Alcohol use disorder is associated with increases in frontocentral phase-amplitude coupling strength during resting state

C.D. Richard[1], B. Porjesz[1], J. L. Meyers[1], A. Bingly[1], D.B. Chorlian[1], C. Kamarajan[1], G. Pandey[1], W. Kuang[1], A. K. Pandey[1], S. Kinreich[1]

[1]SUNY Downstate Health Sciences University, Department of Psychiatry and Behavioral Sciences, Brooklyn, NY 11203-2098 USA.

ABSTRACT

Compromised functional connectivity in the brain seen in fMRI and EEG coherence is a key feature of alcohol use disorder (AUD). Phase-amplitude coupling (PAC) represents another mechanism by which functional connectivity is achieved, and to date, the role played by PAC in understanding the development of AUD has yet to be investigated. In the current study, we compare PAC strengths between participants with severe AUD, defined as presenting with 6 or more symptoms (DSM-5), and unaffected controls. Associations between phase-amplitude coupling and AUD status were assessed using frontal EEG signals acquired during the resting state eyes closed condition as part of the Collaborative Study on the Genetics of Alcoholism (COGA). COGA is a national project following families affected with AUD and comparison families for over 35 years with data collection in multiple domains. COGA participants between 25 and 50 years old with severe AUD were compared to an age-matched group of unaffected controls (Women: N = 360; Men: N = 406). PAC calculations were made on EEG recordings from midfrontal channel FZ to generate high resolution comodulograms covering phase frequencies between 0.1-13 Hz and amplitude frequencies between 4-50 Hz. Comodulograms were generated for each 30 second EEG segment for a given visit. Average comodulogram for a visit was calculated for the first two minutes of EEG in the resting state condition for subsequent statistical analyses. PAC differences between AUD and unaffected controls were assessed at each frequency pair using Mann-Whitney test, and the resulting effect sizes and p-values were used to generate difference comodulograms and significance comodulograms, respectively. Results showed that severe AUD was associated with greater alpha-gamma PAC in both men and women compared to the unaffected groups. Men with AUD exhibited significant increases in PAC across large parts of theta-gamma. In women with AUD, increases in theta-gamma PAC were restricted to smaller domains, and accompanied significant decreases in neighboring theta-gamma subdomains. PAC strength in theta-alpha and alpha-beta frequency pair domains were also significantly greater in AUD for both men and women. The AUD-associated changes in PAC strength within the alpha-gamma, theta-beta, alpha-beta, and to a lesser degree in theta-gamma domains indicates some form of aberrant hyperconnectivity between networks within the medial prefrontal cortex during resting state of the brain.

Key Words: cross-frequency coupling, phase-amplitude coupling, alcoholism, brain oscillatory dynamics, resting state, volition

INTRODUCTION

Alcohol use disorder (AUD) is characterized by a loss of executive control over the timing and extent of alcohol consumption that is concretely manifests as an inability to moderate alcohol craving, seeking, and ingesting despite adverse consequences (Ghin et al., 2022). Investigations into the neurobiological mechanisms underlying AUD and other substance abuse disorders point to dysregulation in brain regions that mediate decision making, planning, and reward (Koob & Volkow, 2016). There has been a growing body of evidence indicating that compromised functional connectivity (FC) contributes to the dysregulation in these brain networks (Kinreich, McCutcheon, et al., 2021; Meyers et al., 2021; Song et al., 2024). Conceptually, FC refers to a statistical measure of coordination of neural activity between different brain regions across time, and several methods for extracting FC metrics from functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) data have been developed (Constable et al., 2013; Wang et al., 2014). AUD-associated changes to FC have been reported using methods such as fMRI seed-based connectivity analyses and EEG coherence (Kamarajan et al., 2020; Kinreich, McCutcheon, et al., 2021; Suk et al., 2021; Woisard et al., 2021), though these measures do not exhaust the ways in which connectivity can be realized. Brain generates oscillations across a wide range of frequencies and neural assemblies operating under different frequency regimes coordinate their activity to achieve functional connectivity (Canolty et al., 2006).

Cross-frequency coupling (CFC) is an umbrella term referring to putative mechanisms for coordinating the activity of neural assemblies oscillating at different frequencies, and these mechanisms have been associated with both healthy functioning as well as psychiatric and neurological disorders (Yakubov et al., 2022). Phase-amplitude coupling (PAC) is one such mechanism where the phase at one brain frequency modulates the amplitude at another typically higher frequency (Canolty et al., 2010). PAC is one way by which functional connectivity can be achieved where fast, high amplitude oscillations in one neuronal network are preferentially generated at a phase angle, often at peak or trough, of a slower frequency oscillation from another network (Deshpande et al., 2022; Huber et al., 2021; Marzetti et al., 2019). Early studies investigating PAC found significant relationships between theta phase and high amplitude gamma between different regions of rat hippocampus during exploratory behaviors (Bragin et al., 1995). Subsequent studies further elaborate the role of hippocampal theta-gamma PAC in learning and memory (Axmacher et al., 2010; Canolty et al., 2006; Lega et al., 2016; Wulff et al., 2009). PAC is not limited to hippocampus but involves several cortical regions. Cortical PAC has been found between cortical layer-specific neural networks oscillating at different frequencies, with gamma activity from cortical layers 4/5 being modulated by phase of alpha rhythms generated in layers 2/3 (Spaak et al., 2012).

Many of the studies investigating putative roles that PAC plays in addictive disorders have centered on drug effects on the medial prefrontal cortex (mPFC), a core part of the brain reward system that has been shown to be intimately involved with alcohol and drug-related learning and memory (Abernathy et al., 2010; Sun et al., 2011). Increased

theta-gamma PAC strength within prelimbic cortex, a part of mPFC, has been demonstrated in heroin addicted rats during conditioned place preference (Zhu et al., 2019). Rats trained to associate cocaine delivery with foot shock persisted in cocaine seeking behavior after inactivation of prelimbic cortex by GABA agonists highlighting the role this part of the mPFC plays in terminating motivated behaviors that are harmful or noxious (Limpens et al., 2015). Moreover, long-term alcohol use appears to modify the mPFC in such a way to facilitate impulsive or compulsive behaviors, co-morbid features of AUD (Klenowski, 2018). The mPFC appears to encode the intention to drink alcohol, and when contribution of mPFC in decision-making to drink alcohol is diminished, subcortical brain regions involved in habitual behaviors are possibly left as primary driver of alcohol consumption (Linsenbardt et al., 2019).

Our understanding of the neurophysiological, genetic, and environmental underpinnings of AUD has benefited greatly over the past several decades from the Collaborative Study on the Genetics of Alcoholism (COGA), an interdisciplinary project that has been continuously accumulating multi-modal, multi-generational longitudinal data from families afflicted by AUD (Agrawal et al., 2023; Dick et al., 2023; Johnson et al., 2023). Resting state EEG recordings from COGA participants represent just one of the multiple test batteries from which important discoveries related to functional connectivity mechanisms of AUD have been made (Kinreich, Meyers, et al., 2021; Meyers et al., 2023). Resting state EEG has previously been shown to be a stable individual characteristic and highly heritable (Chorlian et al., 2007; van Beijsterveldt et al., 1996). Researchers using COGA's resting state EEG data found evidence indicating that increased beta (12-28 Hz) band power could be a risk factor for the development of AUD as it was found not only in individuals with AUD (Rangaswamy et al., 2002), but also in the young offspring of men with AUD (Rangaswamy et al., 2004). Investigations of the effects of AUD on EEG coherence, a measure of neural network synchronization, during resting state found increases in inter-hemispheric coherence in the theta band (6-7 Hz), indicating significant alterations in functional connectivity of cortico-cortical and thalamocortical networks from non-alcoholic controls (Porjesz & Rangaswamy, 2007).

While compromised functional connectivity in the brain has been seen with fMRI and EEG coherence in AUD, to date, there have not been any investigations into possible associations between AUD diagnosis and PAC, though acute alcohol intoxication in healthy subjects has revealed reductions in theta-gamma and delta-gamma PAC in frontal and parietal EEG channels during resting state (Lee & Yun, 2014). Identifying new measures to characterize brain networks and functions underlying AUD will deepen our understanding of risk factors and resilience and enable designing effective treatments for AUD.

In the current project, we seek to identify the phase-amplitude frequency pair domains in which significant differences in AUD-associated PAC appear, and characterize the magnitude and direction of change in AUD-associated PAC. EEG resting state data drawn from COGA participants is used to compare resting state PAC estimates between those with severe AUD (DSM-5, 6+ symptoms) and unaffected controls We focused on

the frontocentral EEG channel FZ to illuminate any possible associations between AUD and PAC in the mPFC.

METHODS

Sample

The sample in the current study was drawn from the Collaborative Study on the Genetics of Alcoholism (COGA), a decades-long longitudinal national project following families affected with AUD and comparison families in a carefully characterized enriched family sample with data collection in multiple domains to investigate biological mechanisms underlying risk, development and consequences of alcohol addiction (Agrawal et al., 2023; Ehringer, 2023; Johnson et al., 2023; Meyers et al., 2023).

COGA participants completed comprehensive diagnostic clinical interviews, including determining whether they satisfied DSM-5 criteria for AUD (Dick et al., 2023), along with a battery of EEG assessments including resting state recordings (Meyers et al., 2023). In this study, associations between AUD and PAC were assessed using EEG recordings acquired during resting state eyes closed condition as part of COGA project.

COGA participants were selected when they were between 25 and 50 years old so that results from this sample would reflect the typical adult brain without potential confounds in interpretation from the effects of adolescence or senescence. The human brain, and the prefrontal cortex in particular, doesn't reach full maturity to adulthood until the mid-to-late 20s (Arain et al., 2013). Control and experimental groups were age-matched for further control over possible age-related confounds (Table 1). We compared unaffected controls with participants diagnosed with severe AUD, defined as having 6 or more of the 11 criteria for AUD diagnosis (DSM-5).

Table 1. Participant demographics

	Ages		**Age matching**
	AUD	Unaffected	t-test statistic (p-value)
Males	34.8 ± 6.5 (N = 203)	34.1 ± 7.0 (N = 203)	1.0235 (p = 0.3067)
Females	36.6 ± 6.5 (N = 180)	36.6 ± 6.5 (N = 180)	0.0000 (p = 1.0)

Overall, 766 subjects were included in this study. Specifically, the study cohort includes 203 AUD males. 203 unaffected males, 180 AUD females and 180 unaffected females (Table 1). Analysis was stratified by sex due to previous studies showing differences in brain structure and function between the sexes.

EEG acquisition and preprocessing

Participants were fitted with a multi-channel electrode cap that included channel FZ in the EEG montage with electrodes positioned at the nose as reference, and forehead as ground. During the acquisition of resting state EEG data, participants were seated in low lighting conditions in a temperature-controlled, sound-attenuated booth, and given instructions to remain awake and relaxed with eyes closed for the duration of the 4.25

minutes. The sampling rate was 256 Hz or 512 Hz depending on when COGA project data was collected. Impedances were kept below 5 kΩ for all EEG recordings.

Preprocessing of raw EEG signals included a low pass (1 Hz) and high pass (100 Hz) filtering with a zero-phase notch filter to remove the 60 Hz line noise. EEG signals were re-referenced to the average across EEG montage to permit use of MNE-ICAlabel package that identifies and removes non-brain artifacts. Independent components analysis was performed using infomax method generating 15 independent components for use in MNE-ICAlabel artifact processing. Only independent components classified as 'brain' or 'other' were retained for signal reconstruction, while those labeled as 'artifacts' were removed. Python package MNE was used for preprocessing steps. Coding infrastructure for this project which includes EEG preprocessing, PAC comodulogram image generation, and statistical analyses was built using Python and is available at https://github.com/lifepupil.

Phase-Amplitude Coupling

Phase frequency by amplitude frequency plots of PAC estimates, or comodulograms, were calculated using EEG recordings from midfrontal channel FZ for every 30 seconds of EEG data to capture the dynamics of the signal over time. PAC estimates were calculated for phase frequencies between 0.1-13 Hz, and amplitude frequencies between 4-50 Hz across a 224 x 224 matrix using 1 Hz window width at 0.1 Hz step to generate high resolution comodulograms. To remove bias in estimates of PAC strength, a null distribution was generated by swapping amplitude time blocks in each comodulogram (200 permutations). TensorPAC package was used to generate PAC comodulograms (Combrisson et al., 2020).

PAC Comodulogram Statistical Analysis

Average comodulogram for each participant visit was calculated for the first two minutes of the resting state task (first 4 comodulograms) to maximize the likelihood that participants were relaxed and awake but not drowsy. Statistical analyses were conducted on the resulting set of average comodulograms. For each phase-amplitude frequency pair in the 224 x 224 comodulogram matrix, PAC strength from AUD and unaffected participants were compared using Mann-Whitney non-parametric t-test. Mean differences between the AUD and unaffected groups and resulting p-values were written to corresponding frequency pair in 224 x 224 effect size and significance matrices, respectively. Once all frequency pairs had been tested, the significance matrix was used to identify any clusters of adjacent frequency pairs where PAC differences were significant. The significant PAC clusters from this initial set were then further tested by comparing PAC strength across the phase-amplitude frequency pair domain within which each of these clusters were situated. For each participant, all PAC values falling within the specified frequency pair domains were averaged, grouped by AUD diagnosis, then compared using non-parametric Mann-Whitney test for significance testing.

RESULTS

Comparisons of resting state PAC comodulograms from those with severe AUD and unaffected controls revealed patterns of increased PAC strength in the AUD group across different phase-amplitude frequency pair domains (Figure 1A) within which an initial set of significant clusters were found (Figure 1B). In AUD men, significant clusters of stronger PAC were found in the delta-gamma, theta-gamma, and alpha-gamma frequency pair domains (Figure 1B, men) that aligned with PAC “hotspots” in effect size comodulograms. Similar PAC hotspots can be found in gamma amplitude frequencies in women (Figure 1A, women) though to less a degree in the delta-gamma and theta-gamma domains and were small compared to the alpha-gamma cluster.

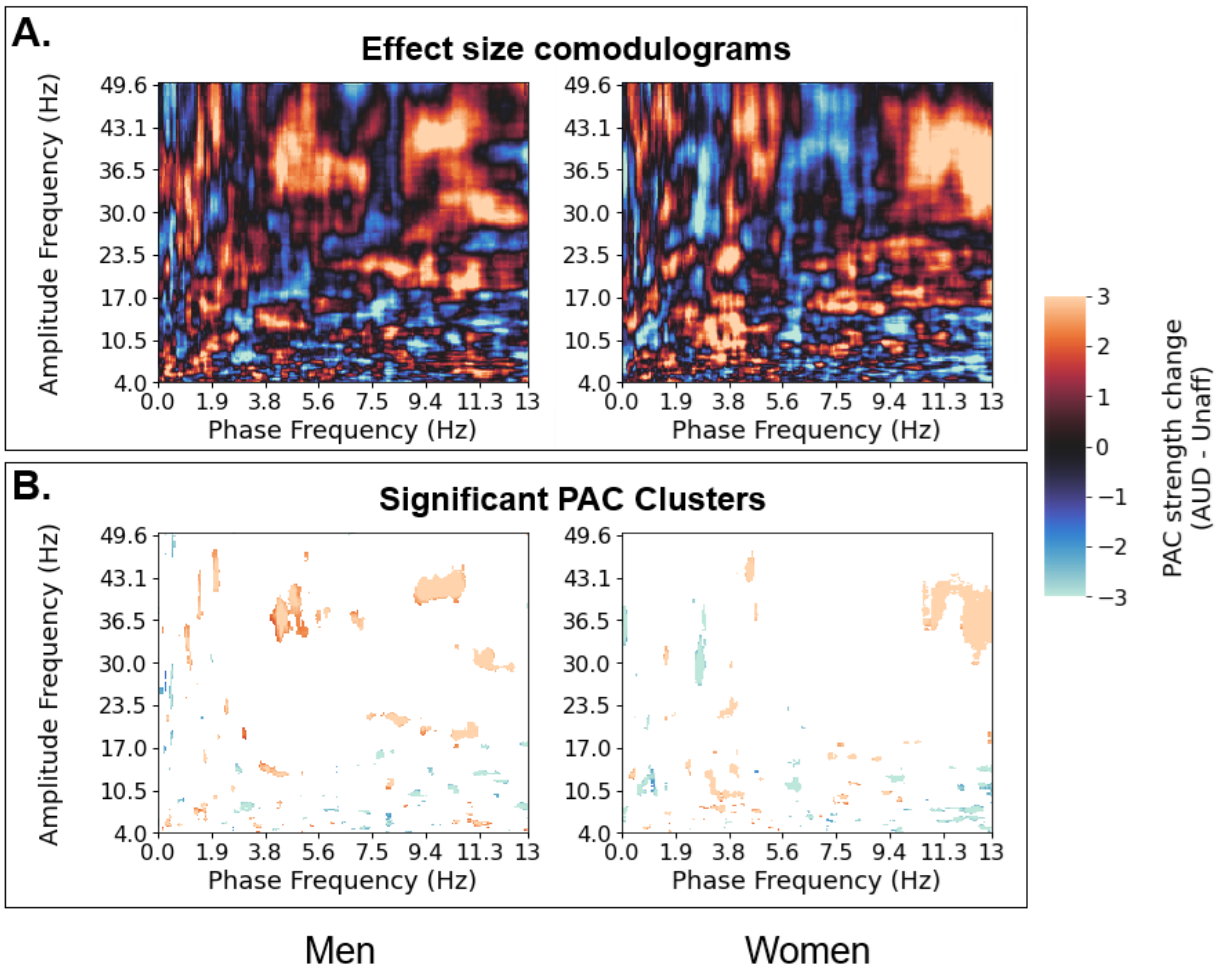

Figure 1. Differences in PAC strength between AUD and unaffected groups comodulograms by sex. (A) Effect size comodulograms depicting direction and magnitude of difference between groups for men (left) and women (right). Values reflect the mean change between AUD and unaffected groups (AUD – unaffected) with hot colors indicate greater PAC strength in AUD than in unaffected, and cool colors indicate reductions of PAC strength in AUD compared to unaffected. “Hotspots” of increased PAC strength in the AUD group can be seen across multiple PAC domains, most prominently in alpha-gamma, but also in theta-gamma, alpha-beta, and theta-alpha domains. (B) Initial set of significant PAC clusters by sex. Significant clusters appear where group differences in PAC strength at multiple, adjacent frequency pairs were found to be significant (*Mann-Whitney*, $p < 0.05$). Hot and cool colors indicate magnitude and direction of PAC differences within significant clusters. White regions indicate non-significance.

Assessment of the initial set of significant clusters using phase-amplitude frequency pair domains framed around each of the clusters in the set revealed significant AUD-associated PAC differences in both men and women at four PAC domains (Figure 2). Each of the four PAC clusters identified in the initial comodulogram analysis were tested in men and women (Table 2). Even though men and women were analyzed separately, there was considerable overlap in the PAC domains where significant differences were found.

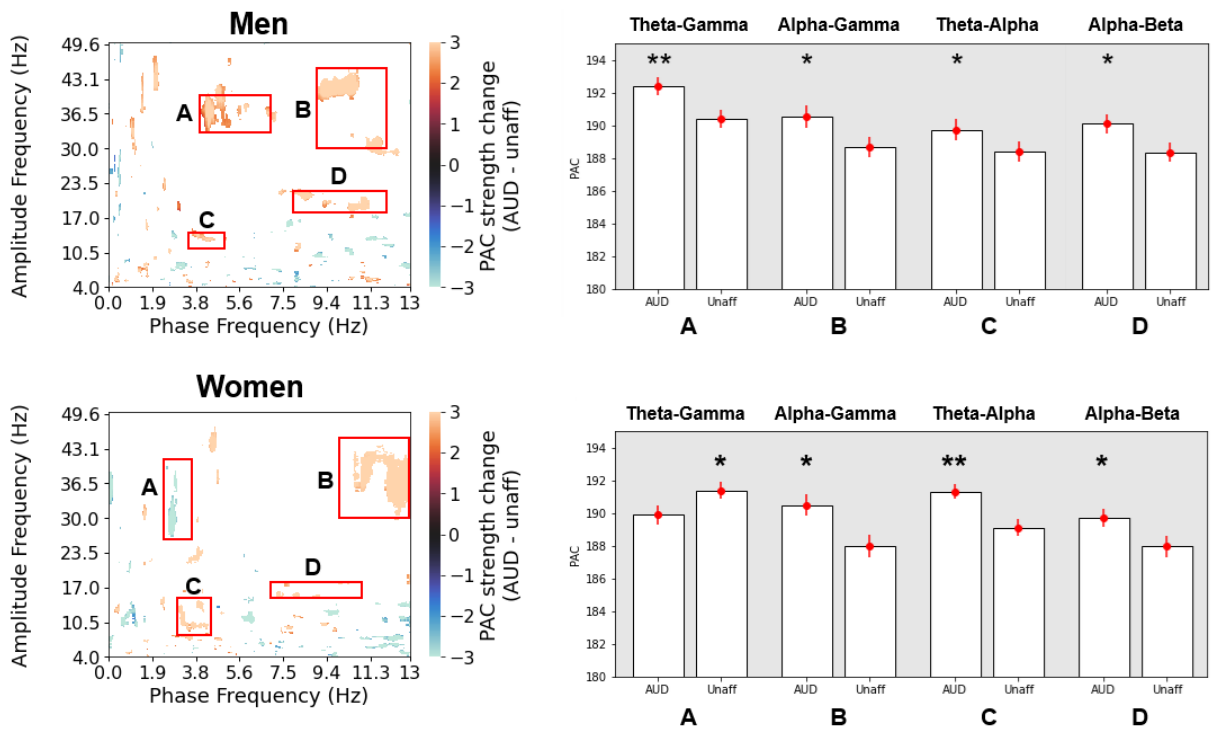

Figure 2. Cluster-bounding PAC domains where significant differences between AUD and unaffected groups were corroborated. Assessment of the initial set of significant clusters was made by comparing average PAC values from within phase-amplitude frequency pair domains framed around each of the initial set of significant clusters. Significant PAC differences were found in theta-gamma (A), alpha-gamma (B), theta-alpha (C), and alpha-beta (D) PAC domains in both men (top figures) and women (bottom figures). Bar graphs of PAC strength by group and PAC domain for each sex on right side of figure. See Table 2 for details of statistical results. Significance: $p < 0.05$ (*), $p < 0.01$ (**)

Men with severe AUD exhibited significantly elevated PAC strength compared to unaffected men at all cluster-bounding PAC domains. PAC strength for the AUD group was greater in the theta-gamma (PAC domain A, p=0.006), alpha-gamma (PAC domain B, p=0.014), theta-alpha (PAC domain C, p=0.032), and alpha-beta (PAC domain D, p=0.038) domains. Women with severe AUD exhibited, like the men with AUD, had significantly elevated PAC strength in alpha-gamma (PAC domain B, p=0.019), theta-alpha (PAC domain C, p=0.002), and alpha-beta (PAC domain D, p=0.044) domains, though unlike men, women with AUD exhibited significant decreases in PAC strength in the theta-gamma domain (PAC domain B, p=0.036).

Table 2. Results of cluster analysis for significant PAC domains						
		PAC mean ± SEM			**Phase-Amplitude frequency ranges (Hz)**	
PAC domain	**Sex**	**AUD**	**Unaffected**	**p-value**	**Phase**	**Amplitude**
Alpha-gamma	F	190.5 ± 0.7	188.0 ± 0.7	0.019	10 - 13	30 - 45
	M	190.5 ± 0.7	188.7 ± 0.6	0.014	9 - 12	30 - 45
Theta-gamma	F	189.9 ± 0.6	191.4 ± 0.5	0.036	2.4 - 3.6	26 - 41
	M	192.4 ± 0.6	190.2 ± 0.6	0.006	4 - 7	33 - 40
Alpha-beta	F	189.7 ± 0.6	188.0 ± 0.7	0.044	7 - 11	14 - 17
	M	190.1 ± 0.6	188.4 ± 0.6	0.038	8 - 12	18 - 22
Theta-alpha	F	190.9 ± 0.5	188.6 ± 0.7	0.002	3 - 4.5	8 - 15
	M	189.8 ± 0.7	188.5 ± 0.6	0.032	3.5 - 5	11 - 14

DISCUSSION

The present study examined whether severe AUD diagnosis was associated with any changes in PAC strength in the midline prefrontal region as measured from channel FZ during EEG resting state eyes closed condition when compared to unaffected controls. Findings revealed significant AUD-associated changes to PAC strength in the alpha-gamma, theta-gamma, alpha-beta, and theta-beta frequency pair domains. Both men and women with severe AUD were found to have significantly increased alpha-gamma PAC, though the elevated PAC strength in AUD men was shifted to slower alpha rhythms than in AUD women. Increased alpha-beta PAC was also seen in severe AUD regardless of sex. In AUD women, the range of amplitude frequency in the alpha-beta domain was in low beta (14-17 Hz) while in AUD men it was in mid-beta band (18-22 Hz). Both men and women with severe AUD exhibited increased theta-alpha PAC than unaffected members of both sexes though with sex-specific differences in how wide the amplitude frequency range where significant PAC was seen. Theta phase modulation of alpha band amplitudes in AUD women encompassed the entire alpha frequency band (8-12 Hz). In AUD men, the range of amplitude frequency included high alpha and low beta (11-14 Hz). Difference comodulograms for both men and women revealed increased PAC strength in overlapping theta-gamma domains (Figure 1A), though subsequent cluster analysis showed significant increases only in AUD men (Table 2). The only significant decrease in PAC was found among AUD women in a slow theta-gamma subdomain.

The results of this study reveal a pattern of significant differences, mostly increases, in resting state PAC in those with severe AUD compared to unaffected controls. Assessing these results at the minimum requires addressing (1) how to interpret relative changes or differences in coupling strength or weakness to provide a frame of reference to define what constitutes pathological manifestations of PAC, and (2) the functional relevance of PAC results in the context of AUD symptomatology. We address the former by reviewing how differences in the strength or weakness of PAC translate into behavioral and physiological outcomes, and the latter by evaluating primary features of addiction like drug-seeking and drug-cue sensitivity though the neurobiological framework of top-down and bottom-up processing.

INTERPRETATIONS OF PAC STRENGTH

The results we obtained largely reveal an association between severe AUD and increased PAC than in the unaffected controls, however it remains unclear how these effects might reflect the underlying neurophysiology of AUD. The task of interpreting these results is complicated by the absence of any previous studies of putative roles PAC might play in AUD etiology. A review of earlier studies of how PAC strength changes under different experimental conditions can provide helpful context for how to interpret our results.

It is generally understood that the oscillatory dynamics of the brain captured by neuroelectric recordings reflect the coordinated interactions between groups of neurons across multiple temporal and spatial scales (Buzsáki, 2006; van Bree et al., 2025). Neurophysiological interpretations of PAC strength may benefit from comparisons with EEG coherence as they both represent measurements of these oscillatory dynamics.

Prior to any physiological interpretations, PAC is comparable to EEG coherence in that both quantify the statistical relationship between brain signal components. Where EEG coherence is a measure of the consistency of phase differences between two signals oscillating at the same frequency (Srinivasan et al., 2007), PAC measures the relationship between the phase of a lower-frequency oscillation and the amplitude of a higher-frequency oscillation (Canolty & Knight, 2010). Statistical estimates of both PAC and coherence have minimum and maximum possible values with coherence ranging between the absence of synchrony to perfect synchronization, and PAC strength ranging from the absence of any modulatory relationship between the phase of one frequency to the amplitudes at a higher frequency (no coupling) to perfect coupling.

When comparing EEG coherence or PAC strength between two conditions or with a control baseline, these differences are often interpreted as falling along an axis of hypo-connectivity to hyper-connectivity (Gonzalez et al., 2016; Hu et al., 2010; Leocani & Comi, 1999). The application of this interpretive heuristic to PAC strength, as a measure of connectivity between neuronal populations oscillating at different frequencies, might similarly predict that decreased or increased PAC should both be associated with functional deficits or extremes of functioning. Supporting evidence for this interpretation includes reports of reduced PAC strength associated with diminished emotional face discrimination by those with autism spectrum disorder (Khan et al., 2013), lower cognitive functioning scores in patients with mild cognitive impairment (Musaeus et al., 2020), and poor sleep quality in Insomnia disorder (Guo et al., 2023), while excessive PAC magnitude has been associated with pathological symptoms in obsessive compulsive disorder (Bahramisharif et al., 2016; Treu et al., 2021; Yakubov et al., 2022), and in Parkinson's disease (de Hemptinne et al., 2013; López-Azcárate et al., 2010; van Wijk et al., 2016; Yin et al., 2022). As research into cross frequency coupling in the brain has expanded over the past two decades, this initial interpretation has given way to more sophisticated models where changes in PAC strength have different effects depending on the neural circuits where they appear and their interaction with coherence of other within-frequency and cross-frequency manifestations of neural synchrony.

TOP-DOWN AND BOTTOM-UP BRAIN PROCESSES IN ADDICTION

The brains of those with AUD, as with other substance addiction disorders, are modified in such a way that their behavior is persistently biased towards drug seeking and consumption despite recurring negative consequences of such actions (Koob et al., 2016). Achieving a comprehensive understanding of the etiology of AUD is predicated on the development of data-driven conceptual frameworks that permit the mapping of symptomatology to neurobiological functioning. One such framework for brain functioning delineates top-down and bottom-up processes (Corbetta & Shulman, 2002; Rauss & Pourtois, 2013). Top-down processes mediate voluntary attentional deployment by goal-driven (re)orientation of sense organs towards planned targets in organism's environment, for example, when an organism is searching for food or mates, while bottom-up brain networks mediate involuntary orienting reflexes to that "capture" attention to salient changes in an organism's environment (Bowling et al., 2020). In the context of addiction, compulsive or impulsive alcohol-seeking behavior reflects top-down processes, while bottom-up processes mediate sensitivity to alcohol-associated cues (Arias et al., 2021; Camchong et al., 2013a; Camchong et al., 2013b; Cardenas et al., 2018; Fein et al., 2017).

Interpretation of the results reported here benefits from several studies that have investigated changes in phase-amplitude coupling either explicitly or implicitly referencing top-down and bottom-up processes.

BOTTOM-UP PROCESSES: PAC AND REWARD CUE CONDITIONING

Conceptually, bottom-up processes are stimulus-driven. Raw information from sensory organs is organized as it passes through sensory-specific brain networks to multi-modal association areas that bind manifold information streams into unitary percepts of bodily and environmental conditions within an organism's sensorium. In the development and maintenance of addiction, bottom-up processes are thought to bias attention towards drug-associated stimuli which, in turn, elicit top-down processes that promote drug-seeking behavior (Nestor et al., 2011; Rauss & Pourtois, 2013).

The increases in theta-gamma PAC strength we report here are consistent with the handful of previous studies investigating the effects of other drugs commonly associated with substance abuse disorders on PAC. Notable among them are several animal models of addiction based on conditioned place preference (CPP). The CPP paradigm employs a test chamber divided into two sides separated by a wall; in the conditioning stage, animals are administered a drug or other reward prior to placement in one side of the chamber in which they are restricted, and no reward when placed on the opposite side. During the post-conditioning stage, animals are allowed unrestricted access, without reward treatment, to both sides of the chamber during which time spent on either side is measured (Fattahi et al., 2023). Animals spend more time on the side of the test chamber in which they had undergone repeated reward-pairing, having learned to associate the side-specific sensory stimuli with reward. In one such study, Zhu and colleagues gathered local field potentials (LFP) from the prelimbic area of mPFC in

male rats before and after CPP induction with heroin (Zhu et al., 2019). As expected, heroin-addicted rats spent significantly more time on the drug-paired side than the saline-paired side. During the post-conditioned stage, LFP revealed increased relative theta power accompanied by decreased relative gamma power, and significantly greater theta-gamma PAC in the same heroin-addicted rats. In another CPP animal study targeting the basolateral amygdala for LFP recordings (Nukitram et al., 2021), researchers found that methamphetamine-treated male mice exhibited significantly enhanced theta-gamma PAC during the post-conditioning stage compared to pre-conditioning baseline. This pattern of elevated theta-gamma PAC reported in these studies are not limited to drugs of abuse but has also been seen when testing place preference conditioned by highly palatable food (Samerphob et al., 2017), indicating that increases in theta-gamma PAC are reflecting some aspect of reward related sensory cues. Our results of AUD vs. unaffected controls, adding to these accumulated results, suggest that theta-gamma frontal PAC can serve as a biomarker for neural processes involved in addiction-related processes

TOP-DOWN PROCESSES - PAC IN VOLUNTARY MOVEMENT

Top-down processes are thought to mediate volitional, goal-directed behavior in a moment-to-moment determination of what sensory information from bottom-up processes are salient, how attention is deployed, predictions about outcomes based on prior learning, and options for behavioral responses to bottom-up information about environmental conditions and the body milieu (Le Pelley et al., 2024). When these processes are functioning properly, a mismatch between bottom-up processes and outcome predictions from top-down processes facilitates learning to update the predictive model encoded in top-down brain networks.

Frontal EEG resting state measures of excessive alpha-gamma PAC strength that we found in the severe AUD group has also been reported in obsessive-compulsive disorder (OCD) patients undergoing deep brain stimulation (Figee et al., 2013; Treu et al., 2021). Abnormally elevated functional connectivity of ventrolimbic corticostriatal regions in patients with OCD has been positively correlated with severity of symptoms (Harrison et al., 2009). Compared to controls, OCD patients exhibited significant increases in alpha-gamma and low beta-gamma PAC over frontal midline and parietal electrodes when deep brain stimulation (DBS) of nucleus accumbens (NAc) was turned off, and was reduced when NAc-DBS was active (Treu et al., 2021). In another study, researchers found that excessive beta-gamma PAC in fronto-striatal circuits of OCD during resting state, eyes open was reduced with deep brain stimulation (DBS) of nucleus accumbens as was symptom severity (Figee et al., 2013). Previous studies have demonstrated alpha-gamma PAC between visual cortical sources of alpha and gamma in cortical layers 2/3 and 4/5, respectively

Excessive resting state PAC when phase frequency is in the high alpha to beta frequency range (10-25 Hz) and amplitude frequency in low to high gamma (30-200 Hz) has also been reported in Parkinson’s disease (PD) in primary motor cortex and adjacent motor regions (de Hemptinne et al., 2013; López-Azcárate et al., 2010; van

Wijk et al., 2016; Yin et al., 2022). Pathologically strong beta-gamma PAC seen in unmedicated Parkinson's disease patients was associated with more severe motor symptoms, both of which were dramatically reduced following levodopa treatment (López-Azcárate et al., 2010; van Wijk et al., 2016). PD patients also exhibited strong beta-gamma PAC in the motor cortex accompanying freezing of gait with gait freezing temporally aligned with increased beta-gamma PAC (Yin et al., 2022). It has been suggested that observed excessive PAC might reflect a pathological restriction of motor cortex to a monotonous pattern of coupling that make it less responsive to signals from brain regions mediating voluntary movement (de Hemptinne et al., 2013). In fact, results from a recent study have provided evidence indicating that temporal PAC dynamics may be as important as changes in magnitude of PAC strength. EEG measured during a finger tapping task revealed a PAC motif unfolding across movement execution that was seen in both PD patients and controls, with bradykinesia-related deficits in the PD patients associated with aberrant expressions of this PAC motif (Gong et al., 2022). These results indicate the possibility that dynamic regulation of PAC across time might be at least as important as overall changes in PAC strength.

It is interesting that AUD, OCD, and PD all represent disorders characterized by some form of dysregulated volition, with loss of voluntary control in OCD compulsive behaviors, patterns of alcohol craving and relapse, and disruptions to smooth initiation of voluntary movement in PD. Perhaps the excessive alpha-gamma and beta-gamma PAC these conditions share reflect dysfunction in overlapping brain networks underlying volitional behavior.

CONCLUSIONS

- The AUD-associated changes in resting state alpha-gamma PAC, and to a lesser degree in theta-gamma domains, may indicate resting state hyperconnectivity in medial prefrontal cortex or neighboring brain networks of individuals with severe AUD, though it remains to be determined what the functional significance of these changes to PAC strength might be.
- Evidence exists supporting an interpretation of increased theta-gamma PAC strength in mPFC of severe AUD underlying enhanced sensitivity to alcohol-related sensory cues, while increases in alpha-gamma PAC could be related to inflexible orientation towards alcohol seeking and consumption, though at this early stage there is no ruling out some other intermediary roles.

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