NeuroRegulation

Event-related Theta and Gamma Oscillations in Cue-Reactivity Test in Individuals with Opiate Use Disorder in Buprenorphine-Maintenance Program

Estate Sokhadze[1,2] and Mohamed Shaban[3]*

[1]Prisma Health-Upstate, Greenville, South Carolina, USA
[2]University of South Carolina School of Medicine-Greenville, Greenville, South Carolina, USA
[3]University of South Alabama, Mobile, Alabama, USA

Abstract

Opioid use disorder (OUD) is a major public health problem. Maintenance treatment with medication for OUD (MOUD), such as buprenorphine, has been associated with reductions in physical symptoms of withdrawal, but attentional bias towards drug cues may contribute to the high rates of noncompliance and relapse. The cue-reactivity test can be used to investigate specifics of EEG responses to drug cues. This study was aimed at comparison of EEG oscillations during exposure to drug-related and neutral images in MOUD and control participants for investigation of attention biases persistent in MOUD. We recruited 13 MOUD outpatients and 13 age-matched controls. The cue-reactivity test used emotionally neutral and drug-related images. The study used blocked design (16 images/block, 3 s/image). Time-frequency analysis of EEG from four frontal sites was performed to assess evoked, induced, and late oscillations, and theta-gamma phase-amplitude coupling during neutral and drug blocks. Exposure to drug cues in the MOUD group resulted in increased gamma and decreased theta oscillations with higher theta-gamma coupling effect. These cue-reactivity indices reflect heightened attentional bias to drug items and vulnerability to relapse in patients on MOUD and may serve as objective treatment outcomes complementing craving reports and clinical evaluations.

Keywords: EEG theta and gamma oscillations; phase-amplitude coupling; opioid use disorder; drug cue reactivity; craving; attentional bias

Citation: Sokhadze, E., & Shaban, M. (2022). Event-related theta and gamma oscillations in cue-reactivity test in individuals with opiate use disorder in buprenorphine-maintenance program. *NeuroRegulation*, *9*(1), 16–28. https://doi.org/10.15540/nr.9.1.16

***Address correspondence to**: Dr. Estate (Tato) Sokhadze, University of South Carolina School of Medicine-Greenville, 701 Grove Rd., Greenville, SC 20605, USA. Email: sokhadze@greenvillemed.sc.edu

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Opioid use disorder (OUD) is a neurobehavioral disorder characterized by repeated compulsive seeking and use of opioids that causes significant distress or impairment. OUD is accompanied by well-described physical dependence with a withdrawal syndrome and tolerance. Opioid addiction includes not only abuse of illicit heroin and other opium derivates but also misuse and abuse of prescription medications, such as hydrocodone, oxycodone, codeine, etc. OUD is now a major health problem, with initiation of prescription opioid abuse exceeding cocaine abuse in young people (SAMHSA, 2019). OUD represents a severe public health problem because of severe morbidity and high mortality. Medications for opioid use disorder (MOUD), including buprenorphine and methadone, represent evidence-based interventions for treating OUD (Blanco & Volkow, 2019). Although maintenance treatment with buprenorphine has been associated with reductions in heroin and other opiate use, concerns for intravenous misuse and other diversions exist (Simojoki et al., 2008). However, despite low physical symptoms of withdrawal, MOUD patients still demonstrate

vulnerability to relapse (MacLean et al., 2018). Craving and physiological arousal in response to drug cues may contribute to the high rates of noncompliance and relapse among opioid-dependent individuals in buprenorphine maintenance treatment.

Cue reactivity refers to a phenomenon in which individuals with a substance use disorder exhibit excessive cognitive, physiological, and behavioral responses to cues linked with their preferred substance of abuse (Carter & Tiffany, 1999; Drummond, 2001; Lubman et al., 2000). Cue-reactivity research studies typically include individuals with a substance use disorder who are exposed to a wide range of drug-specific cues (e.g., the sight of drugs, drug-use situations, etc.), and cue presentation modes such as photo images, words, imagery-based, or in virtual reality presentations (Carter & Tiffany, 1999). Cue reactivity is measured across several domains of functioning, and several measures are collected, including subjective self-reports (i.e., craving) and a wide range of physiological responses. There is a strong rationale for using the cue-reactivity test and monitoring attentional bias in individuals on MOUD. MacLean et al. (2018) found that participants with OUD exhibit a robust attentional bias and reactivity to drug-related cues even if they are engaged in MOUD, including methadone and buprenorphine. In clinical care of patients with OUD, methadone or buprenorphine dose is titrated to minimize craving, withdrawal symptoms, and use of nonprescribed opioids (Ayanga et al., 2016; Dematteis et al., 2017). Nevertheless, it is very likely that, even on MOUD, individuals with OUD continue to be reactive and sensitive to stimuli associated with opioid use. For example, some researchers have suggested that MOUD does not reduce cue-induced craving (Fatseas et al., 2011; Hyman et al., 2007). While MOUD may reduce tonic craving, acute craving associated with situational or environmental cues can persist. The impact of MOUD on attentional bias for opioids remains to be determined in future studies and warrants further investigations.

Preoccupation with drug and drug-related items is a typical characteristic of people living with a substance use disorder. Several research studies have provided support for the hypothesis that the process of alteration of attention—an attentional bias for reward stimuli—takes place in those with substance use disorder (Franken et al., 1999; Robinson & Berridge, 2008; Zijlstra, et al., 2009), and drug-related cues attain a greater salience and motivational significance (Robbins & Ehrman, 2004). One of the cognitive components of cue reactivity in substance users is the preferential allocation of attentional resources to drug-related items (Lubman et al., 2000). Patients on MOUD may show less attentional bias towards drug-related stimuli than active drug users, but they still show excessive psychophysiological responses during exposure to drug cues.

Craving, a process in which a stimulus is recurrently associated with feelings of pleasure, such as those elicited by drugs, is a key factor that motivates compulsive substance use (Drummond, 2001; Rosenberg, 2009). Through this stimulus-response learning process, drug-related stimuli attain a strong incentive-motivational value and elicit expectations of drug consumption and the feelings of pleasure associated with such consumption (Wilson et al., 2004). These drug-associated stimuli can elicit both subjective reports of craving and heightened activation as reflected by evoked EEG responses. The cue-reactivity paradigm is a widely used method for investigating drug craving. If MOUD treatment does influence reactivity to drug cues, such effects would be observed in physiological responses that reflect brain regions that mediate integration of motivational or affective responses. Surprisingly, few studies have investigated the association between attentional biases to drug-related information, cue reactivity, the level of craving, and their EEG manifestations during craving elicited in drug cue-reactivity tests in laboratory conditions. Assessing the level of craving as a measure of the subjective and affective experience of wanting opiates with concurrent psychophysiological measures provides a critical opportunity to investigate such an association. As attentional bias to drug cues may be predictive of poorer recovery outcomes, it is important to identify such underlying affective and neurophysiological processes (Frankland et al., 2016). It is possible that individuals on MOUD may exhibit diminished subjective and physiological cravings for opioids, suggesting an important MOUD may diminish the attention bias for drug-related stimuli. Therefore, it is important to investigate whether individuals on MOUD still exhibit attentional biases and excessive reactivity to drug-related cues.

The present study examined whether the opioid-related attentional bias operates in early pre-attentive sensory processes, such as initial orienting, in sustained attention and emotional responses, as reflected by time-frequency measures of EEG oscillations during exposure to drug-related pictorial stimuli. Of particular interest in this regard are theta (4–8 Hz) and 40 Hz-centered gamma oscillations.

Previous research suggests that theta oscillations are indicative of neural processes involved in the integration of perceptual stimuli and subsequent sequential ordering of that information, which are reflected in gamma synchronization processes (Köster et al., 2019; Lisman & Jensen, 2013). Gamma frequencies are closely associated with sensory processing, working memory, attention, and long-term memory (Lisman & Jensen, 2013).

Event-related oscillations are divided into "evoked" and "induced" components in terms of the relationship of the oscillations to the event or stimulus; these different components reflect different neural processes (Başar, 2013; Bertrand & Tallon-Baudry, 2000; Herrmann & Demiralp, 2005; Herrmann & Mecklinger, 2000; Herrmann et al., 2014). With regard to gamma oscillatory activity, there is an early, evoked gamma response that is phase-locked to stimulus onset and occurs within 150 ms of stimulus onset. This response seems to reflect matching of bottom-up signals with memory content at a perceptual processing level. There is also induced gamma activity that is not phase-locked to stimulus onset and occurs later with a variable onset, although it has been reported to start at around 250 ms (Herrmann et al., 2014; Tallon-Baudry & Bertrand, 1999). This response might be a signature of utilization processes such as response selection or context updating (Herrmann et al., 2014; Tallon-Baudry & Bertrand, 1999). Evoked gamma-band activity is indicative of early sensory processing and the integration of perceptual information within the same cortical region. In contrast, induced gamma-band activity reflects the integration of feed-forward and feedback processing in a broad network of cortical brain regions (Herrmann & Mecklinger, 2000).

EEG oscillations exhibit phase–phase coupling in certain physiological states or during performance of specific tasks, such as processing of new memories, spatial navigation, and memory retrieval. The prefrontal cortex has also been reported to engender interactions between neural oscillations, such as coupling of theta and gamma oscillations waves, in individuals with substance use disorders (Zhu et al., 2019). Research on neural oscillations suggests that the interaction between the brain regions is processed by a cross-frequency coupling between low-frequency band phase and high-frequency band amplitude. In particular, the cross-frequency coupling between the theta (4–8 Hz) phase and the gamma (predominantly in 40 Hz centered range, e.g., 35–45 Hz) amplitude may play an important functional role in emotion-related cognitive activities, as well as learning and memory (Canolty et al., 2006; Canolty & Knight, 2010). Based on the important function of coupling between theta and gamma in a large number of affective and cognitive processes, in this study we chose the wavelet-based EEG analysis of theta and gamma as the target frequency bands (Wang, 2021). Specifically, EEG responses to visual stimuli are known to be marked by readily observed changes in theta and gamma oscillations. Cross-frequency coupling measures the association between the theta oscillation phase and the gamma power. Higher-magnitude theta–gamma coupling values translate into greater gamma amplitude during the theta phase (Lisman & Jensen, 2013). Theta–gamma coupling has been shown to be a functionally important functional role for processes related to long-term memory and affective responses. Previous research suggests that phase-amplitude coupling between the prefrontal theta phase and posterior gamma amplitudes represents signaling between prefrontal cognitive control mechanisms and processing of ordered, sequential information during memory encoding or the reactivation of ordered, sequential information during memory retrieval in posterior cortical regions (Köster et al., 2014).

Many studies have analyzed EEG parameters by computing average values across only evoked and induced phases of gamma activity (Herrmann & Demiralp, 2005; Herrmann et al., 2014; Tallon-Baudry, 2003; Tallon-Baudry & Bertrand, 1999). However, besides responses within the first 500 ms window (e.g., N100, P200, N200, P300, N400), the late positive potential (LPP), also provides a valuable event-related potential (ERP) measure sensitive to affective responses (Hajcak et al., 2010). The LPP is a positive-going waveform that begins approximately 300 to 2000 ms after the onset of a stimulus that can persist for several seconds (Hajcak et al., 2011). The LPP signals processing of attention toward highly salient, motivating positive or negative affective stimuli (Castro et al., 2019; Hajcak et al., 2010; Schupp et al., 2000; Schupp et al., 2004). Because the LPP reflects the processing of motivationally salient affective stimuli, it may play an important role in the affective processing alterations observed among individuals with substance use disorders. In particular, the LPP may indicate excessive reactivity to emotionally negative stimuli. Theta and gamma oscillations within 600–800 ms occur within the window typical for the maximum of LPP and should be assumed to be reflecting similar motivational and affective processes.

This study aimed to explore the mechanism of processing drug-related cues in people with OUD receiving MOUD using frontal EEG responses elicited during exposure to neutral and drug-related pictorial stimuli. Our hypothesis was that participants with OUD on MOUD as compared to age-matched participants without OUD will show excessive reactivity to drug-related cues manifested in event-related theta and gamma EEG oscillations and their phase-amplitude coupling.

Methods

Participants

All participants in the MOUD group were recruited from the local office-based addiction recovery program and their diagnosis and eligibility were confirmed by clinical evaluations and drug tests. Participants in the control group were recruited from the community with advertisements posted using various media. Eligibility criteria for control group participants included being at least 18 years old, having no substance use disorders, and having no history of psychiatric conditions. Eligibility was confirmed through prescreening surveys.

Each participant signed informed consent approved by the local Institutional Review Board (IRB). The mean age of participants in the MOUD group (N = 13) was 36.77 ± 6.86 years, while in the control group (CNT, N = 13), the mean age was 33.38 ± 10.81 years. Age difference between group was not statistically significant, $t(12) = 1.69$, $p = .114$). Patients in the MOUD group were already enrolled in buprenorphine maintenance treatment for 10.2 ± 10.9 months. Gender was not matched between groups, as there were seven males in the MOUD group and one male in the CNT group.

Cue Reactivity Testing

Cue reactivity to salient drug or alcohol cues provides a means to examine neurophysiological activity indices of craving among individuals with substance use disorders (Back et al., 2014; MacLean et al., 2018; Zijlstra et al., 2009). The study used the pictorial drug- and affective cue reactivity test procedure to measure subjective drug craving and neurophysiological responses. Images for this procedure have been obtained from a standardized database (International Affective Picture System [IAPS]; Lang et al., 2001). Blocks of emotionally positive, negative, neutral, and drug-related pictures were presented using a blocked design, and participants provided a subjective rating of drug craving after each block. Each block of pictures consisted of 16 images that were each presented for 3 s. Order of the blocks was counterbalanced, but block of neutral cues was always preceding the drug cues block. The current study focused only on analysis of the EEG responses to neutral and drug-stimuli blocks.

Data Acquisition and Signal Processing

Physiological activity during cue reactivity test was recorded with Nexus-10 psychophysiological monitor with BioTrace+ software (Mind Media, BV, Herten, The Netherlands) with custom-made protocol. EEG activity was acquired at 256-Hz sampling rate (bandpass filter, 1–45 Hz, Notch filter at 60 Hz). Electroencephalogram (EEG) was recorded from four frontal sites (Fp1, Fp2, F3, and F4) prepared using NuPrep with Bluetrode Ag/AgCl electrodes with Ten20 gel referenced to linked earlobes with ground electrode placed at the nasion. Analysis of EEG responses was initially conducted to assess absolute amplitude and absolute power, as well as relative amplitude and relative power of delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (35–45 Hz) bands during resting conditions and event-related EEG responses to emotionally neutral and drug-related stimuli. Our pilot study (Ortiz et al., 2021) showed most prominent group differences in relative amplitude and relative power of theta and gamma responses in neural and drug cue conditions and our wavelet-based analysis in this study was focused only on theta (4–8 Hz) and gamma (35–45 Hz) oscillatory responses.

Method of Wavelet Analysis and Phase-Amplitude Coupling Evaluation

1. EEG segments of 256 time-samples corresponding to each of the 16 stimuli at each EEG channel is filtered in the frequency domain into theta (θ, 4–8 Hz), and gamma (γ, 35–45 Hz) using a sequence of Continuous Wavelet Transform (CWT) and a frequency-localized inverse CWT operations (Torrence & Compo, 1998). The CWT of the EEG segment *x(t)* (i.e., $X(\tau, s)$) is calculated as follows:

$$X(\tau, s) = \frac{1}{\sqrt{s}} \int_0^{\infty} x(t)\, \psi\left(\frac{t-\tau}{s}\right) dt$$

where ψ is the Morlet analysis wavelet, τ is the time shift of the wavelet, and s is the scale of the wavelet. The scale s is inversely proportional to the Fourier frequency (Torrence & Compo, 1998).

2. To extract the frequency components of the EEG signal within the theta and gamma frequency bands, a frequency-localized inverse CWT is used where the coefficients $X(\tau, s)$ corresponding to the respective frequency range are extracted and an inverse CWT is applied to the extracted coefficients $X(\tau, s)$ as follows:

$$y(t) = \frac{1}{C}\int_{s_2}^{s_1}\int_{0}^{\infty}\left(\frac{1}{s}\right)^{\frac{5}{2}} X(\tau, s)\,\varphi\left(\frac{t-\tau}{s}\right) d\tau ds$$

where *y(t)* is the theta or gamma component of the EEG signal, φ is the dual function of ψ such that both functions are orthonormal, and *C* is a constant. Also, s_1 and s_2 correspond to the lowest and highest frequencies respectively in the frequency bands of the theta or gamma waves.

3. Artifacts or anomalies within the theta and gamma time-series are discarded such that:

$$\mu_{y(t)} - 2\sigma_{y(t)} \leq y(t) \leq \mu_{y(t)} + 2\sigma_{y(t)}$$

where $\mu_{y(t)}$ and $\sigma_{y(t)}$ are the mean and standard deviation of *y(t)*.

4. The peak amplitude and latency for the evoked, induced and late waves are determined from the theta and gamma time-series as follows:

$$A_p = \max_t y(t) \qquad t_0 \leq t \leq t_f$$
$$\mathrm{y}\left(T_p\right) = \max_t y(t) \qquad t_0 \leq t \leq t_f$$

where A_p and T_p are the amplitude and latency of the peak. Also, t_0 and t_f represent the start and the end of the time-interval within which the evoked, induced or late waves are existent.

5. Phase amplitude coupling (*PAC*) is also calculated as follows (Tort et al., 2010):

a. A Hilbert transform is applied on *y(t)* for the evoked, induced, and late theta and gamma waves to generate a complex signal *h(t)* whose phase h_{ph} *(t)* is calculated for the theta wave and amplitude h_{amp} *(t)* is calculated for the gamma wave. The Hilbert transform can be represented as a linear convolution of *y(t)* with the Hilbert operator function ($1/\pi t$) as follows:

$$h(t) = y(t) * \left(\frac{1}{\pi t}\right)$$

b. A linear phase interval *P* is defined from -π to π and split into a number of bins (N_b).

c. The bin indices (i_b) of the phase values in *P* at which each value in h_{ph} *(t)* approximately matches are estimated. Further, the means of h_{amp} *(t)* values (i.e., μ_{Gm}) for each distinct value of i_b are calculated. μ_{Gm} is further normalized where

$$\hat{\mu}_{Gm} = \frac{\mu_{Gm}}{\sum_{n=1}^{N_b}\mu_{Gm}}$$

d. The Kullback-Leibler Distance (d_{KL}) which represents the divergence of the amplitude distribution of $\hat{\mu}_{Gm}$ from a uniform distribution (u_{Gm}) is derived as follows:

$$d_{KL} = \sum_{n=1}^{N_b} \hat{\mu}_{Gm} .* \log\left(\hat{\mu}_{Gm} ./ u_{Gm}\right)$$

where the product and division operations are executed in an elementwise fashion. Further, u_{Gm} is represented as follows:

$$u_{Gm} = \frac{1}{N_b}$$

e. The *PAC* is then derived from the d_{KL} as follows:

$$PAC = {}^{d_{KL}}\!/_{\log(N_b)}$$

Statistical Data Analysis

The data for all dependent variables was analyzed using repeated-measures ANOVA with factors (all within-participants) such as *Condition* (Neutral vs. Drug) and *Hemisphere* (Left vs. Right) for four EEG sites (Fp1, Fp2, F3, and F4), and only the *Condition* factor for their combinations (prefrontal, Fp1-Fp2, frontal F3-F4). The between subject factor in this cue-reactivity task was *Group* (MOUD vs. Controls). Single trial EEG theta and gamma oscillations were analyzed for above four anterior frontal EEG sites and time window (40–180 ms [evoked], 240–500 ms [induced], and late [600–800 ms] post-stimulus). All datasets were evaluated for normality and confidence intervals were defined for each set. Amplitude, latency, and PAC coupling coefficients were calculated for evoked, induced, and late theta and gamma oscillations at all four EEG sites and averaged during neutral and drug blocks (16 pictures per block) in MOUD and CNT groups. Each measure was analyzed for individual EEG sites (e.g.,

Fp1, Fp2, F3, F4) and for their combinations (Fp1-Fp2, F3-F4). Post-hoc analysis was conducted using the Tukey test for groups with equal sample size. Some group differences were tested with two-tailed Student's *t*-tests and/or one-way ANOVA. In all repeated measures ANOVAs, Greenhouse-Geisser (GG)-corrected *p*-values were employed where appropriate. Effect size was estimated using partial eta squared (η^2) and observed power measures. IBM SPSS software (v.27) was used for statistical analysis.

Results

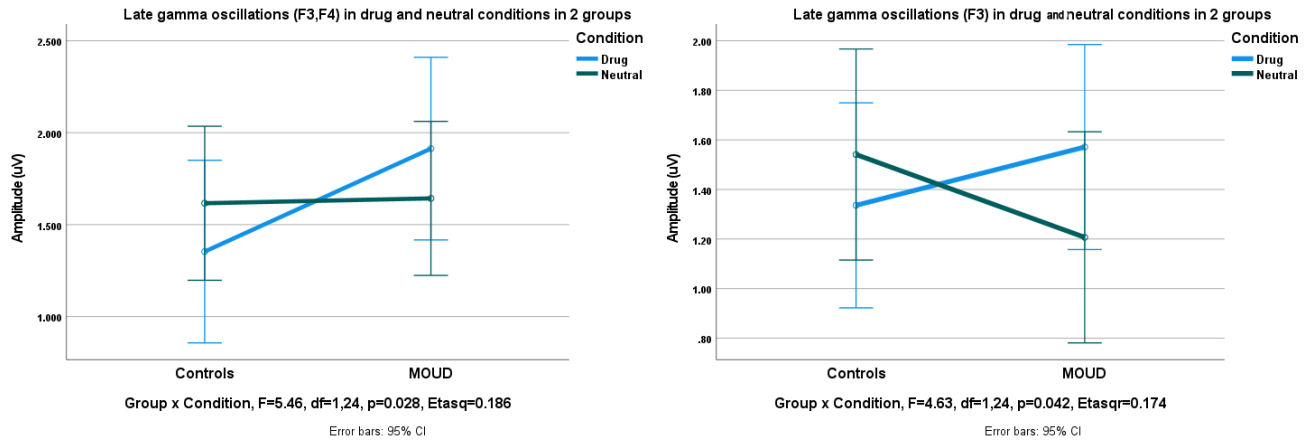
Evoked, Induced, and Late Theta and Gamma Amplitude and Latency

***Gamma Oscillations*.** ANOVA results showed a main effect of *Condition* (Drug vs. Neutral) on evoked, induced, and late gamma oscillations only in the MOUD group (all *p*s < .01). Prefrontal sites Fp1 and Fp2 had higher amplitude of evoked gamma in MOUD as compared to control group in the drug stimuli condition, 1.42 ± 2.46 μV in MOUD vs. 0.98 ± 1.60 μV in controls, $F(1, 24) = 5.57$, $p = .028$. In the neutral condition at Fp1-Fp2 sites, the amplitude of gamma in the MOUD group was lower than in the neutral condition as compared to the control group, 1.19 ± 0.52 μV in MOUD vs. 1.74 ± 0.72 μV in the control group, $F(1, 24) = 4.58$, $p = .043$. In the MOUD group, induced gamma amplitude at Fp1-Fp2 was also higher than in the control group, $F(1, 24) = 6.06$, $p = .022$. More significant group differences were found for the late gamma at F3 and F4 sites.

In particular, for these frontal sites *Condition* (Drug vs. Neutral) x *Group* (MOUD vs. Control) interaction was statistically significant for late gamma oscillation, $F(1, 24) = 5.46$, $p = .028$, $\eta^2 = .186$, observed power = 0.613. Significant group differences were found for the late gamma at the F3 site. For this frontal site *Condition* (Drug vs. Neutral) x *Group* (MOUD vs. Control) interaction was statistically significant for late gamma oscillation, $F(1, 24) = 4.63$, $p = .042$, $\eta^2 = 0.174$, observed power = 0.570. This effect for combined F3-F4 and F3 late gamma oscillations is illustrated in Figures 1 and 2.

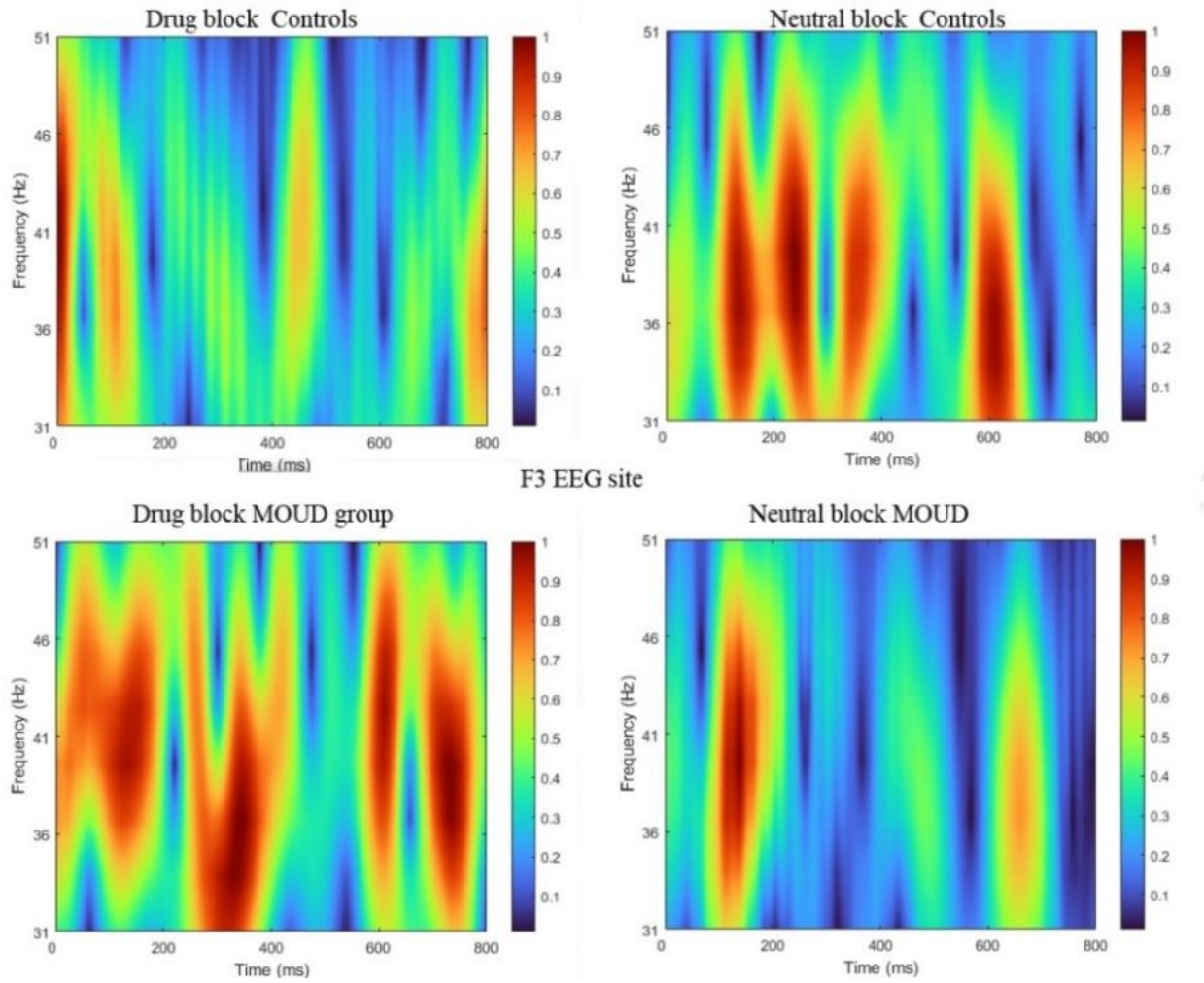
Latency of induced gamma oscillations at F3-F4 sites in drug conditions was shorter in the MOUD group, 412 ±70 ms in controls vs. 351± 62 ms in MOUD, $F(1, 24) = 5.07$, $p = .035$.

Figure 1. *Late Gamma Oscillations in Drug and Neutral Conditions in Two Groups.*



Note. Late gamma oscillations at the frontal sites (F3, F5) shows *Group* x *Condition* interaction with lower gamma oscillations amplitude in neutral condition (left). Similar interaction is presented for the left frontal site (F3) showing in addition higher late gamma amplitude in the drug condition (right).

Figure 2. *Normalized Images of Time-Frequency Power of Gamma Oscillations at the Left Frontal Site (F3) Illustrate Group Differences in Neutral and Drug Conditions.*



Note. MOUD group has higher power of induced and late gamma oscillations in the drug condition.

Theta Oscillations. Most notable group differences and interactions were found for induced theta oscillations at the frontal sites (F3, F4). *Condition (*Drug vs. Neutral*)* x *Hemisphere (*F3, F4*)* x *Group (*MOUD vs. Control*)* effect was statistically significant and expressed in a lower theta amplitude in the MOUD and was especially well pronounced at the right hemisphere (F4). This interaction is illustrated in Figure 3. The effect expressed in higher theta in the control group as compared to the MOUD group in neutral and drug conditions is depicted at Figure 4.

Latencies of the late theta oscillations at the prefrontal sites (Fp1, Fp2) showed *Condition x Group* interaction (F = 7.24, p = .014) with shorter latencies in the neutral cues condition in the CNT group (703 ± 49 ms) as compared to the MOUD group (720 ± 54 ms). Latency of induced frontal (F3, F4) oscillations in the drug cue condition was shorter in the MOUD group as compared to controls (351 ± 64 ms vs. 412 ± 71 ms).

Figure 3. *Condition* x *Hemisphere x Group Interaction of Induced Theta Oscillations Was Statistically Significant with Lower Power of Theta at the Right Hemisphere (F4, on the Left) in the MOUD Group in Drug Condition.*

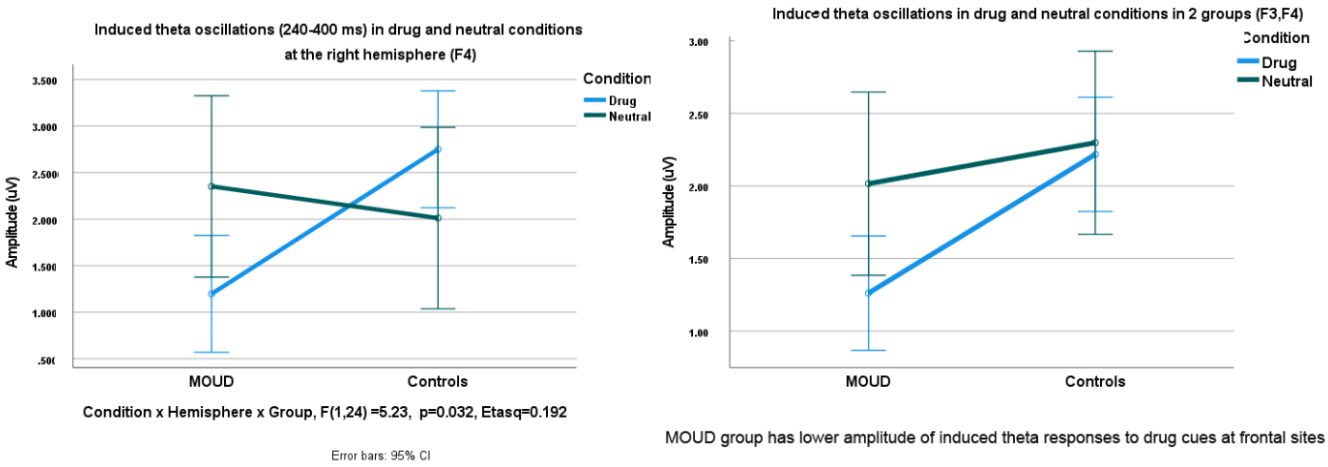
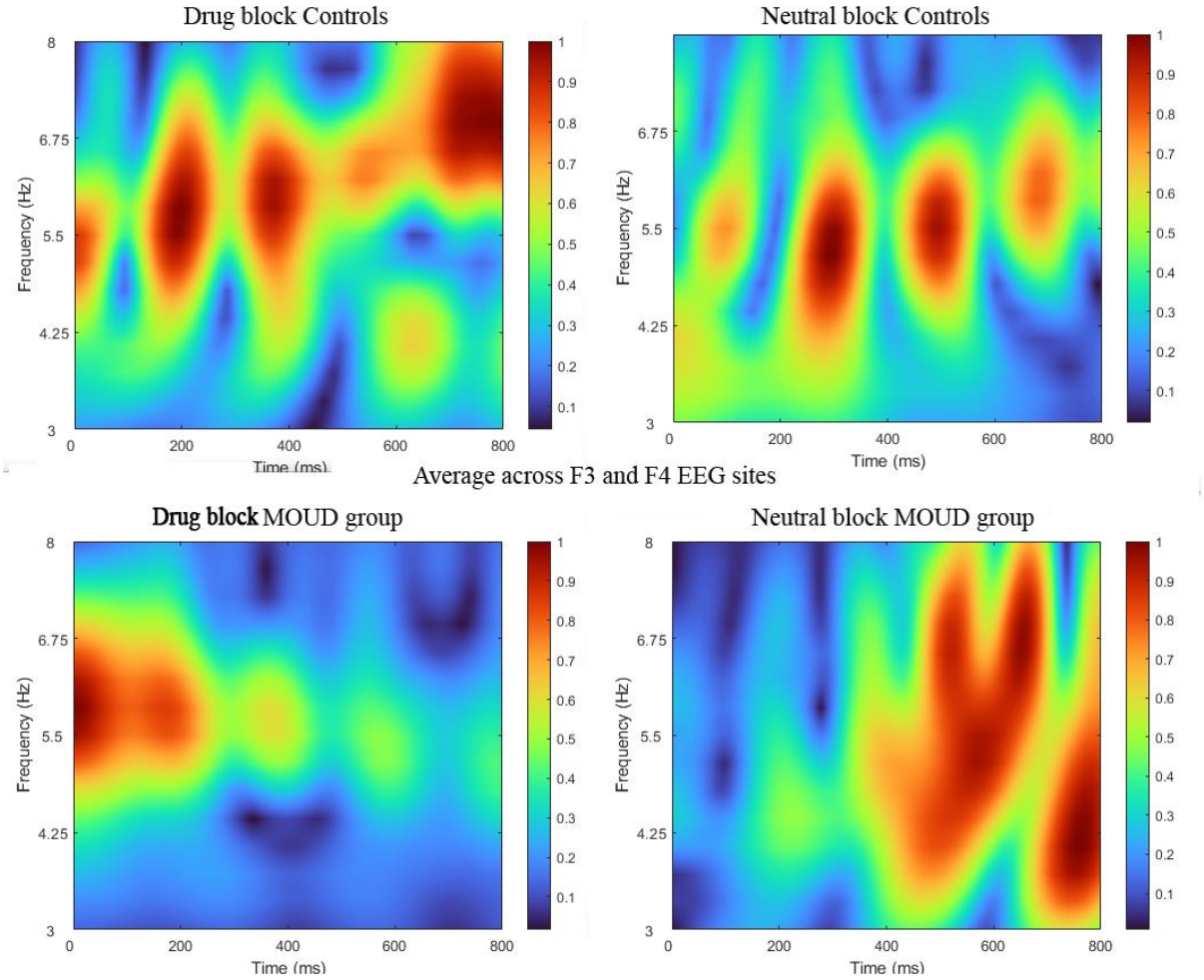


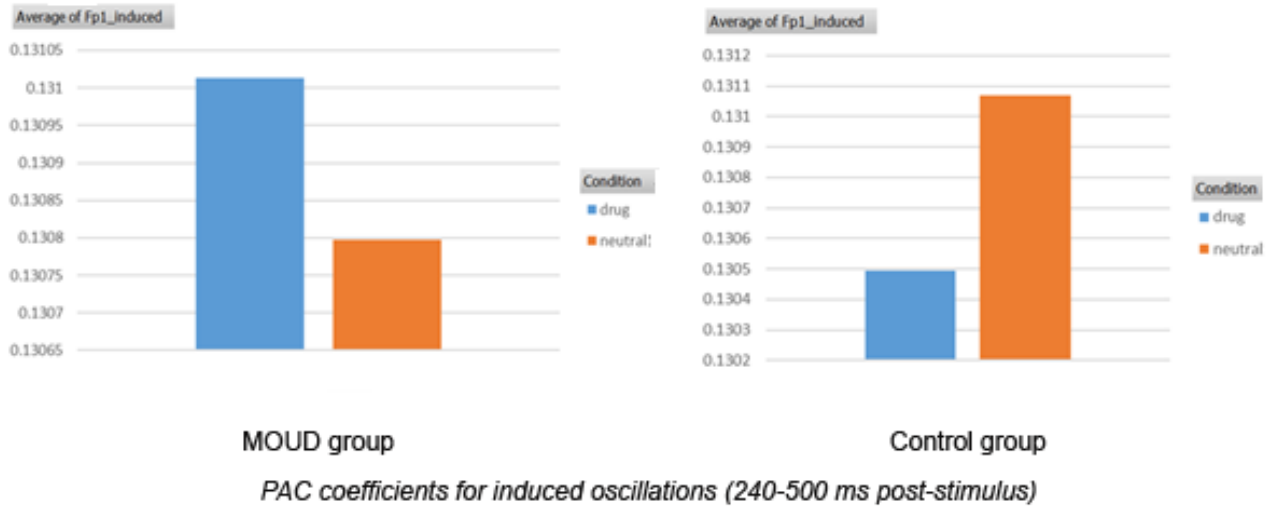
Figure 4. *Normalized Time-Frequency Power of Theta Images at the Frontal Sites (F3-F4) Illustrate Group Differences in Neutral and Drug Conditions.*



Note. MOUD group has lower power of induced and late theta oscillations in the drug condition. Control group has comparable theta oscillations in both conditions.

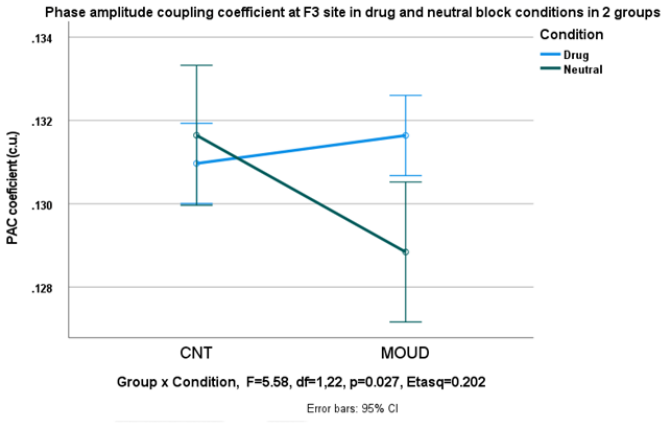
Most of the statistically significant interactions of theta–gamma phase–amplitude coupling was found during induced theta and gamma oscillations (240–500 ms range). At the left prefrontal site (Fp1) *Condition* x *Group* interaction of induced theta–gamma PAC was significant, $F(1, 24) = 5.19$, $p = .033$, $\eta^2 = 0.191$, observed power = 0.586); while at the frontal F3 site this interaction had even higher-powered effect, $F(1, 22) = 5.58$, $p = .027$, $\eta^2 = 0.202$, observed power = 0.618. These interactions are presented in Figures 5 and 6.

Figure 5. *Theta–Gamma Phase-Amplitude Coupling Coefficients in Drug and Neutral Blocks in MOUD and Control Groups (Fp1).*



Note. Induced theta–gamma phase–amplitude coupling coefficients in drug and neutral conditions at the left prefrontal site (Fp1) in both groups. PAC coefficients were higher in drug condition and lower in the neutral one in the MOUD group, whereas controls showed an opposite effect.

Figure 6. *Induced Gamma and Theta Oscillations PAC in MOUD and Control Groups.*



Note. Condition x Group interaction of induced theta and gamma oscillations' PAC at the left frontal site (F3) with lower theta–gamma coupling in the MOUD group during neutral condition. Post-hoc *t*-test yielded group difference of the induced theta–gamma PAC coefficients at Fp1 and F3 between neutral and drug conditions; Fp1, $t(24) = 22.56$, $p < .001$; F3, $t(22) = 2.54$, $p = .032$.

Discussion

Low frequency (4–8 Hz) and high frequency EEG gamma activity within the 35–45 Hz range were examined using time-frequency analysis during exposure to emotionally neutral and drug-related picture in participants with OUD enrolled in buprenorphine-based maintenance treatment (i.e., MOUD participants) and healthy controls. The MOUD participants differed significantly from control group subjects, exhibiting both decreased theta oscillations and increased 40 Hz-centered EEG oscillations with higher phase-amplitude coupling during block with the drug cues. The participants on MOUD, but not control subjects, showed significant increases in activation in the form of several bursts of high frequency oscillations in response to drug-related stimuli. Participants in the control group, but not MOUD subjects, showed significant increases in activation of low frequency theta oscillations in frontal areas while viewing emotionally neutral images with a significant group x stimulus type interaction effect at both prefrontal and frontal EEG sites.

Systemic modulation of the power of gamma oscillations over the course of the theta cycle suggests that there is a relationship between theta–gamma coupling such that attentional and emotional processes are activated during exposure to drug-related cues in individuals in MOUD. Cross-frequency interaction between theta and gamma oscillations during various forms of working memory operations is a well-known phenomenon reflecting memory processes; in the cue reactivity task, this cross-frequency interaction showed enhancement in those on MOUD. Osipova et al. (2006) found that increased frontal theta power coincided with enhanced gamma power in more posterior cortical areas for stimuli that were either remembered later or forgotten. The authors suggested that frontal theta oscillations might reflect top-down processes that modulate gamma band activity related to representations in posterior regions. Our study was limited to the frontal theta and gamma analyses, but it also showed enhancement of theta–gamma coupling during processing salient drug-related stimuli in individuals with OUD on MOUD. Our result may reflect the processes of frontal interregional gamma-theta bands phase synchronization increase during attention orienting within a distributed network of cortical regions activated during attention captured by motivationally relevant stimuli.

Unlike earlier and mid-latency ERP components, such as N100 and N200 and evoked EEG oscillations which are highly sensitive to the perceptual properties of stimuli, or late cognitive potentials like P300, the magnitude of the late theta and gamma oscillations and their phase-amplitude coupling seems to be unaffected by the properties more typical for evoked and induced oscillations. Thus, late theta–gamma oscillation coupling should be considered to reflect stimulus content rather than perceptual features, such as stimulus complexity or size (Wiens et al., 2011). The event-related theta and gamma oscillations response in our study were focused on the time window in which the LPP, which is sensitive to the motivational and salience of a stimulus, is apparent in ERP. It is plausible to suggest that theta and gamma oscillations have similar emotional and motivational relevance as the LPP. The sustained LPP, which in our study was expressed in gamma and theta neural oscillations, is proposed to be larger following both positive and negative affective stimuli compared to neutral stimuli and appears to be generated by an extensive cortical-subcortical network involved in emotional processing and visual attention (Cuthbert et al., 2000; Hajcak & Olvet, 2008; Hajcak et al., 2009; Hajcak et al., 2010). It is plausible to propose that the emotion-elicited late theta and gamma oscillations and their coupling measures might serve as an index of sustained and flexible attentional engagement towards motivationally salient visual stimuli (Hajcak et al., 2009). Consequently, in our study higher amplitude and coupling of theta and gamma EEG oscillations in the MOUD group in response to drug cues might reflect persistence of motivational salience of drug-related cue for individuals with OUD, even when they are being treated with MOUD.

Although the cue-induced opioid craving changes during neutral and drug blocks were comparable in absolute measures of self-reports, the change in craving showed a tendency to increase along with the activation of the attentional and emotional processes among the patients on MOUD. These findings suggest that, even when receiving MOUD treatment, individuals with OUD exhibit greater cue-induced craving. Such craving may reflect greater frontal activation in EEG indices that might be related to reward wanting, craving, and memory retrieval. Proposed assessment technique may provide further understanding of craving and motivation to seek drugs in opiate dependency during MOUD treatment by adding objective physiological measures to subjective reports. Furthermore, it will make possible continuous monitoring of cortical activity during the treatment course. Although individuals in maintenance treatment may classify the drug-related stimuli similar to controls and can rate their current craving scores, they may show a trend to either over or understate actual craving level. These distortions in characterizing one's own affective state are not uncommon among those with substance use disorder due to the pervasiveness of emotional numbing, anhedonia, and other affective deficits in this population (McKernan et al., 2015; Torrado et al., 2015). However, drug cue-evoked EEG oscillations and autonomic responses are capable of revealing objective levels of emotional reactivity by using techniques similar to ones used in polygraphs (i.e., "lie detectors"). Thus, indices of psychophysiological reactivity to drugs may represent a sensitive objective indicator of emotional states and relapse vulnerability supplementing subjective reports.

There are several limitations of our pilot study that should be noted. Only a limited number of EEG leads was used, and EEG was recorded only from prefrontal and frontal sites. Correlation analyses between subjective craving rating scores and individual indices of EEG oscillations (e.g., theta and

gamma amplitude and latency of evoked, induced, and late oscillations, theta-gamma PAC coefficients, etc.) were not conducted in neutral and drug block conditions. Moreover, there were more female participants in the control group, and thus gender-related factors may affect the results. Other potential moderating factors that may affect outcomes might be related to the length of stay in MOUD treatment, length of opioid use history, severity of OUD and other demographic and clinical characteristics of participants in the MOUD group.

The results of the proposed study may have important clinical implications. Most importantly, they are expected to indicate that patients with OUD on MOUD, even after prolonged periods in opiate substitute pharmacotherapy, may present a higher subjective and physiological response to motivationally salient drug-related stimuli and lower psychophysiological reactivity to emotionally neutral cues as compared to control participants. Although drug-cue EEG response is influenced by multiple other variables (such as motivation, craving, classical conditioning, and substance availability), it is possible that MOUD might contribute to a decrease in the attentional bias towards drug cues, which seems to play a critical role in achieving positive outcomes. Objective EEG-based indices of attentional bias and drug cue reactivity might serve as useful outcomes of progress in buprenorphine-maintained individuals with OUD, and potentially for other complementary interventions, such as cognitive-behavioral therapy or neurofeedback training.

Conclusion

Application of advanced assessment of the effects of exposure to drug cues using pictorial stimuli with concurrent recording of evoked, induced, and late EEG oscillations is an innovative approach to more comprehensive functional clinical evaluations. The results of this pilot study add to a body of evidence indicating that coupling between low- and high-frequency EEG oscillations is an important feature of neural networks that mediate cognitive and affective processes among individuals with substance use disorder. People with OUD on MOUD may still experience vulnerability to drug-cue-induced craving. The study findings indicate persistence of attentional bias to drug cues in individuals with OUD, even when they are in maintenance treatment. Further research should examine whether modification of this bias by cognitive behavioral treatment or neurotherapy may reduce risk of relapse. Quantitative EEG measures used in our study may serve as useful objective indices reflecting both physiological, behavioral, clinical, and subjective outcomes of interventions in individuals enrolled in MOUD treatment.

Author Disclosure

Authors have no financial interests or conflicts to disclose.

References

Ayanga, D., Shorter, D., & Kosten, T. R. (2016). Update on pharmacotherapy for treatment of opioid use disorder. *Expert Opinion on Pharmacotherapy, 17*(17), 2307–2318. https://doi.org/10.1080/14656566.2016.1244529

Back, S. E., Gros, D. F., McCauley, J. L., Flanagan, J. C., Cox, E., Barth, K. S., & Brady, K. T. (2014). Laboratory-induced cue reactivity among individuals with prescription opioid dependence. *Addictive Behaviors, 39*(8), 1217–1223. https://doi.org/10.1016/j.addbeh.2014.04.007

Başar, E. (2013). A review of gamma oscillations in healthy subjects and in cognitive impairment. *International Journal of Psychophysiology, 90*(2), 99–117. https://doi.org/10.1016/j.ijpsycho.2013.07.005

Bertrand, O., & Tallon-Baudry, C. (2000). Oscillatory gamma activity in humans: A possible role for object representation. *International Journal of Psychophysiology, 38*(3), 211–223. https://doi.org/10.1016/s0167-8760(00)00166-5

Blanco, C., & Volkow, N. D. (2019). Management of opioid use disorder in the USA: Present status and future directions. *The Lancet, 393*(10182), 1760–1772. https://doi.org/10.1016/S0140-6736(18)33078-2

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science, 313*(5793), 1626–1628. https://doi.org/10.1126/science.1128115

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences, 14*(11), 506–515. https://doi.org/10.1016/j.tics.2010.09.001

Carter, B. L., & Tiffany, S. T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction, 94*(3), 327–340. https://doi.org/10.1046/j.1360-0443.1999.9433273.x

Castro, M. K., Bailey, D. H., Zinger, J. F., & Martin, E. A. (2019). Late electrophysiological potentials and emotion in schizophrenia: A meta-analytic review. *Schizophrenia Research, 211*, 21–31. https://doi.org/10.1016/j.schres.2019.07.013

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52*(2), 95–111. https://doi.org/10.1016/s0301-0511(99)00044-7

Dematteis, M., Auriacombe, M., D'Agnone, O., Somaini, L., Szerman, N., Littlewood, R., Alam, F., Alho, H., Benyamina, A., Bobes, J., Daulouede, J. P., Leonardi, C., Maremmani, I., Torrens, M., Walcher, S., & Soyka, M. (2017). Recommendations for buprenorphine and methadone therapy in opioid use disorder: A European consensus. *Expert Opinion on Pharmacotherapy, 18*(18), 1987–1999. https://doi.org/10.1080/14656566.2017.1409722

Drummond, D. C. (2001). Theories of drug craving, ancient and modern. *Addiction, 96*(1), 33–46. https://doi.org/10.1046/j.1360-0443.2001.961333.x

Fatseas, M., Denis, C., Massida, Z., Verger, M., Franques-Rénéric, P., & Auriacombe, M. (2011). Cue-induced reactivity, cortisol response and substance use outcome in treated

heroin dependent individuals. *Biological Psychiatry, 70*(8), 720–727. https://doi.org/10.1016/j.biopsych.2011.05.015

Franken, I. H. A., de Haan, H. A., van der Meer, C. W., Haffmans, P. M. J., & Hendriks, V. M. (1999). Cue reactivity and effects of cue exposure in abstinent posttreatment drug users. *Journal of Substance Abuse Treatment, 16*(1), 81–85. https://doi.org/10.1016/s0740-5472(98)00004-x

Frankland, L., Bradley, B. P., & Mogg, K. (2016). Time course of attentional bias to drug cues in opioid dependence. *Psychology of Addictive Behaviors, 30*(5), 601–606. https://doi.org/10.1037/adb0000169

Hajcak, G., Dunning, J. P., & Foti, D. (2009). Motivated and controlled attention to emotion: Time-course of the late positive potential. *Clinical Neurophysiology, 120*(3), 505–510. https://doi.org/10.1016/j.clinph.2008.11.028

Hajcak, G., MacNamara, A., & Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: An integrative review. *Developmental Neuropsychology, 35*(2), 129–155. https://doi.org/10.1080/87565640903526504

Hajcak, G., & Olvet, D. M. (2008). The persistence of attention to emotion: Brain potentials during and after picture presentation. *Emotion, 8*(2), 250–255. https://doi.org/10.1037/1528-3542.8.2.250

Hajcak, G., Weinberg, A., MacNamara, A., & Foti, D. (2011). ERPs and study of emotion. In S. J. Luck & E. S. Kappenman (Eds.), *The Oxford handbook of event-related potential components* (pp. 361–372). New York, NY: Oxford University Press.

Herrmann, C. S., & Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clinical Neurophysiology, 116*(12), 2719–2733. https://doi.org/10.1016/j.clinph.2005.07.007

Herrmann, C. S., & Mecklinger, A. (2000). Magnetoencephalographic responses to illusory figures: Early evoked gamma is affected by processing of stimulus features. *International Journal of Psychophysiology, 38*(3), 265–281. https://doi.org/10.1016/s0167-8760(00)00170-7

Herrmann, C. S., Rach, S., Vosskuhl, J., & Strüber, D. (2014). Time–frequency analysis of event-related potentials: A brief tutorial. *Brain Topography, 27*(4), 438–450. https://doi.org/10.1007/s10548-013-0327-5

Hyman, S. M., Fox, H., Hong, K.-I., Doebrick, C., & Sinha, R. (2007). Stress and drug-cue-induced craving in opioid-dependent individuals in naltrexone treatment. *Experimental and Clinical Psychopharmacology, 15*(2), 134–143. https://doi.org/10.1037/1064-1297.15.2.134

Köster, M., Martens, U., & Gruber, T. (2019). Memory entrainment by visually evoked theta-gamma coupling. *NeuroImage, 188*, 181–187. https://doi.org/10.1016/j.neuroimage.2018.12.002

Köster, M., Friese, U., Schöne, B., Trujillo-Barreto, N., & Gruber, T. (2014). Theta–gamma coupling during episodic retrieval in the human EEG. *Brain Research, 1577*, 57–68. https://doi.org/10.1016/j.brainres.2014.06.028

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2001). International affective picture system (IAPS): Instruction manual and affective ratings. (Tech. Rep. No. A–5). Gainesville, FL: University of Florida.

Lisman, J. E., & Jensen, O. (2013). The θ-γ neural code. *Neuron, 77*(6), 1002–1016. https://doi.org/10.1016/j.neuron.2013.03.007

Lubman, D. I., Peters, L. A., Mogg, K., Bradley, B. P., & Deakin, J. F. W. (2000). Attentional bias for drug cues in opiate dependence. *Psychological Medicine, 30*(1), 169–175. https://doi.org/10.1017/s0033291799001269

MacLean, R. R., Sofuoglu, M., Brede, E., Robinson, C., & Waters, A. J. (2018). Attentional bias in opioid users: A systematic review and meta-analysis. *Drug and Alcohol Dependence, 191*, 270–278. https://doi.org/10.1016/j.drugalcdep.2018.07.012

McKernan, L. C., Nash, M. R., Gottdiener, W. H., Anderson, S. E., Lambert, W. E., & Carr, E. R. (2015). Further evidence of self-medication: Personality factors influencing drug choice in substance use disorders. *Psychodynamic Psychiatry, 43*(2), 243–275. https://doi.org/10.1521/pdps.2015.43.2.243

Ortiz, E., Coleman, A., Pericot-Valverde, I., Byrne, K., Litwin, A., Shaban, M., & Sokhadze, E. (2021). Pictorial cue reactivity and craving measures in individuals with opiate use disorder enrolled in buprenorphine-maintenance program. International Journal for Psychophysiology, 168 (Suppl.), S137–138. https://doi.org/10.1016/j.ijpsycho.2021.07.395

Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., & Jensen, O. (2006). Theta and gamma oscillations predict encoding and retrieval of declarative memory. *The Journal of Neuroscience, 26*(28), 7523–7531. https://doi.org/10.1523/JNEUROSCI.1948-06.2006

Robbins, S. J., & Ehrman, R. N. (2004). The role of attentional bias in substance abuse. *Behavioral and Cognitive Neuroscience Reviews, 3*(4), 243–260. https://doi.org/10.1177/1534582305275423

Robinson, T. E., & Berridge, K. C. (2008). Review. The incentive sensitization theory of addiction: Some current issues. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 363*(1507), 3137–3146. https://doi.org/10.1098/rstb.2008.0093

Rosenberg, H. (2009). Clinical and laboratory assessment of the subjective experience of drug craving. *Clinical Psychology Review, 29*(6), 519–534. https://doi.org/10.1016/j.cpr.2009.06.002

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology, 37*(2), 257–261.

Schupp, H. T., Junghöfer, M., Weike, A. I., & Hamm, A. O. (2004). The selective processing of briefly presented affective pictures: An ERP analysis. *Psychophysiology, 41*(3), 441–449. https://doi.org/10.1111/j.1469-8986.2004.00174.x

Simojoki, K., Vorma, H., & Alho, H. (2008). A retrospective evaluation of patients switched from buprenorphine (Subutex) to the buprenorphine/naloxone combination (Suboxone). *Substance Abuse Treatment, Prevention, and Policy, 3*, 16. https://doi.org/10.1186/1747-597X-3-16

Substance Abuse and Mental Health Services Administration (SAMHSA). (2019). *Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health* (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

Tallon-Baudry, C. (2003). Oscillatory synchrony and human visual cognition. *Journal of Physiology–Paris, 97*(2–3), 355–363. https://doi.org/10.1016/j.jphysparis.2003.09.009

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Sciences, 3*(4), 151–162. https://doi.org/10.1016/s1364-6613(99)01299-1

Torrence, C., & Compo, G. P. (1998). A practical guide to wavelet analysis. *Bulletin of the American Meteorological Society, 79*(1), 61–78. https://doi.org/10.1175/1520-0477(1998)079<0061:APGTWA>2.0.CO;2

Torrado, M., Silva, H., Eusébio, S., Fred, A., & Ouakinin, S. (2015). Alexithymia, physiological reactivity and cognitive appraisals of emotional stimuli in opiate dependents: A pilot study. *Journal of Neurology & Neurophysiology, 6*(1), 1–8. https://doi.org/10.4172/2155-9562.1000263

Tort, A. B. L., Komorowski, R., Eichenbaum, H., & Kopell, N. (2010). Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *Journal of Neurophysiology, 104*(2), 1195–1210. https://doi.org/10.1152/jn.00106.2010

Wang, W. (2021). Brain network features based on theta–gamma cross-frequency coupling connections in EEG for emotion recognition. *Neuroscience Letters, 761*, 136106. https://doi.org/10.1016/j.neulet.2021.136106

Wiens, S., Sand, A., & Olofsson, J. K. (2011). Nonemotional features suppress early and enhance late emotional electrocortical responses to negative pictures. *Biological Psychology, 86*(1), 83–89. https://doi.org/10.1016/j.biopsycho.2010.11.001

Wilson, S. J., Sayette, M. A., & Fiez, J. A. (2004). Prefrontal responses to drug cues: A neurocognitive analysis. *Nature Neuroscience, 7*(3), 211–214. https://doi.org/10.1038/nn1200

Zhu, Z., Ye, Z., Wang, H., Hua, T., Wen, Q., & Zhang, C. (2019). Theta–gamma coupling in the prelimbic area is associated with heroin addiction. *Neuroscience Letters, 701*, 26–31. https://doi.org/10.1016/j.neulet.2019.02.020

Zijlstra, F., Veltman, D. J., Booij, J., van den Brink, W., & Franken, I. H. A. (2009). Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. *Drug and Alcohol Dependence, 99*(1–3), 183–192. https://doi.org/10.1016/j.drugalcdep.2008.07.012

Received: January 10, 2022
Accepted: January 13, 2022
Published: March 28, 2022