Drug cue reactivity and craving correlates in buprenorphine-maintained opioid addicts

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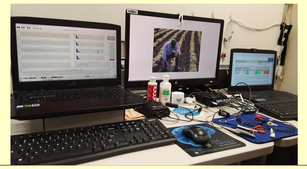
Abstract

- ***Background***: Opioid use disorder (OUD) is a major public health problem in the US that is expected to continue to increase (Blau, 2017; Hadland et al., 2018; O'Donnell et al., 2017). Maintenance treatment with buprenorphine in medication assisted treatment (MAT) has been associated with reductions in opiate use in individuals with OUD. However, despite low physical symptoms of withdrawal, buprenorphine-treated opioid-dependent patients still demonstrate vulnerability to relapse (Hyman, 2005; Nunes et al., 2004; Robinson & Berridge, 2001). Craving and attentional bias towards drug-related items may contribute to the high rates of non-compliance and relapse in OUD individuals undergoing MAT. The cue-reactivity paradigm (Carter & Tiffany, 1999) has been among the most prominent methods for investigating drug craving and psychophysiological responses to drug-related items.
- ***Purpose:*** We propose that craving and excessive reactivity to drug-related cues could be considered the core mechanisms underlying relapse risk. Comparing the central and autonomic nervous systems activity profiles and correlates of craving, drug-cue responsiveness, and more general emotional processes may provide with more knowledge towards the comprehension of the interaction between craving, affective states, motivation and clinical outcomes of OUD patients enrolled in MAT.
- ***Methods:*** In a pilot study were recruited ten participants from outpatient individuals being treated with MAT for opioid addiction. Drug screens were conducted using saliva drug test and eligibility was confirmed by clinical and behavioral evaluations. Pictorial cue reactivity test was conducted using exposure to emotionally neutral pictures from the International Affective Picture System (IAPS, Lang & Bradley, 2001) and drug-related images matching IAPS -pictures by color, size and background. The study used blocked design of presentation and each block was followed by subjective rating of craving. Responses were recorded with Nexus-10 psychophysiological monitor with BioTrace+ software (Mind Media, BV, The Netherlands). Photoplethysmogram (PPG), pneumogram, and electrodermal activity were acquired to measure skin conductance level (SCL), time domain heart rate variability (HRV) measures (RMSSD, SDNN), and respiration rate and amplitude. EEG was recorded from four frontal sites referenced to linked earlobes.
- ***Results:*** Analysis of the frontal EEG conducted to assess power of slow (theta, alpha) and fast (high beta, gamma) rhythms in neutral and drug blocks showed higher relative power of gamma (35-45 Hz), along with trends to lower power of theta activity and higher alpha-to-theta ratio in response to drug cues. Autonomic responses to drug cues were featured by increased SCL, higher frequency and lower amplitude of respiration and decrease pulse volume. Psychophysiological response profile is indicative of increased attention and orienting during exposure to drug cues.
- ***Conclusions:*** Psychophysiological indices of heightened arousal and attention to drug cues were found to be useful objective measures to complement subjective reports of craving. Craving, cue-reactivity, attentional and emotional biases are important clinical precipitants of relapse in opioid abusers and their measures may serve as useful objective outcomes of behavioral therapies. Furthermore, they could be used for guiding better targeted behavioral self-regulation interventions.

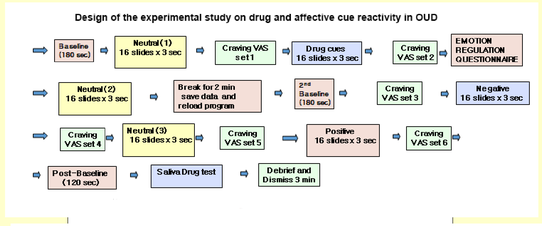
Acknowledgement: Supported by Prima Health Transformative Seed Grant

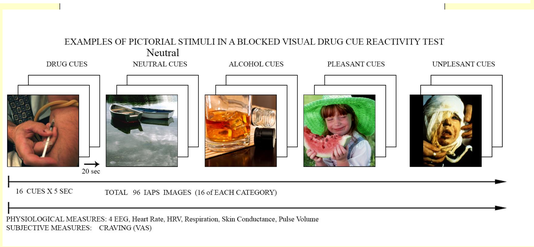
Methods: EEG & ANS Instrument

Equipment (Nexus-10 with BioTrace+ software): EEG was sampled at 256 *Hz* with 0.1–100 *Hz* filtering. EEG data was segmented off-line into epochs spanning 1000 ms post-stimulus. Datasets were digitally screened for artifacts and contaminated trials were removed. Remaining data were sorted by condition and averaged to create averaged event-related oscillations (focusing on evoked (40-180 ms), induced (180-520 ms) and late (600-820 ms theta and 40 Hz gamma) and autonomic responses in each condition.



Design of the study and affective cues

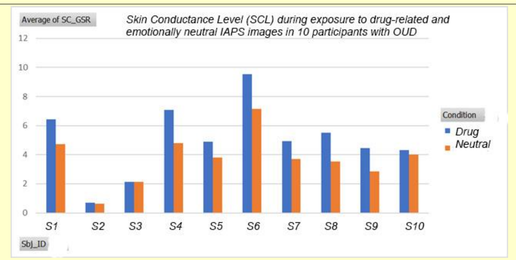




Subjects: Individuals with OUD in MAT program

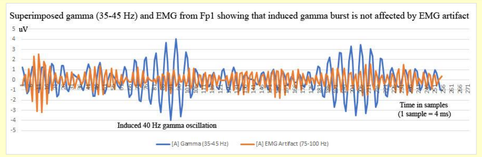
There were recruited ten participants from outpatient individuals being treated with MAT (sublingual Suboxone) for opioid addiction at the Prisma Health-Upstate IMC Recovery Program (Greenville, SC). Mean age of participants was 38 years, SD=7.07 years, 5 participants were female. Drug screens were conducted using saliva drug test and eligibility was confirmed by clinical and behavioral evaluations. Subjective reports of craving were evaluated by a VAS Craving Questionnaire (Huhn et al., Prefrontal cortex response to drug cues, craving, and current depressive symptoms are associated with treatment outcomes in methadone-maintained patients *Neuropsychopharmacology, 44*, 826–833, 2019).

Skin Conductance Level (SCL) to drug cues



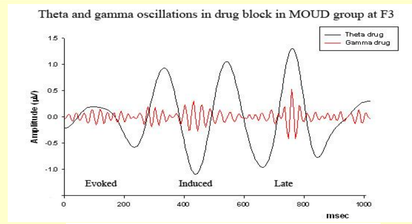
SCL increased from 4.35 ± 2.68 μS to emotionally neutral cues to 5.61 ± 2.99 μS in response to drug-related cues, t(9)=4.44, p= 0.002

Recording prefrontal EEG gamma and EMG



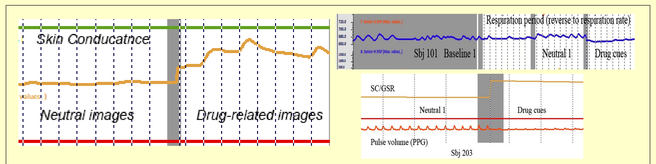
Gamma oscillations in 40 Hz range were not affected by EMG artifacts

Evoked, Induced and Late EEG oscillations (1024 ms)



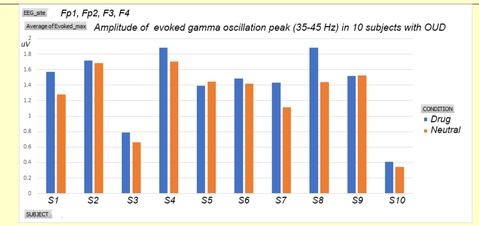
Prefrontal and frontal EEG oscillations in theta (4-8 Hz) and gamma (35-45 Hz) during exposure to neutral and drug-related cues

Autonomic Responses Screenshots: SCR, Respiration & Pulse volume

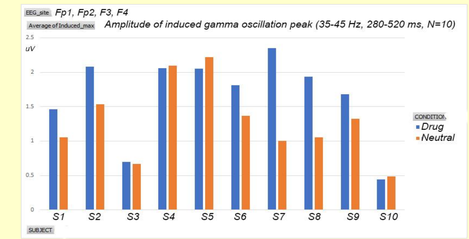


Screenshots illustrate electrodermal activity increase (SCRs), reduced respiration rate and amplitude and attenuated pulse volume during exposure to drug cues

Amplitude of evoked and induced 40 Hz gamma

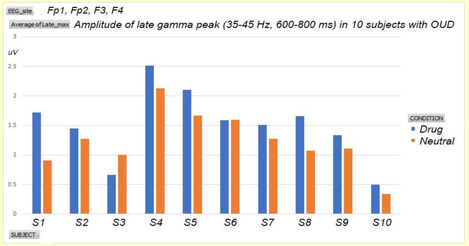


Amplitude of evoked gamma to drug cues (1.46 ± 0.48 μV) was higher than to neutral cues (1.22 ± 0.43 μV), t(9)=3.06, p=0.014)



Amplitude of induced gamma to drug cues (1.66 ± 0.62 μV) was higher than to neutral cues (1.28 ± 0.55 μV), t(9)=2.52, p=0.033)

Amplitude of the late gamma oscillations



Amplitude of late gamma oscillations to drug cues (1.50 ± 0.59 μV) was higher than to neutral cues (1.23 ± 0.48 μV), t(9)=2.63, p=0.027)

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