hz (4-55Hz) or 5Hz (70-110Hz). Single-trial power spectra were averaged across time (0.1s to trial RT) and frequency to calculate average pre-response power in each frequency band. Band power was normalized for each trial by a log power ratio relative to a 500ms baseline period preceding stimulus onset.

Spectral coherence[72] was used to measure amplitude and phase synchronization of frontotemporal oscillations. Coherence between channel pairs in conflict-encoding regions (see Statistical Analysis) during low and high conflict trials was estimated at time-frequency points between 4-110Hz from 0 to +2s with a time resolution of 46.9ms and frequency resolution of 1Hz:

$$Coherence_{xy}(t,\omega) = \frac{|S_{xy}(t,\omega)|}{\sqrt{S_{xx}(t,\omega)S_{yy}(t,\omega)}} \quad (1)$$

where for each time-frequency point (t, ω), S_{xy} denotes the trial-averaged cross spectral density of signals x and y, and $\boldsymbol{S_{xx}}$ and $\boldsymbol{S_{yy}}$ denote their respective trial-averaged power spectral densities.

To examine conflict effects on phase synchronization independently from amplitude correlation, we estimated Phase Locking Value[73] (PLV) between selected channel pairs during low and high conflict trials across the same time bins as coherence:

$$PLV_{xy}(\omega,t) = \left|\frac{1}{n}\sum_{k=1}^{n} e^{i(\phi_x(\omega,t,k)-\phi_y(\omega,t,k))}\right| \quad (2)$$

where ϕ_x and ϕ_y denote the phase of signals x and y respectively, and n is the number of trials at a given conflict level.

Statistical analysis

We used generalized linear mixed-effects models (GLME) to estimate the effects of conflict (low, high) and participant group (EC, A/D) on behavioral and neural response data. GLMEs allowed for analysis of single-trial data while accounting for inter-participant variance (via random effect coding) in behavior and spectral responses, unequal sample sizes between regions, and missing data from artifactual trials. We estimated distributions of behavioral and neural responses (*allfitdist*[74]) and selected fitted distributions with the lowest Akaike information criterion (AIC) for GLMEs. Models were then fit to raw or transformed response variables with corresponding link functions. Model performance was assessed by visually inspecting normal Q-Q plots of model residuals. For behavioral analysis, log-transformation of RT and an identity link function produced approximately normal residuals. Log-transformed power approximated a normal distribution whereas Coherence and PLV approximated log-normal distributions. Models of log transformed power, coherence, and PLV with an identity link yielded approximately normal residuals.

Behavior

Accuracy rates of EC and A/D were compared using Wilcoxon rank-sum tests. Trials with missing or incorrect responses were subsequently excluded from models of RT and neural data. Log-transformed response times (RT) during low and high conflict trials were fit to a GLME using *fitglme*:

$$RT \sim Conflict + Group + Conflict*Group + (1|Participant)$$

where Conflict (low, high) and Group (EC, A/D) are encoded as binary fixed-effects predictors and Participant is a random-effect predictor. Significance of model predictors was determined by Wald tests on GLME coefficients.

Neural data (sEEG)

Separate GLMEs were fit to single-trial normalized pre-response spectral power in each region and frequency band (theta-high gamma):

$$Power \sim Conflict + Group + Conflict*Group + (1|Participant)$$

Models without significant interaction predictors were reduced in subsequent GLMEs:

$$Power \sim Conflict + Group + (1|Participant)$$

Within each frequency band, we estimated coherence between regions where conflict had significant group-dependent (conflict x group) or main effects on band power. For each

participant, coherence estimates between channels in each region pair were averaged from 0.1s to their median RT during low or high conflict trials, then log transformed. Separate GLMEs were performed for region pairs in each frequency band:

$$Coherence \sim Conflict + Group + Conflict*Group + (1|Participant)$$

For region pairs where conflict had significant group-dependent effects on coherence (conflict x group interaction), we performed follow-up GLMEs of log-transformed PLV to determine the effects of conflict on phase synchronization. PLV between channel pairs were averaged as coherence values above, then log-transformed and grouped by region pair and frequency band. Separate GLMEs were performed for each region pair and frequency band:

$$PLV \sim Conflict + Group + Conflict*Group + (1|Participant)$$

Models of coherence and PLV without significant interaction terms were reduced in subsequent GLMEs:

$$Coherence\ or\ PLV \sim Conflict + Group + (1|Participant)$$

Significance of predictors in neural models was determined by Wald tests on GLME coefficients. Interaction effects were interpreted post-hoc by Wald tests on GLME coefficient contrasts to compare estimated power at each conflict and group level (high>low, A/D>EC). *P* values within each analysis were corrected for multiple comparisons using a false discovery rate (FDR) step-up procedure (*fdr_bh*[75]) with q=0.05.

Results

Demographic data

Of the 29 participants recruited at MGH/BWH and UCMC, 13 were categorized as A/D and 16 participants were designated as EC (Supplementary Table 1). Psychiatric histories obtained from neurobehavioral interviews and chart reviews aligned with symptom severity scores for 17 of the 19 participants who completed self-reported assessments. One MGH participant (P16) who reported depression symptoms and minimal BDI and BAI scores was categorized as EC as supporting clinical documentation was not available. One UCMC participant (P28) with a history of anxiety/depression and minimal/mild GAD-7 and PHQ-9 scores was categorized as A/D upon further discussion with their clinical psychologist. A/D and EC did not significantly

differ in age ($t(28)$=0.389, P=0.7), sex (χ^2=0.386, P=0.534), or handedness (χ^2=0.057, P=0.811).

Behavior data

We collected 6602 MSIT trials from 29 participants during sEEG recording. Accuracy during the MSIT was 95.05±6.6% (Mean±SD), with no significant difference in overall accuracy (z=1.387, P=0.165), as well as accuracy during low conflict (z=0.181, P=0.856) or high conflict trials (z=1.52, P=0.129) between A/D and EC. We focused on successful cognitive conflict resolution; therefore, we rejected 361 trials (5.47%) with incorrect/omitted responses and retained 6241 trials for analysis. To determine whether A/D and EC exhibited behavioral differences in RT, we fit log-transformed RT to a GLME with fixed-effects of conflict (low, high) and group (EC, A/D), and a random-effect of participant. We found a significant conflict x group interaction effect on RT (P=0.001) (Supplementary Table 3). Post-hoc contrasts showed that A/D responded faster than EC during low conflict trials, and experienced greater response slowing by conflict compared to EC (Table 1, Fig. 1D).

Neural data: Frontotemporal spectral power

Recordings from 2981 bipolar-referenced channels in frontotemporal regions were included in spectral analyses. Out of the 6241 correct trials, 5963 trials were retained after artifact rejection (278 or 4.45% of trials rejected). To determine whether neural responses to conflict differed between A/D and EC, we modeled single-trial theta, alpha, beta, gamma, and high gamma power in frontotemporal regions using GLMEs with fixed effects of conflict and group, and a random effect of participant. P-values reported were FDR-corrected across 80 models of band power with critical P-values of 0.008 (conflict) and 0.009 (conflict x group). No group predictors achieved significance in full models (uncorrected P>0.05). Significant conflict x group interactions were interpreted post-hoc by Wald tests on GLME coefficient contrasts (FDR-corrected for 64 comparisons, critical P-value=0.015).

Frontotemporal spectral responses to conflict were enhanced in A/D compared to EC

We found significant conflict x group interaction effects on left dlPFC theta/alpha (P<0.001) and beta power (P=0.043), left dmPFC beta power (P<0.013), right dmPFC theta power (P<0.001), right dACC alpha power (P<0.02), left LTL theta-gamma power (P<0.001), right LTL theta-beta and high gamma power (P<0.001), right hippocampus theta power (P=0.003), and amygdala alpha power (P<0.001). (Figs. 2A-B, Supplementary Table 4). Post-

hoc contrasts of conflict (high>low) by group revealed theta, alpha, and beta power in left LTL increased with conflict in A/D to a greater extent than EC (all $P<0.001$) (Figs. 2C-E, Table 2). Conflict had opposing effects by group on right dmPFC theta power, which was increased by conflict in A/D ($P=0.001$) and reduced by conflict in EC. ($P<0.001$).

Additional effects of conflict on frontotemporal power were observed in either A/D or EC (Table 2). In A/D, conflict increased theta/alpha power in left dlPFC, theta power in right hippocampus ($P=0.002$), alpha power in right amygdala, and power between theta-beta and high gamma bands in right LTL (all $P<0.001$). In EC, conflict reduced alpha power in right dACC ($P<0.001$) and increased beta power in left dmPFC ($P=0.01$). Contrasts of group (A/D>EC) showed A/D had greater beta power in left dlPFC compared to EC during high conflict ($P=0.048$).

Conflict modulated broadband frontotemporal spectral responses in both A/D and EC

We reduced 64 models without significant conflict x group interaction predictors in subsequent GLMEs to determine main effects of conflict and group on frontotemporal band power. *P*-values were FDR-corrected with a critical *P*-value of 0.015 (conflict). We found significant main effects of conflict on frontotemporal power that were independent of group (Supplementary Table 5). In both A/D and EC, conflict increased high gamma power in left dlPFC and right dACC, theta, alpha, and high gamma power in left dmPFC, gamma power in left vlPFC, beta power in right OFC, theta/alpha power in left dACC, theta-gamma power in left amygdala and hippocampus, and theta and beta power in right amygdala, and reduced right dACC theta and right dlPFC beta power. We found no significant group effects on frontotemporal power in reduced models (uncorrected $P>0.05$).

Neural data: Frontotemporal coherence

We first modeled pre-response band power in frontotemporal regions to determine whether A/D and EC differentially encode conflict prior to response selection. Next, we defined theta, alpha, beta, gamma, and high gamma conflict-encoding regions from models with significant conflict effects on band power in one or both groups (significant conflict contrast or main effect of conflict in reduced models). We then estimated pre-response coherence between conflict-encoding region pairs to determine whether frontotemporal connectivity was altered in A/D during conflict encoding. Coherence values were log-transformed and modeled by GLMEs with fixed effects of conflict and group and a random effect of participant. *P*-values were FDR-corrected for 139 coherence models with critical *P*-values of 0.014 (conflict) and

0.01 (conflict x group). Group predictors were not significant in coherence models (uncorrected $P>0.05$). Post-hoc analyses were performed as previously described (FDR-corrected for 116 comparisons, critical P-value=0.014).

Theta coherence between dlPFC-LTL and dlPFC-amygdala was reduced in A/D during conflict encoding

Conflict x group interactions predicted theta coherence between left dlPFC-bilateral LTL and right amygdala, right dmPFC-right LTL, right dACC-left dmPFC, left LTL, and right hippocampus, and right amygdala-left hippocampus (Supplementary Table 6). In the alpha band, interaction effects predicted coherence between left dlPFC-right LTL, right dACC-left LTL, left LTL-right LTL, and left hippocampus-bilateral LTL, bilateral dACC, and right amygdala. Significant interaction effects were also observed on beta coherence between left dlPFC-left amygdala, left dmPFC-right dlPFC, left LTL, right LTL, and left hippocampus, right OFC-bilateral LTL, left LTL-right LTL and right amygdala, right LTL-left amygdala and hippocampus, and right amygdala-left hippocampus, and on gamma coherence between left LTL-left hippocampus. Post-hoc contrasts of conflict (high>low) found theta coherence between left dlPFC-right LTL was increased in EC (P=0.001) and reduced in A/D (P<0.001) by conflict, whereas theta coherence between left dlPFC-left LTL was increased by conflict to a lesser extent in A/D (P=0.001) compared to EC (P<0.001) (Fig. 3A-B, Table 3). Conflict also increased beta coherence between left dmPFC-right dlPFC, right OFC-left and right LTL, right LTL-left amygdala, and right amygdala-left hippocampus to a greater extent in A/D compared to EC, and had opposing effects by group on theta coherence between left LTL-right dACC, which was increased in A/D and reduced in EC.

Additional effects of conflict on frontotemporal coherence were group-dependent (Table 3). In A/D, conflict reduced theta coherence between left dlPFC-right amygdala while increasing theta coherence between right dmPFC-right LTL, and right amygdala-left hippocampus, alpha coherence between left LTL-right LTL and right dACC, left hippocampus-bilateral LTL, bilateral dACC, and right amygdala, beta coherence between left dlPFC-left amygdala, left dmPFC-left LTL, left LTL-right LTL and amygdala, and right LTL-left hippocampus, and gamma coherence between left LTL-left hippocampus. In EC, conflict increased theta coherence between left dmPFC-right dACC and right dACC-right hippocampus, alpha coherence between left dlPFC-right LTL, and beta coherence between left

dmPFC-right LTL and left hippocampus. Group (A/D>EC) contrasts of coherence were not significant during low or high conflict (P>0.05).

Conflict induced widespread effects on frontotemporal coherence in both A/D and EC

We reduced 110 models without significant conflict x group interaction predictors in subsequent GLMEs to determine main effects of conflict and group on coherence networks. FDR-correction was performed for reduced models with a critical P-value of 0.023 (conflict). In both groups, conflict broadly increased coherence across conflict-encoding networks in theta, alpha, beta, gamma, and high gamma bands while reducing alpha coherence between right dACC-right LTL (Supplementary Table 7). We found no significant group effects on frontotemporal coherence in reduced models (uncorrected P>0.05).

Neural data: Frontotemporal PLV

In a follow-up analysis of coherence models, we sought to determine whether group-dependent effects of conflict on frontotemporal coherence were primarily due to changes in phase synchrony. We used PLV as an amplitude-independent measure of phase synchronization, which was estimated between region pairs where conflict x group was a significant predictor of coherence. PLVs for each region pair and frequency band were log transformed, then fit to GLMEs with fixed effects of conflict and group and a random effect of participant. P-values were FDR-corrected for 29 PLV models with critical P-values of 0.012 (conflict) and 0.024 (conflict x group). Group predictors were not significant in PLV models (uncorrected P>0.05). Post-hoc tests were performed as previously described (FDR-corrected for 76 comparisons, critical P-value=0.009).

Phase synchrony between dlPFC, LTL and amygdala was reduced in A/D during conflict encoding

We found similar conflict x group interaction effects as coherence models on PLV across bilateral dlPFC, right OFC, bilateral LTL, bilateral amygdala, and left hippocampus (Supplementary Table 8). Post-hoc contrasts showed that opposing changes in left dlPFC-right LTL theta coherence between EC and A/D were due to respective increases or decreases in phase synchronization by conflict (Fig. 3B, Table 4). A/D had greater increases in alpha PLV between left LTL-left HC, beta PLV between left dmPFC-right dlPFC, right OFC-bilateral LTL, and right LTL-left amygdala and hippocampus, and gamma PLV between left LTL-left hippocampus with greater conflict compared to EC. In A/D, but not EC, conflict reduced theta

PLV between left dlPFC-right amygdala, and increased theta PLV between right amygdala-left hippocampus, alpha PLV between right LTL-left hippocampus, and alpha/beta PLV between left and right LTL, and right amygdala-left hippocampus. Importantly, reduced theta coherence with greater conflict between left dlPFC, right LTL, and right amygdala in A/D was consistent with changes in PLV. Group (A/D>EC) contrasts of PLV were not significant during low or high conflict (P>0.05).

Conflict induces widespread effects on frontotemporal PLV in both A/D and EC

We reduced 10 models without significant conflict x group interaction predictors in subsequent GLMEs to estimate main effects of conflict and group on PLV (Supplementary Table 9). FDR-correction was performed across models with a critical P-value of 0.001 (conflict). Similar to reduced coherence models, both A/D and EC demonstrated widespread increases in frontotemporal PLV across conflict-encoding networks in theta, alpha, and beta bands. We found no significant group effects on frontotemporal PLV in reduced models (P>0.05).

Discussion

We recorded sEEGs from frontotemporal regions of epilepsy patients with and without comorbid anxiety and/or depression symptoms (A/D and EC) during MSIT performance to determine whether A/D and EC exhibit differential behavioral and neural responses during conflict encoding. We found (1) A/D responded faster in low conflict trials and exhibited greater response slowing with conflict but similar accuracy as EC, (2) A/D exhibited significantly greater theta/alpha responses in PFC and amygdala, and broadband spectral responses in the LTL compared to EC during successful conflict resolution, (3) conflict was broadly encoded across frontotemporal regions in both A/D and EC, and (4) theta coherence between the PFC, LTL, and amygdala was reduced by conflict in A/D, whereas frontotemporal coherence was globally increased by conflict in EC. A follow-up analysis of PLV confirmed that effects of conflict on coherence between the PFC, LTL, and amygdala were due to effects on phase synchronization. In summary, our findings indicate that A/D individuals show enhanced low frequency oscillations and aberrant functional connectivity in frontotemporal networks when encoding cognitive conflict without impairment in task performance compared to EC.

A/D exhibit greater conflict-induced response slowing while maintaining task performance

A/D and EC achieved similar accuracy on the MSIT, but responses in the A/D group were slowed by conflict to a greater extent than EC. Behavioral evidence from cognitive control studies on anxiety/depression is mixed, with some studies showing no effects of anxiety or depression on behavioral performance,[76-82] while others report higher error rates and slower response times in anxious/depressed individuals compared to controls.[83-86] Our findings suggest A/D were able achieve task demands, but may have required greater cognitive resources allocated over a longer period of time to maintain comparable performance as EC. While it is unclear why A/D were faster than EC on low conflict trials, this could reflect differences in motor function due to neurologic conditions outside of anxiety/depression, or how quickly they were able to access computer keys while positioned on an EMU bed. In sum, impaired cognitive control in A/D, if any, may be more robustly characterized by neural mechanisms of conflict encoding, rather than overt behavioral deficits.[17,87,88] Therefore, we focused on neural responses to conflict as a more sensitive measure of cognitive control function.

A/D and EC encode conflict in distributed frontotemporal oscillatory networks

In addition to increasing frontal theta oscillations commonly associated with cognitive control,[28] conflict modulated power, coherence, and phase synchronization of theta, alpha, beta, gamma, and high gamma activity across frontotemporal regions. To date, few intracranial studies have directly examined conflict encoding outside of the PFC and ACC.[35,38,89] One reason for this sparsity may be that most neuroimaging and scalp EEG studies have focused primarily on cognitive processes in frontal regions. However, sEEG may be more sensitive for observing distributed oscillatory responses during cognitive control. Indeed, intracranial studies have previously reported conflict encoding in the OFC,[90-92] amygdala,[93] and hippocampus.[94,95] Our findings suggest conflict encoding may occur through multiplexed oscillatory signals[96] across distributed frontotemporal networks, and may provide further insight into the underlying mechanisms of cognitive control.

Enhanced frontotemporal oscillations in A/D reflects greater need for cognitive/attentional control

Conflict had greater effects on PFC theta/alpha power in A/D during exercise of response inhibition. While we previously reported theta oscillations in frontal regions including

the dlPFC were increased by conflict,[35] we did not examine how such oscillations differentially encode conflict in participants with anxiety/depression symptoms. Here, we show that theta/alpha oscillations were enhanced in left dmPFC across A/D and EC in congruence with previous sEEG studies evidencing its role in conflict monitoring.[90,97,98] Furthermore, A/D showed enhanced theta/alpha responses to conflict in **right dmPFC and left dlPFC**. Our results may be related to previous reports of "hyperfrontality" exhibited by anxious and depressed individuals during increased cognitive conflict.[22,53,55,56,86] Although this hyperactivity was previously localized to the dACC rather than dmPFC, this may be due to differences in resolution of neural activity between sEEG and other modalities given their significant anatomical and functional overlap.[99] Theta/alpha oscillations in the dmPFC/dACC are elicited by conflict detection, whereas in the dlPFC they are thought to serve top-down cognitive and attention regulation.[16,90,97,100-103] Thus, enhanced dlPFC and dmPFC oscillations in A/D may indicate greater need for cognitive resources in order to meet task demands,[58,104,105] which may be due to inefficient cognitive processing.[53,86]

Along with enhanced prefrontal neural responses during conflict encoding, A/D increased alpha power in right amygdala whereas theta power in bilateral amygdala was increased in both groups. The amygdala is involved in encoding fear and emotional arousal through theta/alpha oscillations,[106-110] but may also play a more general role in shifting attention towards goal-oriented stimuli.[111,112] Furthermore, a recent sEEG study found theta oscillations in the amygdala are enhanced during non-emotional conflict.[93] Our results further extend these findings to a larger sEEG sample and suggest the amygdala may differentially encode conflict in A/D. Enhanced amygdalar responses to conflict in A/D may indicate greater recruitment of attentional systems necessary to maintain orientation to goal-directed stimuli.

Interestingly, differences in conflict encoding between A/D and EC were most striking in the LTL. Although the LTL is not commonly defined as a cognitive control hub, it is shown to be sensitive to multiple sources of conflict,[31,89,113,114] which may be due to its roles in processing visual and semantic information.[114-116] While both A/D and EC encoded conflict through broadband signals in left LTL, only A/D exhibited conflict encoding in right LTL. The right LTL plays a role in a ventral network which re-orients attention to task-relevant stimuli,[117,118] and damage to right LTL more frequently leads to spatial attention deficits.[119] It is possible that heightened alpha responses in right amygdala and broadband responses in right LTL observed in A/D indicate greater recruitment of these bottom-up attention/visual streams. To our knowledge, activity in the LTL and amygdala during neutral interference tasks has not

been previously associated with anxiety or depression, although a previous fMRI study using a Go/No-Go task found greater activation of inferior temporal lobe in depressed participants relative to controls during successful response inhibition.[56] Increased conflict effects in both PFC and temporal regions may further suggest that A/D required greater efforts to maintain cognitive and attentional control during conflict encoding.[118,120]

Reduced frontotemporal synchrony underlies enhanced cognitive/attentional demands in A/D

Conflict reduced theta coherence and PLV between **left dlPFC-right LTL** and **left dlPFC-right amygdala in A/D**, whereas frontotemporal coherence and PLV were increased in EC. Top-down circuits between dlPFC and amygdala are crucial for emotional regulation,[121,122] which is thought to be disrupted in anxiety and depression.[123] Moreover, synchronization of theta signals in the PFC and amygdala occurs during cognitive reappraisal[110] when inhibiting conditioned responses.[109] In addition, the amygdala modulates salience of stimulus representations in the LTL to enhance attention towards arousing stimuli.[124-126] Furthermore, modulation of attentional control by the amygdala is thought to be reduced by dlPFC when processing demands are increased.[124]

While previous imaging and EEG studies have suggested that PFC and LTL connectivity is disrupted in anxiety/depression during resting-state,[127,128] these circuits have not been previously implicated as pathologic during non-emotional cognitive control. Given that the amygdala and LTL are more commonly known to engage in valanced attention processes, an alternate explanation could be that dysregulated frontotemporal circuits led to heightened arousal to conflicting stimuli. This would compete with conflict encoding, requiring enhanced prefrontal control to maintain task focus.[124] While this explanation would align with interpretations of hyperfrontality in the dlPFC as an inability to deactivate limbic responses,[53,129] it is unlikely that A/D would have ascribed emotional valence to neutral task stimuli. Therefore, we speculate that reduced phase synchrony between left dlPFC, right LTL, and right amygdala reflects disrupted communication across frontotemporal cognitive and attentional systems in A/D. In turn, these regions may exhibit compensatory increases in cognitive and attentional signals to achieve comparable behavioral performance as EC during greater cognitive load.

Limitations

The limitations of our study leave several open questions to be further addressed. One important question is whether our findings can be generalized to anxious/depressed individuals without intractable epilepsy. Although we compared A/D to an epilepsy control group, excluded epileptiform activity from analyses, and used mixed-effects models to control for interparticipant variance, we cannot fully isolate effects of anxiety/depression symptoms on conflict encoding from those due to cognitive deficits and pathophysiological abnormalities in epilepsy. Future studies could disentangle these effects by examining cognitive control networks in larger samples of anxious/depressed and non-anxious/depressed individuals with and without epilepsy. While sEEG studies are mostly limited to epilepsy patients, high-density EEG or EEG-fMRI techniques could provide comparable resolution of frontotemporal structures. These methods could also improve upon limitations in regional sampling, which limited further stratification of participants by psychiatric features. Studies of larger clinical samples could determine whether conflict encoding in frontotemporal networks is modulated by anxiety/depression severity, or specific symptom clusters.

Additionally, we combined temporal gyri into a singular LTL region due to sampling limitations, however, the LTL is not functionally homogenous. A larger sample of electrodes within LTL subregions could disentangle their overlapping roles in cognitive, emotional, and attentional processes. Finally, although our results suggest oscillatory communication between the PFC, LTL, and amygdala is dysregulated in A/D during conflict encoding, the evidence presented is correlational in nature. Dynamic causal modeling and/or modulation of these circuits with an external intervention would provide stronger evidence of a causal role in conflict encoding.

Conclusion

In summary, we provide direct intracranial evidence for distributed conflict encoding by frontotemporal networks during cognitive control task performance. We show individuals with epilepsy and comorbid anxiety/depression symptoms exhibit enhanced theta/alpha oscillations in the dlPFC and amygdala as well as broadband oscillations in the LTL when encoding conflict compared to epilepsy controls. Furthermore, heightened frontotemporal oscillations may be compensatory for reduced synchronization between theta activity in the PFC, LTL, and amygdala, resulting in greater cognitive recruitment to meet task demands. Our findings encourage further studies of frontotemporal networks during cognitive conflict, which may yield additional insight into cognitive control deficits in anxiety and depression.

Investigating these circuits may generate novel therapeutic targets for improving cognitive control in neuropsychiatric disorders.

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Competing interests

The authors report no competing interests.

Data availability

MATLAB code for preprocessing, data analyses, and generating figures is available at https://github.com/ashekara/MSIT-Analysis. Neural and behavioral data supporting the findings of this study will be made available upon request.

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Figure legends

Figure 1. Experimental paradigm and response times (RT) during the MSIT. (A) Flowchart of analyses performed to characterize conflict-encoding networks in A/D and EC. **(B)** Example sEEG electrode placements of a single participant.[35] Bolded labels denote regions selected for neural analyses. rACC = rostral ACC; PCC = posterior cingulate cortex; mOFC/lOFC = medial/lateral OFC; NAc = nucleus accumbens; AMY = amygdala; HC = hippocampus; PHG = parahippocampal gyrus. **(C)** Schematic of the MSIT where participants must inhibit pre-potent responses on 50% of trials. **(D)** Log-transformed RT during low and high conflict trials. Central lines are median, bottom and top edges are 25% and 75%, and whiskers denote mean±SD. Markers represent mean RT of individual participants. **P*<0.05, ****P*<0.001 (FDR-corrected).

Figure 2. Changes in frontotemporal oscillatory power during conflict encoding. (A) Time-frequency plots of group-averaged changes in left dlPFC and right LTL power during conflict in A/D and EC. Intensity values correspond to differences in log-normalized power averaged across channels and participants. **(B)** Heatmap of Conflict*Group predictors in GLMEs of regional band power. Interaction β-weights were coded as the mean difference in conflict-induced change in power (high>low) between groups. Asterisks denote significant interaction predictors (FDR-*P*<0.05). **(C-E)** Boxplots of log-normalized spectral power in frontotemporal regions of A/D and EC during low and high conflict trials. Central lines are median, bottom and top edges are 25% and 75%, and bottom and top whiskers are 9% and 91% respectively. Markers represent means of individual participants. **P*<0.05, ***P*<0.01, ****P*<0.001 (FDR-corrected).

Figure 3. Changes in frontotemporal functional connectivity during conflict encoding. (A) Time-frequency plots of group-averaged changes in left dlPFC-right LTL coherence (left) and PLV (right) during conflict encoding in A/D and EC. Intensity values correspond to differences in coherence or PLV averaged across channel pairs and participants. Inset rectangles correspond to theta activity from 0.1s to median high conflict RT. **(B)** Connectograms depicting significant conflict-induced changes in coherence and PLV (FDR-*P*<0.05). Connectivity changes observed in both groups are labeled in red if greater in A/D compared to EC, blue if greater in EC compared to A/D, and purple if opposing between groups. Changes only in A/D (gold) or EC (black) are shown as solid or dashed lines corresponding to increased or decreased connectivity respectively during conflict encoding.

Figure 1. Experimental paradigm and response times (RT) during the MSIT.

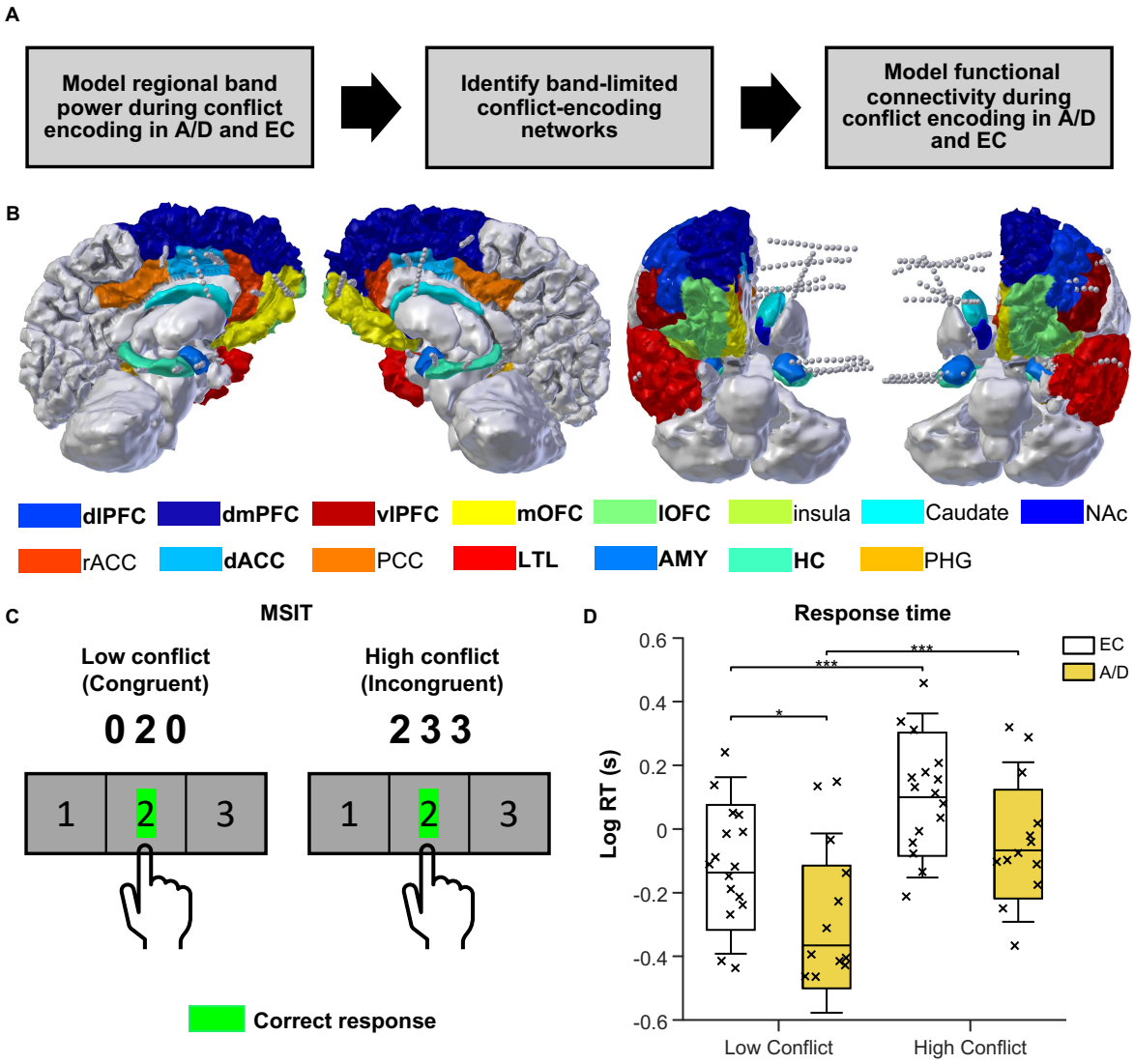

Figure 2. Changes in frontotemporal oscillatory power during conflict encoding.

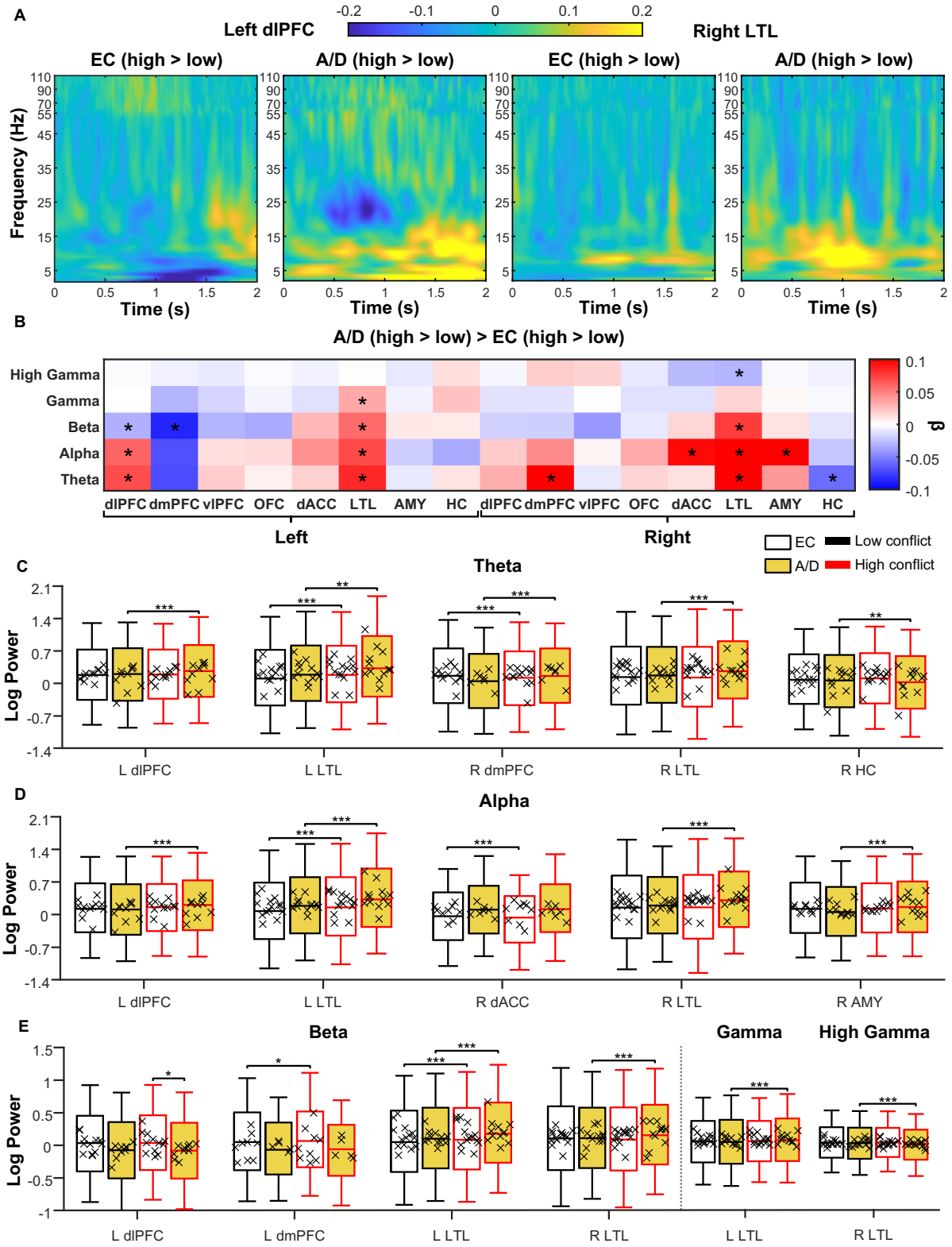

Figure 3. Changes in frontotemporal functional connectivity during conflict encoding.

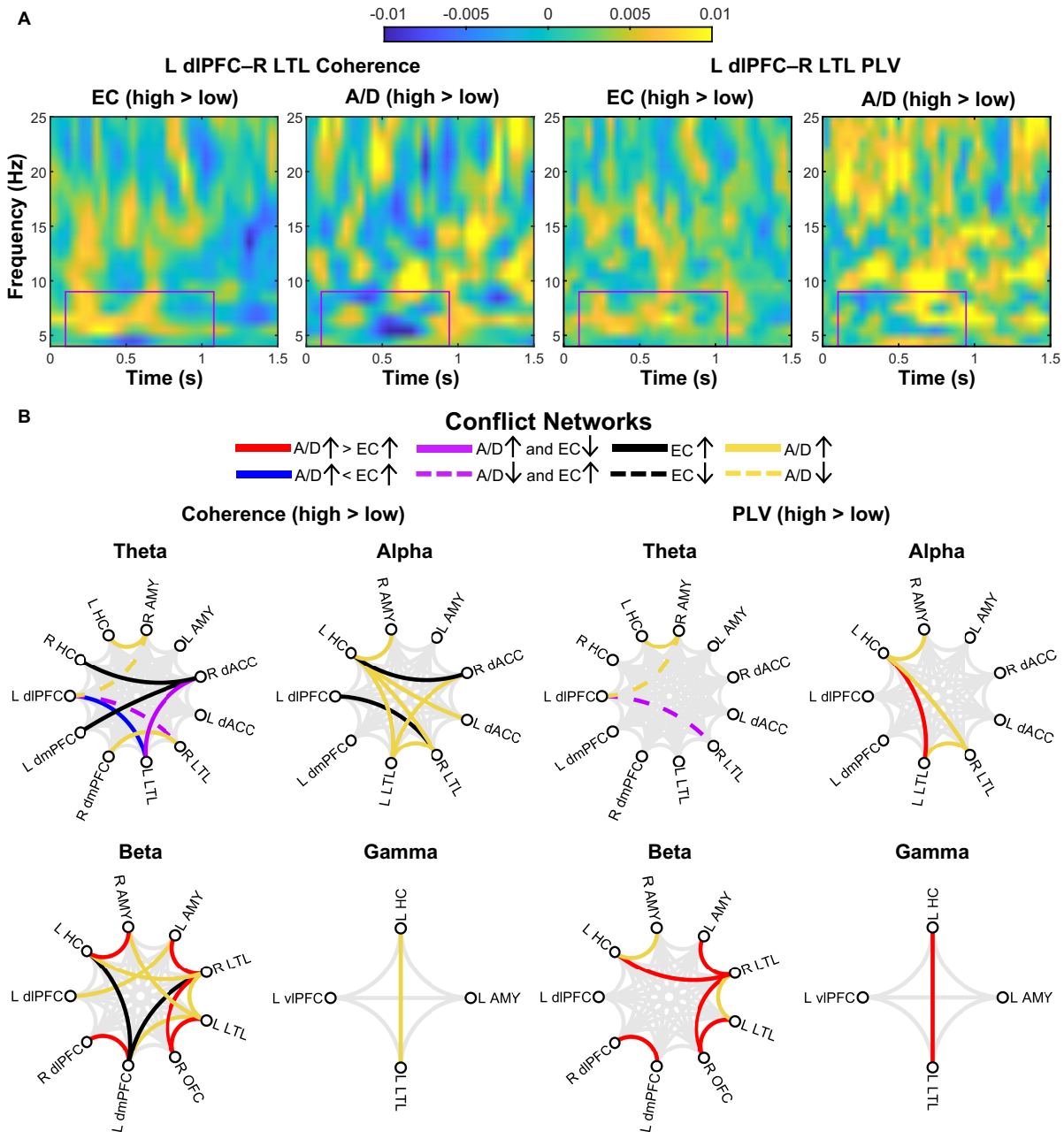

Table 1. Effects of Conflict and Group on response time

Contrast	*β*	*F*	FDR-*P*
Group (AD>HC)			
Low Conflict	-0.170	5.796	0.021
High Conflict	-0.136	3.709	0.054
Conflict (high>low)			
EC	0.224	1129.326	<0.0001
AD	0.257	1177.378	<0.0001

Table 2. Significant effects of Conflict (high>low) on frontotemporal band power

		Epilepsy Controls			Anxious/Depressed		
Frequency Band	**Region**	***β***	***F***	**FDR-*P***	***β***	***F***	**FDR-*P***
Theta							
	L dlPFC				0.074	45.779	<0.001
	R dmPFC	-0.052	19.509	<0.001	0.087	12.906	0.001
	L LTL	0.074	59.471	<0.001	0.158	285.147	<0.001
	R LTL				0.107	97.992	<0.001
	R HC				-0.042	11.969	0.002
Alpha							
	L dlPFC				0.079	52.349	<0.001
	R dACC	-0.104	35.719	<0.001			
	L LTL	0.089	84.125	<0.001	0.159	286.730	<0.001
	R LTL				0.147	173.506	<0.001
	R AMY				0.104	38.655	<0.001
Beta							
	L dmPFC	0.049	8.747	0.010			
	L LTL	0.041	28.749	<0.001	0.099	179.277	<0.001
	R LTL				0.060	48.027	<0.001
Gamma							
	L LTL				0.039	58.171	<0.001
High Gamma							
	R LTL				-0.029	50.379	<0.001

Table 3. Significant effects of Conflict (high>low) on frontotemporal coherence

		Epilepsy Controls			Anxious/Depressed		
Frequency Band	**Region**	***β***	***F***	**FDR-*P***	***β***	***F***	**FDR-*P***
Theta							
	L dlPFC-L LTL	0.052	94.764	0.000	0.021	12.803	0.001
	L dlPFC-R LTL	0.018	12.738	0.001	-0.025	19.922	<0.001
	R dmPFC-R LTL				0.065	16.846	<0.001
	L dmPFC-R dACC	0.088	6.899	0.031			
	R dACC-L LTL	-0.034	7.587	0.022	0.051	17.584	<0.001
	L dlPFC-R AMY				-0.042	15.430	<0.001
	R AMY-L HC				0.076	20.164	<0.001
	R dACC-R HC	0.099	26.225	0.000			
Alpha							
	L dlPFC-R LTL	0.020	24.380	0.000			
	L LTL-R LTL				0.021	26.199	<0.001
	R dACC-L LTL				0.096	84.902	<0.001
	L LTL-L HC				0.081	28.494	<0.001
	R LTL-L HC				0.038	33.375	<0.001
	L dACC-L HC				0.098	19.476	<0.001
	R AMY-L HC				0.071	30.981	<0.001
Beta							
	L dmPFC-R dlPFC	0.018	8.083	0.017	0.050	23.695	<0.001
	L dmPFC-L LTL				0.043	23.195	<0.001
	R OFC-L LTL	0.023	33.835	0.000	0.044	101.437	<0.001
	L dmPFC-R LTL	0.014	6.058	0.045			
	R OFC-R LTL	0.024	23.221	0.000	0.049	69.592	<0.001
	L LTL-R LTL				0.026	90.008	<0.001
	L dlPFC-L AMY				0.029	16.420	<0.001
	R LTL-L AMY	0.024	22.111	0.000	0.062	107.023	<0.001
	L LTL-R AMY				0.037	47.146	<0.001
	L dmPFC-L HC	0.023	7.088	0.027			
	R LTL-L HC				0.052	130.148	<0.001
	R AMY-L HC	0.034	7.525	0.022	0.073	61.622	<0.001
Gamma							
	L LTL-L HC				0.044	26.129	<0.001

Table 4. Significant effects of Conflict (high>low) on frontotemporal PLV

		Epilepsy Controls			Anxious/Depressed		
Frequency Band	**Region**	***β***	***F***	**FDR-*P***	***β***	***F***	**FDR-*P***
Theta							
	L dlPFC-R LTL	0.016	12.593	0.001	-0.013	7.067	0.021
	L dlPFC-R AMY				-0.029	9.201	0.008
	R AMY-L HC				0.081	30.855	<0.001
Alpha							
	L LTL-R LTL				0.025	53.524	<0.001
	L LTL-L HC	0.032	6.384	0.030	0.081	39.978	<0.001
	R LTL-L HC				0.033	31.915	<0.001
	R AMY-L HC				0.059	28.655	<0.001
Beta							
	L dmPFC-R dlPFC	0.029	32.583	0.000	0.054	45.157	<0.001
	R OFC-L LTL	0.018	18.075	0.000	0.053	121.669	<0.001
	R OFC-R LTL	0.013	8.191	0.012	0.056	101.998	<0.001
	L LTL-R LTL				0.035	184.675	<0.001
	R LTL-L AMY	0.021	17.765	0.000	0.051	74.029	<0.001
	R LTL-L HC	0.023	26.923	0.000	0.041	78.951	<0.001
	R AMY-L HC				0.056	41.930	<0.001
Gamma							
	L LTL-L HC	0.020	8.247	0.012	0.050	49.232	<0.001