Boffin Access
FOSTERING KNOWLEDGE

Open Access Journal | Volume: 1.1

JOURNAL OF ALCOHOL AND DRUG ADDICTION

Electroencephalographic Evaluation of Resting-State Functional Connectivity in Prescription Opioid Use Disorder

Renee Baysarowich[1]
Kim Corace[2,3]
Melanie Willows[2,3]
Ashley Baddeley[1]
Nick Schubert[3]
Sara de la Salle[1]
Brooke Carroll[1]
Verner J Knott[1,2,3*]

[1]Clinical Neuroelectrophysiology and Cognitive Research Laboratory, University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada

[2]Faculty of Medicine, University of Ottawa, Institute of Mental Health Research, Ottawa, ON, Canada

[3]Substance Use and Concurrent Disorders Program, The Royal Ottawa Mental Health Centre, Ottawa, ON, Canada

Article Highlights:

- Little is known about the neural mechanisms underlying prescription opioid use disorder (P-OUD).
- Abnormal communication between and within brain regions is thought to be involved in opioid abuse.
- In this study comparing 18 P-OUD and 18 healthy individuals, abnormal EEG connectivity at scalp surface and in salience processing regions in patients were associated with cravings and depression ratings.
- P-OUD is characterized by neuroelectrophysiological dysconnectivity, which may serve as a target for treatment interventions.

Abstract

The existing, though limited, research in Opioid Use Disorder (OUD) has pointed to disruptions in EEG α and β connectivity related to heroin use. Similar studies have yet to examine neural connectivity associated with the non-medical use of prescription opioid medications. This pilot study, comparing 18 patients with prescription OUD and 18 healthy controls assessed 'resting-state' sensor-level connectivity, and intracortical source model-based (eLORETA) lagged functional connectivity in regions of interest within the salience network (SN). The SN serves to signal salient events, including drug-related internal and external stimuli. At the sensor-level, patients revealed reduced α frequency connectivity within and between frontal, temporal, posterior and inter-hemispheric regions. At the source-level, patients showed disrupted β frequency connectivity within the anterior cingulate (ACC) and between ACC-anterior insular (AI) nodes of the SN. In patients, sensor- and source-level α and β frequency connectivity profiles were associated with self-reported cravings (primarily drug desire); sensor-level intra-regional α connectivity correlated with depression scores. These preliminary electrophysiological findings in patients with prescription OUD underline altered neuronal communication during rest and encourage further research on connectivity measures as possible targets for novel treatment interventions.

Keywords

Prescription opioid use disorder; EEG; Functional connectivity; Salience network; Drug craving

Introduction

Rising problematic use of opioids, now expanded to heroin and illicit synthetic drugs (fentanyl and its analogues), is a major health concern worldwide. Although effectively managed with an accepted multifaceted treatment approach, including pharmacological and psychological therapies [1], evidence-based treatment for patients with opioid use disorder (OUD) is accompanied by relapses, overdoses, and multiple treatment failures [2]. OUD is a complex disorder of the brain characterized by disruption in multiple cortical (frontal, temporal, and parietal) and subcortical limbic regions, comprising interacting neural networks implicated in reward, emotional, and cognitive regulation [3-5]. Neuroimaging has been proposed as a potential approach for developing novel targets for treating OUD. This would serve to delineate the neural basis of individual differences associated with OUD vulnerability and maintenance, and to identify individual brain-based factors mediating treatment response and relapse [6].

Article Information

DOI:	10.31021/jada.20201101
Article Type:	Research
Journal Type:	Open Access
Volume:	1 Issue: 1
Manuscript ID:	JADA-1-101
Publisher:	Boffin Access Limited
Received Date:	29 September 2020
Accepted Date:	14 October 2020
Published Date:	16 October 2020

***Corresponding author:**

Verner J Knott

University of Ottawa Institute of Mental Health Research
Royal Ottawa Mental Health Centre
1145 Carling Avenue
Ottawa, Ontario, K1Z 7K4
Tel: 613-722-6521
E-mail: Verner.Knott@theroyal.ca

Citation: Baysarowich B, Corace K, Willows M, Baddeley M, Schubert N, et al. Electroencephalographic Evaluation of Resting-State Functional Connectivity in Prescription Opioid Use Disorder. J Alcohol Drug Addict. 2020 Oct;1(1):101

Research focused on elucidating brain features implicated in substance use disorders has shifted from studies of local brain activation to assessing neural network interactions [7]. This 'network approach' (i.e. brain regions are considered to be functionally connected if they have coherence and synchronized dynamics) has been facilitated by advanced signal processing techniques, which allow for the reliable estimation of functional connectivity – a statistical dependence between time series of measured neurophysiological signals [8]. Neuroimaging studies in substance use disorders using functional magnetic imaging (fMRI) of blood oxygen level-dependent (BOLD) signals (fluctuating at 0.05-0.1Hz) have reported alterations in resting-state functional connectivity (rsFC) within and between large-scale networks supporting higher-order functions (e.g., salience detection, inhibitory control) [9]. Although similar alterations in connectivity have been shown in OUD, the direction and pattern of connectivity features have been inconsistent [4-6,10].

Although possessing high spatial sensitivity, the low temporal resolution of fMRI provides connectivity estimates only for oscillatory couplings with frequencies < 1Hz. This is in contrast to the temporarily-sensitive electroencephalogram (EEG), which can capture direct neural oscillations over broad frequency ranges [11]. Further, EEG has high sensitivity to different aspects of stimulus processing [12,13] and network configurations [14-16], and therefore may allow for a more detailed and unique characterization of fast dynamic interactions in brain networks implicated in OUD compared with fMRI-based connectivity studies. Numerous EEG studies have shown rsFC coherence abnormalities associated with problematic use of substances, including caffeine [17] nicotine [18], alcohol [19], marijuana [20], ecstasy [21], methamphetamine [22], and cocaine [23]. In the only study in patients with OUD who were actively using opioids (vs. healthy controls), reductions in beta (β:13-30 Hz) and alpha (α: 8-12 Hz) frequency connectivity were observed over the cortex. Specifically, reduced connectivity was most prominent in α regionally (right posterior hemisphere) and between long-distance electrode pairs (intra-hemispheric) [24].

This limited electrophysiological evidence suggests that chronic use of opioids modifies dynamic functional connectivity, but, to-date, this work has been focused on heroin use.

Initiation of heroin use is frequently associated with prior problematic use of prescription opioids [25]. Increases in non-medical use of prescription opioids analgesics has occurred in tandem with changes in clinical and demographic features of treatment-seeking patients with OUD [26,27], suggesting different prognoses and treatment implications. As such, there is now an urgent need to understand the neural correlates of prescription opioid use (*vs.* heroin). This objective is further supported by findings of different cognitive profiles (impulsivity, executive function, cue-elicited craving) associated with chronic heroin *vs.* prescription opioid use [28] as well as differences in response to buprenorphine pharmacotherapy. Although not specific to OUD, there are elevated associations between prescription opioid use abuse and depression/anxiety, which need further study to assess their temporal and causal relationships [29].

The primary objective of this EEG pilot study is to examine β and α rsFC in patients with prescription OUD, given the paucity of information on the neural profiles of such individuals. rsFC was assessed using two functional connectivity analyses which are less sensitive (*vs.* conventional head-surface EEG connectivity techniques) to non-physiological artifacts (e.g. distortions from volume conduction, low spatial resolution, and reference electrode placement [30,31]. Namely, Laplacian analysis was used to estimate connectivity at the sensor-level, and exact low resolution electromagnetic tomographic analysis (eLORETA) was used to assess lagged connectivity of intracortical model sources [8,32]. With the latter approach, our present study explored source-level connectivity within and between two regions of interest (ROI) – the anterior insula (AI) and anterior cingulate cortex (ACC); activity in these regions has been associated with self-reported drug craving [33] and the urge for drug-seeking [34]. Structural connectivity has been demonstrated between the AI and ACC [35], and activity in the AI is often associated with ACC activity both during rest and task conditions; thus, these ROIs are considered the two main cortical nodes of the salience network (SN). The SN functions to detect salient events (e.g., drug-related stimuli in people with substance use disorders) events. Through activity in the AI, a state of heightened physiological awareness of the salient stimuli is generated, while strong functional coupling between the AI and ACC, triggers a cascade of top-down cognitive control processes to guide behaviour (e.g., drug seeking in people who abuse substances) and appropriate responses to salient stimuli. Simultaneously, the SIN may play a role in disengaging activity of networks not immediately relevant to behavioural goals (e.g., drug taking in people who abuse substances) [36].

Although our long-term objective is to map electrophysiological connectivity of prescription OUD across the different stages of the disorder, including withdrawal and medication-assisted abstinence, this pilot study was limited to individuals with current prescription OUD, all of whom were treatment-seeking patients in a substance use and concurrent disorders program. Sensor- and source-level rsFC in β and α frequencies were expected to be disrupted in individuals with prescription OUD (vs. healthy controls). As a secondary and exploratory objective, we examined the relationship between EEG connectivity and self-ratings of drug craving. Given the frequent co-occurrence of depressive symptoms and prescription opioid misuse [37] relationships between EEG connectivity and self-rated depression scores were also explored.

Methods

Participants

A sample of 18 patients with prescription OUD (11 males, 7 females, mean age = 27.50 ± 1.39) who were seeking treatment at the Regional Opioid Intervention Service (ROIS), a clinic in the Substance Use and Concurrent Disorders (SUCD) Program at The Royal Ottawa Mental Health Centre (located in Ontario, Canada) were recruited. Patients were required to meet the following inclusion criteria: ≥ 16 years of age, meet DSM-5 criteria for Substance (Opioid) Use Disorder – Moderate or Severe [38], provide a prescription opioid positive urine drug screen at time of consent, and be willing to consent to treatment with an opioid agonist therapy (buprenorphine/naloxone). Exclusion criteria included: positive urine screen for heroin, active psychosis, current suicidal ideation, positive neurological history (loss of consciousness, epilepsy, surgery), electroconvulsive therapy in the past year, and significant medical illnesses. Current or previous psychiatric disorders were not exclusionary. In addition to using the urine screen to help identify what other substances were being co-used with prescription opioids, patients were interviewed with the Alcohol, Smoking, and Substance Involvement Scale (ASSIST) [39,40], with frequency of use of a range of substances over the past 30 days (cannabis, cocaine, amphetamine type, stimulants, inhalents, sedatives, hallucinogens, and alcohol) rated on a 4-point scale (0: never; 1: once or twice; 2: weekly; 3: daily or almost daily). Score means and standard errors (SE) were: cannabis; 1.38(.36); cocaine .59(.22); amphetamine-like stimulants: .38(.20); inhalents: 00(00); sedatives: 1.19(.32); hallucinogens: 00(00); alcohol: 1.06(.21). As alcohol use is positively associated with above prescription opioids [41] patients also completed the Alcohol Use Disorders Identification Test (AUDIT), a 10-item self-report inventory asessing freqency/amount of alcohol consumption and personal/social problems associated with over use [42,43]. The mean (standard error) total score was 4.50(1.01), suggesting that they were generally at low risk for developing alcohol problems. None of the patients scored above 15 (indicating high risk for alcohol abuse) or 20 (addiction likely). Eighteen healthy volunteers (13 males, 5 females, mean age 30.28 ± 2.45) were recruited from the local community and matched as closely as possible for age, sex, and smoking status (patients:14 smokers/4 non-smokers; controls: 13 smokers/5 non-smokers). Regarding educational status, in the patients 11.11% had less than

high school, 50% completed high school, and 27.8% had finished college/university. In the healthy volunteers, 5.5% had less than high school, 44.4% completed high school, and 50% finished college/university. Healthy volunteers underwent a urine drug screen, a medical history screen, and a psychiatric screen using the Structured Clinical Interview for DSM-IV: Non-Patient Version (SCID-NP) [44]. Volunteers were required to have negative urine drug screens, no significant medical illness and no psychiatric disorder. Both patients and healthy volunteers completed the self-administered Patient Health Questionnaire (PHQ-9) to screen for depressive symptoms [45]. All participants signed an informed study consent, which was approved by the Research Ethics Board of the Royal's Institute of Mental Health Research.

Procedures

Patients seeking treatment for opioid use presented to the ROIS clinic for a health assessment visit where their current substance use was evaluated by a physician. They were subsequently referred to the EEG research team if they were found to have active use of primarily prescription opioids (based on a clinical interview and urine drug screen). Urine screen results from the patients at the study screen are presented in Table 1. Consent for study inclusion occurred during this initial health assessment, and the EEG session was subsequently scheduled before initiation of opioid agonist therapy. EEG sessions were conducted anytime between 8 am -1 pm, depending on the participants' availability, and lasted approximately 2 hours. On the day of EEG assessment, patients presented first to the ROIS clinical team and once they had completed their daily assessment, where it was confirmed that they were not in an acute state of withdrawal, they were escorted to the laboratory. Upon arrival, patients were asked to document any substance use in the past 48 hr, including prescription opioids, illicit drugs, cannabis, caffeine, alcohol, and nicotine, followed by the administration of questionnaires to assess current and past substance use. Vital signs were then collected, followed by electrode hook-up, and then EEG recording, which was conducted during a 3-minute eyes-closed resting period. At the end of the session, patient cravings for their prescription opioid were assessed with the self-rated Drug Desire Questionnaire (DDQ) [46]. Finally, a clinical debriefing session was conducted (administered by an addiction counselor, social worker, or registered nurse) to ensure patient safety.

Control volunteers presented to the laboratory the day on the of testing, after which they read and signed a consent form, completed the urine drug screen and subsequently followed the same testing procedure as patients, with the exception of a clinical debrief. Urine drug screens for all healthy volunteers were negative for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, and oxycodone.

EEG

EEG Recording: In line with recommended pharmaco-EEG standards [47,48], EEG activity was recorded while participants were seated reclined with their eyes closed. Using electronically linked mastoids as a reference, Brain Vision Recorder® software (Version 2, Brain Products, Munich, Germany) digitized (1000 Hz) electric signals were obtained from 28 scalp sites as well as vertical (VEOG) and horizontal (HEOG) electro-oculographic signals from supra-orbital canthi. Amplifier band-pass filters were set at 0.1 – 100 Hz, and electrode impedances were < 5 κΩ.

EEG Processing: EEGs were processed off-line using Brain Vision ® Analyzer Version 2 software (Brain Products, Munich, Germany). Recordings were initially inspected visually for elimination of activity with prominent ocular/muscle/cardiac contamination and drowsiness (i.e., alpha suppression combined with increased slow waves). Signals were dowsampled to 500 Hz, bandpass filtered at 0.1-50Hz (24dB/octave roll-off) and segmented into 2 sec epochs (Hanning window of 10% epoch length). Segments were automatically excluded from further analysis if they contained voltages > +/-75 μV. The resulting activity was then ocular-corrected [49] and subjected to independent component analysis (ICA) to remove residual ocular (e.g., micro saccades) artifacts.

Sensor-level connectivity: The processed EEGs (minimum of 120 sec) were transformed into reference-free current source density (CSD) estimates using a spherical Laplacian algorithm. CSD estimates were computed using the 4th order spherical interpolation, and a maximal degree of legender polynomials of 10. Brain Vision Analyzer 2 ® software (version 2.2) used reference-free CSD values to compute connectivity in β_1 (12.0-18.5 Hz), β_2 (18.5-21 Hz), and β_3 (21-30 Hz) frequency bands and into α_1 (8-10.5 Hz) and α_2 (10.5-12 Hz) bands. For control purposes, connectivity estimates were also calculated for delta (δ: 0.5-4 Hz) and theta (θ: 4-8 Hz) frequencies. As previous work showed EEG connectivity in OUD to vary across short- and long-distance connections [50], connectivity was computed for relatively short distance intra-regional electrode pairs within left (LH) and right (RH) hemispheres of frontal (LH: Fp_1-F_3, Fp_1-F_7, F_3-F_7; RH: Fp_2-F_4, Fp_2-F_8, F_4-F_8), temporal (LH: T_7-FC_5, T_7-CP_5, CP_5-FC_5; RH: T_8-FC_6, T_8-CP_6, CP_6-FC_6), and posterior (LH: P_7-P_3, P_7-O_1, P_3-O_1; RH: P_8-P_4, P_8-O_2) scalp regions (Figure 1). Longer distance inter-regional connectivity was computed with frontal-temporal (LH: FP_1-FC_5, FP_1-T_7, FP_1-CP_5, F_7-FC_5, F_7-T_7, F_7-CP_5, F_3-FC_5, F_3-T_7, F_3-CP_5; RH: Fp_2-FC_6, Fp_2-T_8, FP_2-CP_6, F_8-FC_6, F_8-CP_6, F_4-FC_6, F_4-T_8, F_4-CP_6), temporal-posterior (LH: FC_5-P_3, FC_5-P_7, FC_5-O_1, T_7-P_3, T_7-P_7, T_7-O_1, CP_5-P_3, CP_5-P_7, CP_5-O_1; RH: FC_6-P_4, FC_6-P_8, FC_6-O_2, T_8-P_4, T_4-P_8, T_8-O_2, Cp_6-P_4, CP_6-P_8, Cp_6-O_2) and frontal-posterior (Fp_1-P_3, Fp_1-P_7, Fp_1-O_1, F_7-P_3, F_7-P_7, F_7-O_1, F_3-P_3, F_3-P_7, F_3-O_1; RH: Fp_2-P_4, Fp_2-P_8, Fp_2-O_2, F_8-P_4, F_8-P_8, F_8-O_2, F_4-P_4, F_4-P_8, F_4-O_2) electrode pairs. For the pilot study, connectivity was computed only within hemispheres. Inter-hemispheric connectivity estimates were limited to 12 homologous electrode pairs across LH and RH at frontal, temporal, and posterior regions (Fp_1-Fp_2, F_3-F_4, F_7-F_8, C_3-C_4, P_3-P_4, O_1-O_2, T_4-T_8, P_4-P_8, FC_1-FC_2, CP_1-CP_2, FC_5-FC_6, CP_5-CP_6).

Source-level connectivity: EEG source functional connectivity analysis was performed in two steps using eLORETA software (available at http://www/uzh.ch/keynist/loreta.htm) to:

(1) Identify intracerebral current density for designated ROIs;

(2) Compute lagged connectivity for functional connections between ROI sources

ROIs: The current implemented version (2081104) of eLORETA, a

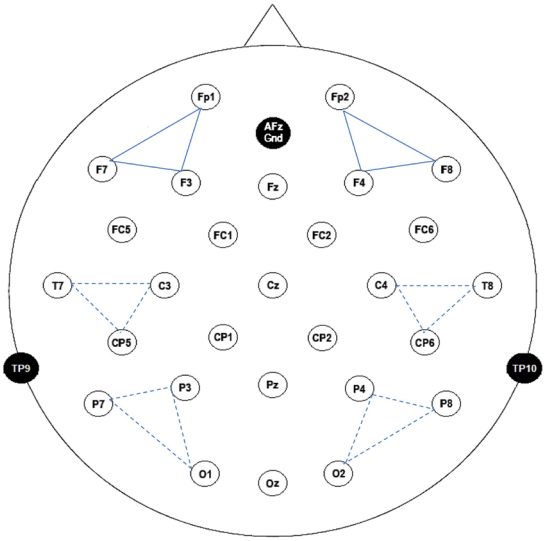

Figure 1: Intra-regional (short distance) electrode pair α1 connectivities (solid lines) at frontal sites and α2 connectivities at temporal and posterior sites (dashed lines) which showed significant reduction in prescription OUD patients compared to controls.

neurophysiological imaging technique based on a weighted minimum norm inverse solution procedure uses a realistic spherical head model based on the Montreal Neurological Institute Template (MNI152) for modelling EEG current density in a 3D solution space restricted to the cortical gray matter and hippocampus [51]. In contrast to the former LORETA version, eLORETA has zero localization error (under ideal noise-free conditions); localization with this methodology, even with relatively few electrodes (as in this study) has been cross-validated with studies combining EEG with fMRI [52,53] or positron emission tomography [54] and with simultaneous EEG-fMRI [55] and intracranial recordings [56]. Analysis of each 2 sec cleaned EEG epoch (each individual had a minimum 120 sec, which surpassed the 40 sec requirements suggested for connectivity analysis [51], resulted in current density being computed for each of the frequency bands at each of 6239 voxels (5 mm spatial resolution). Voxel-based ROIs in this study reflected definitions of the Broadman Areas [BA] provided by eLORETA software and are based on the Talairach Daemon [http://www.talairach.org]. A single voxel (at the centroid of each BA) was used for each ROI due to eLORETA's relatively restricted spatial resolution, which makes it unable to separate two closely spaced sources. The single centroid voxel (the closest to the center of the BA mass), as used in previous work [58], is an excellent representative of the corresponding BA. BAs comprising the representative left (l) and right (r) hemisphere nodes of the SN network included BA 24/32 (anterior cingulate cortex [ACC]) and BA 47 (anterior insula [AI]).

Connectivity: Using the eLORETA computed intracortical current density time series of these ROIs, lagged connectivity were computed for all pairs of ROIs by employing the eLORETA toolbox software options "linear lagged connectivity: LLC" and "non-linear lagged connectivity: LNLC". While eLORETA is able to compute both lagged and instantaneous (zero-lagged) connectivity components, only the former non-instantaneous component was considered for analysis, as zero-lagged connectivity between two sources can be affected by limitations such as volume conduction, third source influence , activity within the reference electrode, or the relatively low spatial resolution [51]. For each ROI pair, EEG amplitude-dependent LLC and EEG phase dependent LNLC were calculated for each of the EEG frequency bands.

Clinical ratings

DDQ: The DDQ consists of 13 items which are intended to assess three components of intent craving: "desire and intention," which contains seven items (e.g., My desire to use prescription opioids now seems overwhelming); "negative reinforcement," which consists of four items (e.g., Using prescription opioids now would make me feel less tense); and "control," which is composed of two items (e.g., If I started to use prescription opioids now I would be able to stop). Patients had to indicate how much they agree with a statement using a 7-point Likert (1 = "not at all" to 7 = "completely"). Scores are summed for total and subscale scores.

PHQ-9: The PHQ-9 assesses depressive severity by deriving total self-reported rating scores ("0" [not at all] to "3" [nearly every day]) of each of the DSM-IV criteria for major depressive disorder [45].

Statistical analyses

Statistical analysis was performed using SPSS 22.9 (IBM Corporation, Aramark, NY). The primary analysis was focused on connectivity in the β and α bands. For the sensor-level measures, separate mixed analysis of variances (ANOVA) were carried out for relatively short distanced and long distanced connectivity. ANOVAs for short distanced, intra-regional connectivity involved a between-group factor (2 groups) and three within-group factors including region (3: frontal, temporal, posterior), hemisphere (left, right) and electrode pair (3 pairs). For each of the analyses of long, inter-regional (frontal-temporal, temporal-posterior, frontal-posterior) connectivity, separate ANOVAs consisted of the same group and hemisphere factors and an electrode pair (9 pairs) factor.

For source-level LLC and LNLC estimates within the β and α frequency bands, separate mixed ANOVAs included a between-group factor and two within-group factors: node (2 intra-nodal and 4 inter-nodal pairs) and hemisphere. For control purposes only, similar analyses were conducted for scalp and source level delta and theta connectivity to help determine specificity of any frequency-dependent findings. Significant Greenhouse-Geisser effects ($p < 0.05$) were followed up with planned comparisons.

Patient ID	Last Reported Use on Day of EEG (Hrs)	Days Between (+) Urine Screen and EEG (Days)	Drug Type(s)
1	>24	ND	Fentanyl
2	17	14	Oxycodone
3	6	3	Morphine, Hydromorphone
4	>24	ND	Fentanyl
5	2	24	Hydromorphone, Oxycodone
6	>24	4	Oxycodone
7	>24	28	Hydromorphone
8	>24	22	Oxycodone
9	2	3	Codeine, Oxycodone
10	24	4	Fentanyl
11	2	ND	Fentanyl
12	2	24	Fentanyl
13	1	0	Codeine, Morphine
14	>24	ND	Oxycodone
15	22	7	Fentanyl
16	1	7	Oxycodone
17	>24	ND	Fentanyl
18	1	4	Hydromorphone, Oxycodone

Table 1: Patient self-reported substance use demographics

Notes: Patients were allowed to refuse a urine screen from the clinical team for legal reasons not originally disclosed to research team at time of consent (i.e., healthcare professional, current legal proceedings). The average time between urine screen and EEG test session was ± 9.94 days with a range of 0-28 days. *ND = No Data available.

In order to determine if time since last prescription drug use affected connectivity measures, we used the patient's time of last reported use of opioids (Table 1, column #1) and segregated patients into two equal sized (n = 9) groups: those reporting a relatively short time interval between last use and EEG testing (≤ 6 hours) and those reporting a longer time interval (≥ 17 hours). T-tests were used to compare subgroups on any EEG connectivity measure that significantly differentiated patients and controls.

In order to examine the possible influence of other used drugs on our outcomes, two contral statistics were carried out whenever the ANOVAs indicated significant connectivity abnormalities in patients (*vs.* healthy volunteers). Frist, analyses were re-run with patients showing positive non-opioid drug screens being removed. This involved separate analyses being carried out for each separate drug class detected, i.e., one analysis was run with 4 patients showing positive THC screen being removed; another analysis was run with 4 patients showing positive sedative screens being removed, and a final analysis was conducted with 3 patients showing positive amphetamine-like users being removed. For the second strategy, patient's connectivity measures were assessed for relationships (Spearman correlations) with ASISST scores for each drug class and with mean AUDIT scores.

Relationships between EEG connectivity and craving/depression ratings within the patient group were assessed with Spearman's correlations. In order to reduce the probability of Type I error, correlational analyses were restricted to α and β frequency connectivity. Further, correlations were only assessed within the patient group and only correlations obtaining significance of $p < 0.01$ were reported.

Results

Sensor-level connectivity: short distanced pairs

Analysis of intra-regional electrode pairs showed a significant group effect (F=7.89, df=1,34, $p < 0.008$) for α_1 frequency, with patients showing reduced connectivity compared to controls. Planned comparisons found reduced connectivity in patients (vs. controls) to be limited to frontal regions ($p < 0.04$). A similar group effect was observed with α_2 frequency (F=6.47, df=1,34, $p > 0.016$), but with reduced connectivity in patients being observed not at frontal recording sites but at temporal ($p < 0.03$) and posterior ($p < 0.03$) areas (Figure 1).

Sensor-level connectivity: long distanced pairs

Analysis of inter-regional connectivity found no group or interactions effects with frontal-temporal electrode pairs but significant group differences were observed for α_2 temporal-posterior (F=5.74, df=1,34, $p < 0.022$) and frontal-posterior connectivity (F=5.74, df=1,34, $p < 0.022$), with patients showing reduced couplings compared to controls (Figure 2,3).

Sensor-level connectivity: inter-hemisphere

For inter-hemispheric α_2 connectivity, follow-up comparisons of a significant group x electrode pair interaction (F=2.78, df=4,156, $p < 0.05$) found reductions in patients vs. controls for posterior O_1-O_2 ($p < 0.03$) and Cp_1-Cp_2 ($p < 0.02$) electrode pairs.

No significant group differences were observed with β, δ, or θ frequency coherences.

Source-level: linear connectivity

Analysis conducted on LLC yielded a significant group x node interaction for the β_1 frequency band (F=3.45, df=5,170, $p < 0.04$). Planned comparisons showed significantly greater intra-ACC connectivity (lACC-rACC) and reduced ($p < 0.04$) inter-nodal connectivity (rAI-rACC) in patients relative to controls (Figure 4). No group differences were observed with connectivity in other frequency bands.

Source-level: nonlinear connectivity

Analysis of LNLC also showed a significant group x node interaction for the β_1 frequency band (F=4.54, df=5,170, $p < 0.01$). Planned comparisons found significantly increased ($p < 0.03$) intra-ACC connectivity (lACC-rACC) in patients compared to controls (Figure 4). No group differences were observed with respect to LNLC in other frequency bands.

Time since last use-connectivity relationships

For any of the EEG connectivity differentiating patients and controls we observed no significant differences between patients with short *vs.* longer time intervals between use and EEG testing.

Co-occuring drug use connectivity relationships

The separate control analyses with patients showing positive illicint drug screen being removed found the same outcomes as the original analyses. For patients, no significant correlations were observed between ASSIST/AUDIT scores and connectivity measures.

Craving/depression-connectivity relationships

Sensor-level

DDQ: No significant correlations were observed for intra-regional

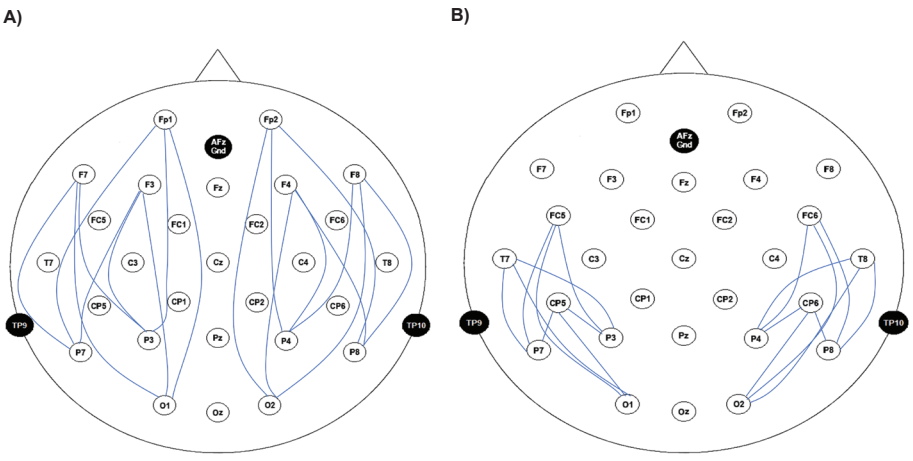

Figure 2: Inter-regional (long distance) α2 connectivities between frontal-posterior (A) and temporal-posterior (B) scalp areas which showed significant reductions in prescription OUD patients compared to controls.

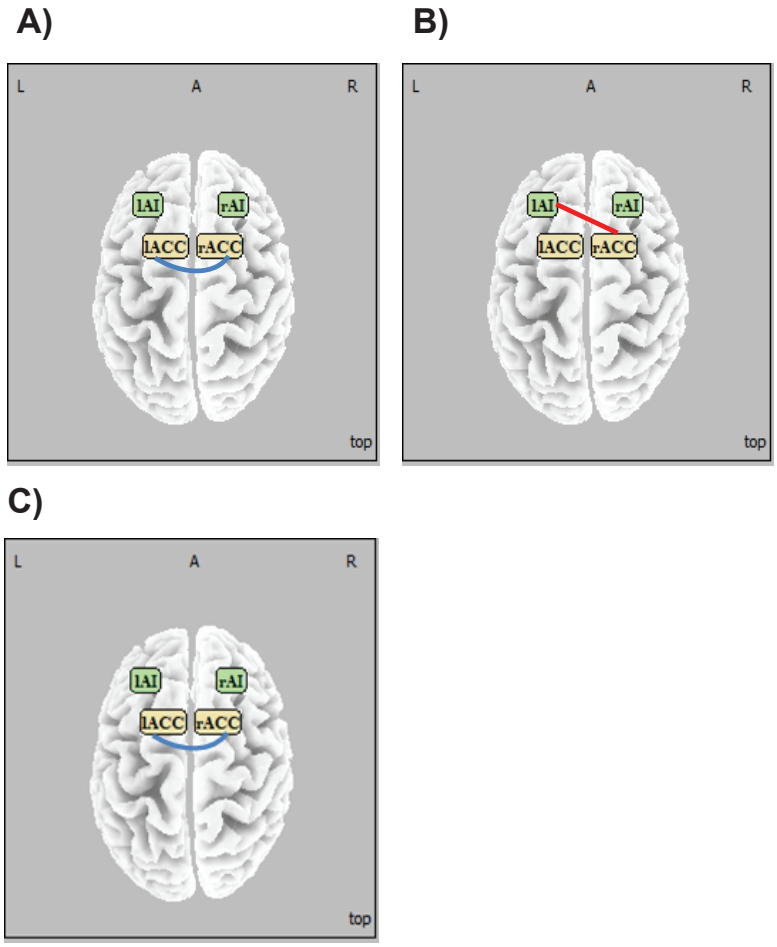

Figure 3: Intra-cortical lagged linear (A and B) and nonlinear β1 (C) SN connectivities showing significant alterations (blue = reductions, red = increases) in prescription OUD patients compared to controls. lAI = left anterior insula, rAI = right anterior insula, lACC = left anterior cingulate, rACC = right anterior cingulate.

or frontal-posterior pairs. Frontal-temporal α_1 connectivity between FP_1-FC_5 (r = .62, $p < 0.006$) and F_7-T_7 (r = -.59, $p < 0.009$), as well as temporal-posterior α connectivity between T_7-P_3 (r=.64, $p < 0.005$) were positively associated with self-ratings on the DDQ-Desire factor. Inter-hemispheric β_1 (r=.60, $p < 0.009$) and β_2 connectivity (r = .68, $p < 0.002$) between FC_1-FC_2 were also associated with DDQ-Desire ratings, and β_1 connectivity between F_3-F_4 was correlated (r = .68, $p < .002$) with DDQ-Negative Reinforcement self-ratings (see Figure 4 for examples).

PHQ-9: A t-test comparison found significantly greater (t = 4.58, df = 34, p < 0.0001) PHQ-9 scores for patients (M = 13.22, SE ± 2.06) compared to healthy volunteers (M = 3.11, SE ± 0.76). Within the patients, significant correlations existed between PHQ-9 scores and average α_1 connectivity in the frontal region (r = .98, $p < 0.0001$) and α_2 connectivity in temporal (r = .98, $p < 0.0001$) and posterior regions (r = .73, $p < 0.0001$).

Source-level

DDQ: No significant correlations were observed with either α or β_1 frequencies, but linear lagged β_2 connectivity between lAI-lACC was negatively associated (r = -.67, $p < 0.002$) with DDQ-Desire scores. Similar trends existed with DDQ-Desire and linear lagged (r = -.55, $p < 0.014$) and nonlinear lagged β_1 connectivity (r = .57, $p < 0.015$) measures (Figure 4).

PHQ-9: No significant relationships were observed between depression symptoms and source connectivity in patients.

Discussion

To the best of our knowledge, this is the first investigation to examine resting-state EEG signals to assess functional connectivity at the level of sensor and source space in patients with prescription OUD. Findings of this pilot study support our prediction of disrupted rsFC as evidenced by frequency-dependent connectivity alterations in short- and long-distanced scalp electrode pairs, and within and between intracortical nodes of the SN. As these neural alterations did not vary with time since last drug use, it can be tentatively assumed they do not reflect the acute effects of opioids. Further, our control analyses provided tentative evidence that this aberrant connectivity were not influenced by co-occurring illicit drug or alcohol use.

α band connectivity (though predominantly with α_2) assessed at the sensor-level was reduced within frontal, and between frontal-posterior, temporal-posterior and inter-hemispheric regions. In the only previous study investigating sensor-level EEG connectivity in patients with active OUD (heroin) [58], α and β hyper-connectivity was found locally (short distanced electrode pairs) while hypo-connectivity was shown remotely (long distanced pairs). Whether or not these aberrant connectivity are specific to chronic prescription opioid use or with heroin is not clear. It is also unclear whether these neural abnormalities pre-date opioid use or reflect irreversible changes resulting from chronic use of prescription opioids. In abstinent (2 weeks) heroin-dependent patients, enhanced connectivity (intra-hemispheric) was observed in the γ band ,but not with α or β oscillations [59]. Also observed in heroin abstinent patients were weaker low-frequency (6-13 Hz) effective (directional) connectivity originating in the parietal region, and stronger high-frequency (13-45 Hz) connectivity into the occipital region [60].

Our findings of abnormal regional interactions limited to α

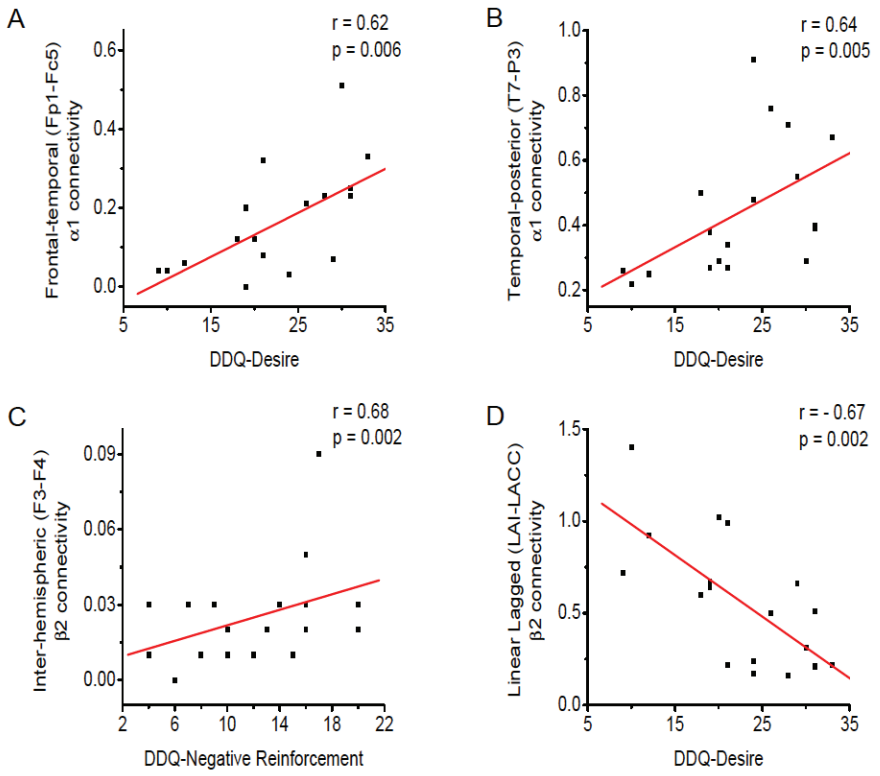

Figure 4: Scatterplot examples of the correlation between sensor-level (A, B, C) and source-level (D) connectivities and patient self-ratings of drug craving measure with the Drug Desire Questionnaire (DDQ) and related factors (Desire, Negative Reinforcement).

oscillations is not specific to heroin use, as such findings have been reported with use of caffeine [17], alcohol [61] and cannabis [62]. Given that these substances are frequently used with opioids, they may contribute to our observation of altered α connectivity in prescription OUD. Although the significance of diminished α connectivity is unclear, lower and upper α frequencies have been associated with working memory and attentional processes, respectively [63,64). α oscillations have also been attributed to stimulus suppression/inhibition and selection function [65,66]. Accordingly, it may be tentatively speculated that during the resting state, α hypo-connectivity in patients reflects reduced functional coupling between cortical regions regulating top-down inhibitory control of attentional/mnemonic processing of drug-related, physiologically salient events (internal bodily sensations), subjectively experienced as intoxication or withdrawal symptoms.

Although our sensor-level EEG findings are of limited use for drawing inferences regarding the underlying sources of electrical activity affected by chronic use of prescription opioids, it is of relevance to know that the ACC is one of the main drivers of spontaneous EEG [67]. Further, inter-areal connectivity (e.g., as quantified by fMRI) is thought to be primarily driven by α and β oscillatory activity within key networks including the SN [15,68,69]. SN alterations in individuals with active prescription opioid use was characterized by β_1 hyper-coupling within the ACC, as evidenced by increased LLC and LNLC between lACC-rACC. Prescription OUD also was associated with reduced inter-nodal β_1 coupling as shown by reduced LLC between rAI-rACC. Use of eLORETA LLC and LNLC solutions in the present study suggests that prescription OUD is associated with enhanced interactions within the ACC, and diminished interactions between AI-ACC. Hyper-connectivity within the ACC may reflect the acute/short-term enhancing effects of opioids on dopamine neurotransmission. Opioid signaling in the reward circuitry stimulates activation of dopamine cells and dopamine release in temporal regions (e.g., nucleus accumbens), which mediates several aspects of reinforced behavior such as incentive salience [70], and is associated with increased SN connectivity [71]. While connectivity within the ACC may reflect the more immediate effects of opioids, hypo-connectivity between rAI-rACC may be related to the down-regulation of opioidergic/dopaminergic systems occurring with chronic drug use.

Altered SN communication may involve disruption in various processes associated with β frequencies, including sensory/attentional/perceptual [72-75] emotional [76,77], reward [13] and salience processing [78]. These disruptions may be particularly relevant for higher-order cognitive operations involving the ACC (e.g., evaluative/emotive processing of salient events; response selection/conflict monitoring). These processes are known to involved β-influenced top-down control mechanisms [79], and may specifically involve complex neural processes as reflected in nonlinear inter-regional interactions index by LNLC [80].

Several influential models of substance use disorders have suggested that impaired salience attribution (drug > other non-drug reinforcers) is associated with abnormal engagement of the SN's AI for heightened interoceptive awareness of both stimulus (drug)-induced and stimulus-independent changes in homeostatic states [81]. The AI, and the rAI node, in particular, is uniquely positioned for bottom-up signaling of the ACC to signal internal/external salient events. Further, it can act as a causal hub for communicating with other network,s including the dorsal fronto-parietal CEN, which is important for maintaining and manipulating information in working memory [82]. In our participants with chronic problematic opioid use, reduced β_1 signaling between rAI-rACC may reflect alterations with normal network switching processes, resulting in impaired attention to natural rewards (e.g., food, sex), diminishing their significance and saliency relative to drugs [83].

Our exploratory analyses yielded significant relationships between chronic problematic opioid use and connectivity, with urges to use drugs being positively and negatively associated with sensor- and source-level connectivity, respectively. Decreased communication between AI and ACC nodes, two SN structures involved in emotional processing of interoceptive (drug-related) states, was found to be associated with increasing subjective drug

urges. The opposite relationship was shown with sensor-level connectivity, whereby increasing interactions within and between frontal, temporal, and posterior cortical regions was associated with greater self-reported drug cravings; this may reflect alterations in one or more non-SN networks. Recent concepts of substance abuse have proposed the involvement of separate but interacting neural networks [84] as those identified in opioid craving [85], which underly different pathological processes (e.g., reward/emotional/cognitive dysregulation) implicated in all substance use disorders [9]. Although possibly involving SN contributions, relationships between sensor-level connectivity and drug cravings may reflect default mode network (DMN) activity, which is typically negatively correlated with activity in cognitive control regions (including ACC, AI) during tasks and "at rest"[86]. Interestingly, DMN prominence appears to be temporarily decreased during the acute intoxication phase, but prominently involved during withdrawal and preoccupation phases [87]. Abnormal connectivity in the DMN is associated with basal craving in individuals who are heroin-dependent [88]. Additional studies are required to assess these relationships during acute withdrawal and abstinence states, as well as during cue-induced drug (opioid) craving, which has been shown to be reduced following neurostimulation of frontal-parietal-temporal scalp areas [89].

Our finding of greater depressive symptoms in our prescription opioid users parallels previous observations that long-term opioid use increases the risk of depression, and that depression increases the risk of non-medical use of prescription opioids [37]. Only sensor-level α connectivity in short-distanced electrode pairs in frontal, temporal, and posterior areas were positively correlated with depression ratings in patients. As these same connectivity features were not associated with self-reported craving, and as persistent α hyper-connectivity in depression has been reported in previous work [90] it is possible that our observed associations reflect trait-dependent associations which predate and promote opioid abuse.

Limitations

There are several limitations to this study that may affect the generalizability of our findings. First, the relatively small sample used in this preliminary analysis was possibly underpowered to detect small differences, and it did not allow stratification to examine effects of moderator variables (presence/absence of Axis I disorders including depression and anxiety, degree and duration of opioid exposure). Also, groups were not matched on sex. There are sex differences in resting EEG α and β connectivity. Sex differences also exist in misuse of prescription opioids [91,92] and in neural mechanisms modulating reward and substance abuse [93]. Second, this was a cross-sectional design, which does not allow us to determine whether the observed connectivity disruptions are state dependent, irreversible consequences of long-term prescription opioid exposure, or are pre-existing trait markers mediating vulnerability to opioid/substance use disorders. Other sensor-level EEG measures (e.g., amplitude, power, asymmetry) have shown neural changes across different stages of OUD [24,50,58,94]. What is needed are longitudinal investigations that can track EEG connectivity in patients across different stages of the disorder (acute withdrawal, long-term abstinence) and in response to pharmacotherapies. It would also be of interest to investigate EEG connectivity in response to newer therapies including behavioural [95] and neurostimulatory interventions [96]. Both have been shown to effect α and β sensor- and source (SN)-level connectivity, potentially altering treatment outcomes in OUD patients. Third, we only evaluated one measure of craving; future work is required to examine different self-report and behavioural measures (e.g., cue-reactivity paradigms) in order to validate relationships between craving and electrophysiological connectivity. Fourth, although our Laplacian and lagged connectivity metrics are less sensitive to volume conduction effects, our limited number of recording sites (28), together with the inherent low spatial resolution of eLORETA, did not allow us to effectively examine sources of electrical activity at deep sources, including subcortical SN loci or sub regions of ACC and AI nodes. Finally, as this pilot work only assessed connectivity strength in limited frequency bands, future work should aim to develop a more comprehensive profile of putative dynamic dysconnectivity features associated with prescription OUD (e.g. integrating gamma; [97-99] as well as to cross-frequency coupling measures.

Conclusion

Our preliminary EEG findings in individuals with prescription OUD indicate abnormal functional connectivity, which may potentially serve as neural underpinnings of craving and potential treatment targets.

Funding Source: This was an investigator-initiated study supported by a grant from the University of Ottawa Medical Research Foundation awarded to Kim Corace, Melanie Willows and Verner Knott.

Role of Funding Sources: The grant sources (see Funding Source) had no role in the conduct of this study, the data analysis, or the preparation of the study manuscript.

Public Significance Statement: The current prescription opioid epidemic is a public health concern requiring a fuller understanding of the neurobiological mechanisms leading to dependency and recovery. This study observed EEG-based evidence of aberrant cortical connectivity in nonmedical prescription opioid users, which was associated with both drug cravings and depressed mood. These neural markers may potentially serve as targets for forging new treatments and for assessing likelihood of treatment response.

References

1. Volkow N, Benveniste H, McLellan AT. Use and misuse of opioids in chronic pain. Annual Review of Medicine. 2018 Jan;69:451-465.
2. Wolf DAPS, Gold M. Treatment resistant opioid use disorder (TROUD): Definition, rationale, and recommendations. Journal of the Neurological Sciences. 2020 Apr;411:116718.
3. Fareed A, Kim J, Ketchen B, Kwak WJ, Wang D, et al. Effect of heroin use on changes of brain functions as measured by functional magnetic resonance imaging, a systematic review. J Addict Dis. Apr-Jun 2017;36(2):105-116.
4. Ieong HFH, Yuan Z. Resting-state neuroimaging and neuropsychological findings in opioid use disorder during abstinence: a review. Front Hum Neurosci. 2017 Apr;11:169.
5. Pandria N, Kovatsi L, Vivas AB, Bamidis PD. Resting-state abnormalities in heroin-dependent individuals. Neuroscience. 2018 May;378:113-145.
6. Moningka H, Lichenstein S, Worhunsky PD, DeVito EE, Scheinost D, et al. Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research. Neuropsychopharmacology. 2019;44(2):259-273.
7. Stam CV, Van Straaten ECW. The organization of physiological brain networks. Clin Neurophysiol. 2012 Jun;123(6):1067-1087.
8. Bastos AM, Schoffelen JM. A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. Front Syst Neurosci. 2016 Jan;9:175.
9. Sutherland MT, McHugh MJ, Pariyadath V, Stein EA. state functional connectivity in addiction: lessons learned and a road ahead. Neuroimage. 2012 Oct;62(4):2281-2295.
10. Stewart JL, May AC, Aupperle RL, Bodurka J. Forging neuroimaging targets for recovery in opioid use disorder. Front Psychiatry. 2019 Mar;10:117.
11. Uhlhaas P J. Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia. Current Opinion in Curr Opin Neurobiol. 2013 Apr;23(2):283-290.
12. Leicht G, Troschütz S, Andreou C, Karamatskos E, Ertl M, et al.

Relationship between oscillatory neuronal activity during reward processing and trait impulsivity and sensation seeking. PLoS One. 2013 Dec;8(12):e83414.

13. Marco-Pallares J, Cucurell D, Cunillera T, García R, Andrés-Pueyo A, et al. Human oscillatory activity associated to reward processing in a gambling task. Neuropsychologia. 2008 Jan;46(1):241-248.
14. Palva S, Palva JM. Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. Trends Cogn Sci. 2012 Apr;16(4):219-230.
15. Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK. Large-scale cortical correlation structure of spontaneous oscillatory activity. Nature Neuroscience. 2012 May;15(6):884.
16. Marzetti L, Della Penna S, Snyder AZ, Pizzella V, Nolte G, et al. Frequency specific interactions of MEG resting state activity within and across brain networks as revealed by the multivariate interaction measure. Neuroimage. 2013 Oct;79:172-183.
17. Reeves RR, Struve FA, Patrick G. Topographic quantitative EEG response to acute caffeine withdrawal: a comprehensive analysis of multiple quantitative variables. Clin Electroencephalogr. 2002 Oct;33(4):178-188.
18. Li X, Ma R, Pang L, Lv W, Xie Y, et al. Delta coherence in resting-state EEG predicts the reduction in cigarette craving after hypnotic aversion suggestions. Sci Rep. 2017 May;7(1):2430.
19. Mumtaz W, Vuong PL, Malik AS, Rashid RBA. A review on EEG-based methods for screening and diagnosing alcohol use disorder. Cogn Neurodyn. 2018 Apr;12(2):141-156.
20. Morrison PD, Nottage J, Stone JM, Bhattacharyya S, Tunstall N, et al. Disruption of frontal theta coherence by Δ 9-tetrahydrocannabinol is associated with positive psychotic symptoms. Neuropsychopharmacology. 2011 Mar;36(4):827-836.
21. Dafters RI, Duffy F, O'Donnell PJ, Bouquet C. Level of use of 3, 4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology (Berl). 1999 Jul;145(1):82-90.
22. Ahmadlou M, Ahmadi K, Rezazade M, Azad-Marzabadi E. Global organization of functional brain connectivity in methamphetamine abusers. Clin Neurophysiol. 2013 Jun;124(6):1122-1131.
23. Reid MS, Flammino F, Howard B, Nilsen D, Prichep LS. Topographic imaging of quantitative EEG in response to smoked cocaine self-administration in humans. Neuropsychopharmacology. 2006 Apr;31(4):872-884.
24. Fingelkurts AA, Fingelkurts AA, Kivisaari R, Autti T, Borisov S, et al. Methadone restores local and remote EEG functional connectivity in opioid-dependent patients. Int J Neurosci. 2009;119(9):1469-1493.
25. Muhuri PK, Gfroerer JC, Davies C. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review. Substance Abuse and Mental Health Services Administration. 2013 Aug.
26. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014 Jul;71(7):821-826.
27. Subramaniam GA, Stitzer MA. Clinical characteristics of treatment-seeking prescription opioid vs. heroin-using adolescents with opioid use disorder. Drug Alcohol Depend. 2009 Apr;101(1-2):13-19.
28. A Baldacchino, D J K Balfour, K Matthews. Impulsivity and opioid drugs: differential effects of heroin, methadone and prescribed analgesic medication. 2015 Apr;45(6):1167-1179.
29. Amari E, Rehm J, Goldner E, Fischer, B. Nonmedical prescription opioid use and mental health and pain comorbidities: a narrative review. Can J Psychiatry. 2011 Aug;56(8):495-502.
30. Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, et al. EEG coherency: I: statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. Electroencephalography and Clinical Neurophysiology. 1997 Nov;103(5):499-515.
31. Nunez PL, Silberstein RB, Shi Z, Carpenter MR, Srinivasan R, et al. EEG coherency II: experimental comparisons of multiple measures. Clinical Neurophysiology. 1999 Mar;110(3):469-486.
32. Stam CJ, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multi-channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp. 2007 Nov;28(11):1178-1193.
33. Kühn S, Gallinat J. Common biology of craving across legal and illegal drugs–a quantitative meta-analysis of cue-reactivity brain response. Eur J Neurosci. 2011 Apr;33(7):1318-1126.
34. Naqvi NH, Bechara A. The hidden island of addiction: the insula. Trends Neurosci. 2009 Jan;32(1):56-67.
35. Van Den Heuvel MP, Mandl RC, Kahn RS, Hulshoff Pol HE. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Human Brain Mapping. 2009 Oct;30(10):3127-3141.
36. Menon V. Salience network. Brain Mapp: An encyclopedic Ref. 2015; 2,597-611.
37. Sullivan MD. Depression effects on long-term prescription opioid use, abuse, and addiction. Clin J Pain. 2018 Sep;34(9):878-884.
38. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub. 2013.
39. Humeniuk R, Ali R, Babor T, Souza-Formigoni MLO, de Lacerda RB, et al. A randomized controlled trial of a brief intervention for illicit drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in clients recruited from primary health-care settings in four countries. Addiction. 2012 May;107(5):957-966.
40. Medge ND, Lang J. Screening instruments for detecting illicit drug use/abuse that could be useful in general hospital wards: a systematic review. Addict Behav. 2011 Dec;36(12):1111-1119.
41. Fiellin LE, Tetrault JM, Becker WC, Fiellin DA, Hoff A. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. J Adolesc Health. 2013 Feb;52(2):158-163.
42. Saunders JB, Aasland OG, Amundsen A, Grant M. Alcohol consumption and related problems among primary health care patients: WHO collaborative project on early detection of persons with harmful alcohol consumption—I. Addiction. 1993 Mar;88(3):349-362.
43. Saunders JB, Aasland OG, Babor TF, De la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993 Jun;88(6):791-804.
44. First MS, Spitzer L, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/PW/PSY Screen). Biometrics Research, New York State Psychiatric Institute, New York, NY. 2001.
45. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine. 2001 Sep;16(9):606-613.
46. Franken IH, Hendriks VM, van den Brink W. Initial validation of two opiate craving questionnaires: the Obsessive Compulsive Drug Use Scale and the Desires for Drug Questionnaire. Addict Behav. Sep-Oct 2002;27(5):675-685.
47. Jobert M, Wilson FJ, Ruigt GS, Brunovsky M, Prichep LS. et al. Guidelines for the recording and evaluation of pharmaco-EEG data in man: the International Pharmaco-EEG Society (IPEG). Neuropsychobiology. 2012;66(4):201-220.
48. Knott VJ. Quantitative EEG methods and measures in human

psychopharmacological research. Hum Psychopharmacol. 2000 Oct;15(7):479-498.

49. Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol. 1983 Apr;55(4):468-484.
50. Fingelkurts AA, Fingelkurts AA, Kivisaari R, Autti T, Borisov S, et al. Opioid withdrawal results in an increased local and remote functional connectivity at EEG alpha and beta frequency bands. Neurosci Res. 2007 May;58(1):40-49.
51. Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, et al. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2011 Oct;369(1952):3768-3784.
52. Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, et al. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage. 2004 May;22(1):83-94.
53. Mulert C, Menzinger E, Leicht G, Pogarell O, Hegerl U. Evidence for a close relationship between conscious effort and anterior cingulate cortex activity. Int J Psychophysiol. 2005 Apr;56(1):65-80.
54. Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry. 2004 Apr;9(4):325:393-405.
55. Olbrich S, Mulert C, Karch S, Trenner M, Leicht G, et al. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. Neuroimage. 2009 Apr;45(2):319-332.
56. Zumsteg D, Friedman A, Wieser HG, Wennberg RA. Propagation of interictal discharges in temporal lobe epilepsy: correlation of spatiotemporal mapping with intracranial foramen ovale electrode recordings. Clin Neurophysiol. 2006 Dec;117(12):2615-2626.
57. Elmer S, Hänggi J, Jäncke L. Interhemispheric transcallosal connectivity between the left and right planum temporale predicts musicianship, performance in temporal speech processing, and functional specialization. Brain Struct Funct. 2016 Jan;221(1):331-344.
58. Fingelkurts AA, Kähkönen S, Fingelkurts AA, Kivisaari R, Borisov S, et al. Composition of EEG oscillations and their temporal characteristics: Methadone treatment. Int J Psychophysiol. 2007 May;64(2):130-140.
59. Franken IH, Stam CJ, Hendriks VM, van den Brink W. Electroencephalographic power and coherence analyses suggest altered brain function in abstinent male heroin-dependent patients. Neuropsychobiology. 2004;49(2):105-110.
60. Hu B, Dong Q, Hao Y, Zhao Q, Shen J, et al. Effective brain network analysis with resting-state EEG data: a comparison between heroin abstinent and non-addicted subjects. J Neural Eng. 2017 Aug;14(4):046002.
61. Cardenas, VA, Price M, Fein G. EEG coherence related to fMRI resting state synchrony in long-term abstinent alcoholics. Neuroimage Clin. 2017 Nov;17:481-490.
62. Prashad S, Dedrick ES, Filbey FM. Cannabis users exhibit increased cortical activation during resting state compared to non-users. Neuroimage. 2018 Oct;179:176-186.
63. Doesburg SM, Green JJ, McDonald JJ, Ward LM. From local inhibition to long-range integration: a functional dissociation of alpha-band synchronization across cortical scales in visuospatial attention. Brain Res. 2009 Dec;1303:97-110.
64. Klimesch W. EEG-alpha rhythms and memory processes. Int J Psychophysiol. 1997 Jun;26(1-3):319-340.
65. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition–timing hypothesis. Brain Res Rev. 2007 Jan;53(1):63-88.
66. Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci. 2012 Dec;16(12):606-617.
67. Coito A, Michel CM, Vulliemoz S, Plomp G. Directed functional connections underlying spontaneous brain activity. Human Brain Mapping. 2019;40(3):879-888.
68. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M. Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A. 2007 Aug;104(32):13170-13175.
69. Briley PM, Liddle EB, Groom MJ, Smith HJ, Morris PG, et al. Development of human electrophysiological brain networks. J Neurophysiol. 2018 Dec;120(6):3122-3130.
70. Karkhanis A, Holleran KM, Jones SR. Dynorphin/kappa opioid receptor signaling in preclinical models of alcohol, drug, and food addiction. Int Rev Neurobiol. 2017;136:53-88.
71. McCutcheon RA, Nour MM, Dahoun T, Jauhar S, Pepper F, et al. Mesolimbic dopamine function is related to salience network connectivity: an integrative positron emission tomography and magnetic resonance study. Biol Psychiatry. 2019 Mar;85(5):368-378.
72. Singer W. Synchronization of cortical activity and its putative role in information processing and learning. Annu Rev Physiol. 1993;55:349-374.
73. Haenschel C, Baldeweg T, Croft RJ, Whittington, M, Gruzelier J. Gamma and beta frequency oscillations in response to novel auditory stimuli: a comparison of human electroencephalogram (EEG) data with in vitro models. Proc Natl Acad Sci U S A. 2000 Jun 20;97(13):7645-7650.
74. Wróbel A. Beta activity: a carrier for visual attention. Acta Neurobiologiae Experimentalis. 2000;60(2):247-260.
75. van Ede F, Köster M, Maris E. Beyond establishing involvement: Quantifying the contribution of anticipatory α-and β-band suppression to perceptual improvement with attention. J Neurophysiol. 2012 Nov;108(9):2352-2362.
76. Maeoka H, Matsuo A, Hiyamizu M, Morioka S, Ando H. Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: a study using electroencephalographic power spectrum analysis. Neurosci Lett. 2012 Mar;512(1):12-16.
77. Zhang W, Lu J, Liu X, Fang H, Li H, et al. Event-related synchronization of delta and beta oscillations reflects developmental changes in the processing of affective pictures during adolescence. Int J Psychophysiol. 2013 Dec;90(3):334-340.
78. Chand GB, Dhamala M. The salience network dynamics in perceptual decision-making. Neuroimage. 2016 Jul;134:85-93.
79. Fries P. Rhythms for cognition: communication through coherence. Neuron. 2015 Oct;88(1):220-235.
80. Anzellotti S, Coutanche MN. Beyond functional connectivity: investigating networks of multivariate representations. Trends Cogn Sci. 2018 Mar;22(3):258-269.
81. Goldstein, RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011 Oct;12(11):652–669.
82. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010 Jun;214(5-6):655–667.
83. Lubman DI, Yücel M, Kettle JW, Scaffidi A, MacKenzie T, et al. Responsiveness to drug cues and natural rewards in opiate addiction: associations with later heroin use. Arch Gen Psychiatry. 2009 Feb;66(2):205-212.
84. Noël X, Brevers D, Bechara A. A triadic neurocognitive approach to addiction for clinical interventions. Front Psychiatry. 2013 Dec;4:179.
85. Daglish MR, Weinstein A, Malizia AL, Wilson S, Melichar JK, et al.

Functional connectivity analysis of the neural circuits of opiate craving: "more" rather than "different"?. Neuroimage. 2003 Dec;20(4):1964-1970.

86. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005 Jul;102(27):9673-9678.
87. Zhang R, Volkow ND. Brain default-mode network dysfunction in addiction. Neuroimage. 2019 Oct;200:313-331.
88. Li Q, Li Z, Li W, Zhang Y, Wang Y, et al. Disrupted Default Mode Network and Basal Craving in Male Heroin-Dependent Individuals: A Resting-State fMRI Study. J Clin Psychiatry. 2016 Oct;77(10):e1211-e1217.
89. Wang Y, Shen Y, Cao X, Shan C, Pan J, et al. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates cue-induced craving for heroin. J Psychiatr Res. 2016 Aug;79:1-3.
90. Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PloS one. 7(2):e32508.
91. Hemsing N, Greaves L, Poole N, Schmidt R. Misuse of prescription opioid medication among women: a scoping review. Pain Res Manag. 2016;2016:1754195.
92. Serdarevic M, Striley CW, Cottler LB. Gender differences in prescription opioid use. Curr Opin Psychiatry. 2018 Jul;30(4):238.
93. Becker JB, Chartoff E. Sex differences in neural mechanisms mediating reward and addiction. Neuropsychopharmacology. 2019 Jan;44(1):166-183.
94. Fingelkurts A, Kähkönen S, Fingelkurts A, Kivisaari R, Borisov S, et al. Reorganization of the composition of brain oscillations and their temporal characteristics during opioid withdrawal. J Psychopharmacology. 2008 Feb;22(3):270-284.
95. Shtark MB, Kozlova LI, Bezmaternykh DD, Mel'nikov MY, Savelov AA, et al. Neuroimaging study of alpha and beta EEG biofeedback effects on neural networks. Appl Psychophysiol Biofeedback. 2018 Jun;43(2):169-178.
96. Weinrich CA, Brittain JS, Nowak M, Salimi-Khorshidi R, Brown Pet al. Modulation of long-range connectivity patterns via frequency-specific stimulation of human cortex. Curr Biol. 2017 Oct 9;27(19):3061-3068.e3.
97. Khajehpour H, Makkiabadi B, Ekhtiari H, Bakht S, Noroozi A, Mohagheghian F. Disrupted resting-state brain functional network in methamphetamine abusers: A brain source space study by EEG. PLoS One. 2019 Dec;14(12):e0226249.
98. De Nadai AS, Little TB, McCabe SE, Schepis TS. Diverse diagnostic profiles associated with prescription opioid use disorder in a nationwide sample: One crisis, multiple needs. J Consult Clin Psychol. 2019 Oct;87(10):849-858.
99. Zumsteg D, Friedman A, Wennberg RA, Wieser HG. Source localization of mesial temporal interictal epileptiform discharges: correlation with intracranial foramen ovale electrode recordings. Clinical Neurophysiology. 2005 Dec;116(12):2810-2818.