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Clavulanic Acid-Mediated Increases in Anterior Cingulate Glutamate Levels are Associated With Decreased Cocaine Craving and Brain Network Functional Connectivity Changes

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ABSTRACT

Background: There is an urgent need for pharmacological treatment for cocaine (COC) use disorder (CUD). Glutamatergic transmission in the prefrontal cortex is affected by addictive behaviors. Clavulanic acid (CLAV), a glutamate transporter GLT-1 (excitatory amino acid transporter) activator, is a clinical-stage medication that has potential for treating CUD.

Methods: In a pilot study, nine participants with CUD received 500 mg CLAV with dose escalations to 750 mg and 1000 mg over 10 days. In 5 separate magnetic resonance imaging (MRI) sessions, brain anterior cingulate cortex (ACC) glutamate level and resting state network (RSN) functional connectivity (FC) were assessed using MR spectroscopy and functional MRI. Craving was assessed at the same time points, between baseline (before CLAV), 6 days, and 10 days of CLAV. Independent component analysis with dual regression was used to identify RSN FC changes from baseline to Days 6 and 10. Relationships among glutamate, craving, and resting state FC values were analyzed.

Results: Participants who achieved high ACC glutamate levels after CLAV treatment had robust decreases in COC craving ($r = -0.90$, $P = 0.0009$, $n = 9$). The salience network (SN) and executive control network (ECN) demonstrated an association between increased FC after CLAV treatment and low baseline ACC Glu levels (SN CLAV 750 mg, $r = -0.82$, $P = 0.007$) (ECN CLAV 1000 mg, $r = -0.667$, $P = 0.050$; $n = 9$).

Conclusions: Glutamate associated changes in craving and FC of the salience and executive control brain networks support CLAV as a potentially efficacious pharmacological treatment for CUD.

Introduction

Cocaine (COC) related deaths have increased dramatically since 2016.[1] COC-related deaths disproportionally affect older non-Hispanic Black people, and effective COC treatment is urgently needed.[2] In the US in 2022, 3.7% of those aged 18 to 25 years and 1.8% of those 26 and older used COC.[3] Currently, there are no FDA-approved medications to treat COC use disorder (CUD). Both glutamatergic and glial-related medications can potentially treat substance use disorders.[4] Activation of excitatory amino acid transporter 2 or GLT-1, the dominant astroglial glutamate transporter, may provide a breakthrough approach to managing COC addiction.[5] Clavulanic acid (CLAV), a component of the commonly used antibiotic Augmentin, and a glutamate transporter GLT-1 activator, reduces COC-seeking behavior in mice.[6]

Changes in brain resting state network (RSN) functional connectivity (FC) may be useful biomarkers to evaluate medications for efficacy in CUD. The salience network (SN) is critical in orienting attention to the most important information for people with

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substance use disorders, and typically includes the anterior insular cortex and dorsal anterior cingulate cortex (ACC).[7] The SN may control the executive control network (ECN) and the default mode network and sits at the center of the "triple network" in addiction.[7] Adults who regularly use COC demonstrate hypoconnectivity in the ECN, including dorsolateral and ventrolateral prefrontal cortical nodes, associated with weakened goal-directed decision-making.[8,9] A medication that strengthens either SN or ECN FC may be useful for COC treatment via executive function improvement. Here we seek to determine whether CLAV treatment has an effect on these addiction-related RSNs.

The ACC is an important part of the COC cue processing network and is associated with COC craving and reward.[10] If CLAV can reverse the effects of diminished ECN connectivity or decrease craving associated with prolonged COC use, CLAV treatment has the potential to improve decision-making and the ability to resist COC. We hypothesized that CLAV would strengthen craving-associated neurocircuitry boosting executive function. Additionally, we hypothesized that CLAV-associated modulation of ACC glutamate level (Glu) would be associated with decreased COC craving.

Material and Methods

Study approval

The study was conducted according to the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Temple University, Philadelphia PA. All subjects gave written informed consent before participation. The study was registered on ClinicalTrials.gov (NCT04411914).

Participants

Thirteen human subjects met DSM-5 criteria for severe CUD with regular (weekly or more) COC use for at least 1 year.[11] Participants had to abstain from COC for 7 days, verified by urine drug screening, prior to randomization. Subjects were medically and psychiatrically stable. No chronic medications affecting brain Glu or gamma-aminobutyric acid were permitted. Cigarette smokers were permitted nicotine patches. For subject welfare, magnetic resonance imaging (MRI) safety was assessed. Upon enrollment, study participants were given a phone number for 24/7 access to a study physician in case of adverse events that did not require emergency evaluation. Participants were randomized at a 3:1 ratio into the CLAV or matched placebo (PBO) groups respectively, with stratification on sex and last COC use (greater or less than 30 days) using a block randomization method. The findings presented here are only from the experimental group ($n = 9$). Three PBO participants were part of the main study but are excluded from the network analyses due to insufficient funding for a larger group. One subject was discontinued for an adverse event on Day 4.

Participants were recruited in Philadelphia, Pennsylvania using media advertisements (Craigslist, print, radio, social media, etc.); resources in public community settings (substance use treatment centers, libraries, health fairs, etc.); and directly contacting patients interested in clinical research. Upon completion of study procedures, subjects were compensated a total of $2340 for their time (11 inpatient days) and 5 1-hour MRI scans required for participation.

Research sites. The inpatient portion of the study was conducted in 2 hospitals at 2 clinical campuses (Episcopal and Health Sciences) of the Temple University Health System during 2020 to 2021 in Philadelphia, PA. Participants were housed in private rooms on a unit with other patients. MRI imaging was performed at Temple University Brain Research and Imaging Center (TUBRIC) with a 3 T Siemens scanner described below.

Experimental design

Medication dosing. In this pilot study, participants received 500 mg CLAV or matched PBO in the morning on Days 1 to 3. All subjects had a forced dose escalation to 750 mg/day (or matched PBO) for Days 4 to 6. Subjects then had a forced dose escalation to 1000 mg (or matched PBO) for Days 7 to 10.

MRI scans were obtained during 5 sessions. The first scan was conducted at baseline prior to study drug administration, the second on Day 3 (after 3 days 500 mg), the third on Day 6 (after 3 days 750 mg), the fourth on Day 10 (after 4 days 1000 mg), and the fifth on Day 11 (24 hours after the final dose).

In addition to magnetic resonance spectroscopy (MRS) and resting state functional imaging (rsfMRI), subjective and cognitive assessments were administered daily for participants to complete privately. The 45-item self-rated COC Craving Questionnaire (CCQ) was used daily to rate COC craving.[12] Success of study drug masking was assessed by asking both the participant and investigator to guess whether participants had been given CLAV or PBO, and how confident they felt in their response from 1 to 10. There was continuity throughout the study for all personnel working with participants.

MRI data acquisition and analysis

MRI data were acquired using a Siemens MAGNETOM Prisma 3-Tesla MRI scanner (Siemens AG, Erlangen, Germany), with a 64-channel phased-array parallel transmit and receive radiofrequency head coil. A high-resolution anatomical scan, used for MRS voxel positioning and rsfMRI registration, was performed with a T1-weighted 3D MPRAGE[13] Siemens product sequence with 160 slices, 1.0 mm thickness, 22 cm field-of-view (FOV), 192×256 matrix, TI/TR/TE = 1100/1630/3 ms. Parallel imaging with 2-fold acceleration was used to shorten acquisition time.

rsfMRI

Resting-state fMRI was performed using Siemens product Gradient-Echo EPI[14] with multiband factor of 3. Each volume had 75 axial slices with 2.0 mm thickness, a gap of 0.1 mm, FOV of 200×200 mm^2, 100×100 matrix; TR/TE = 2000/29 ms; $2 \times 2 \times 2$ mm^3 voxel resolution. There were 445 volumes per fMRI run (14.8 minutes) used to measure FC of whole brain RSNs while subjects were instructed to relax, keep eyes open, and stare at a cross.

Processing and analysis of rsfMRI data were performed using the FSL (FMRIB Software Library, https://fsl.fmrib.ox.ac.uk) toolbox. Standard preprocessing was performed on each rsfMRI time series, involving slice-time correction, head motion correction, nonbrain removal, spatial smoothing, and high-pass temporal filtering. All images were registered to MNI-152 standard space with isotropic 2 mm resolution. We used independent component analysis (ICA) with a dual regression approach of fMRI to compare FC of RSNs between baseline, Day 6 (750 mg), and Day 10 (1000 mg) of CLAV treatment.[15] A group ICA using 20 independent components allowed identifying RSNs common to all participants and sessions, including the default mode network, SN and ECN. FSL Randomize (nonparametric permutation testing with a paired-T design matrix) was used to determine regional FC changes of the SN and ECN, in which FC changes were hypothesized.[16]

Magnetic resonance spectroscopy

MRS was performed using the Siemens product single-voxel spin-echo point-resolved spectroscopy sequence[17] using short echo time (TE = 30 ms), repetition time TR = 2 s with 128 averages, and water suppression to measure Glu, Glu + Glutamine (Glx) and other metabolites.[18] For each water suppressed scan, the un-suppressed water signal was acquired for absolute quantification of metabolites using water scaling. The $1.7 \times 2.8 \times 1.7$ cm^3 (8.1 mL) MRS voxel

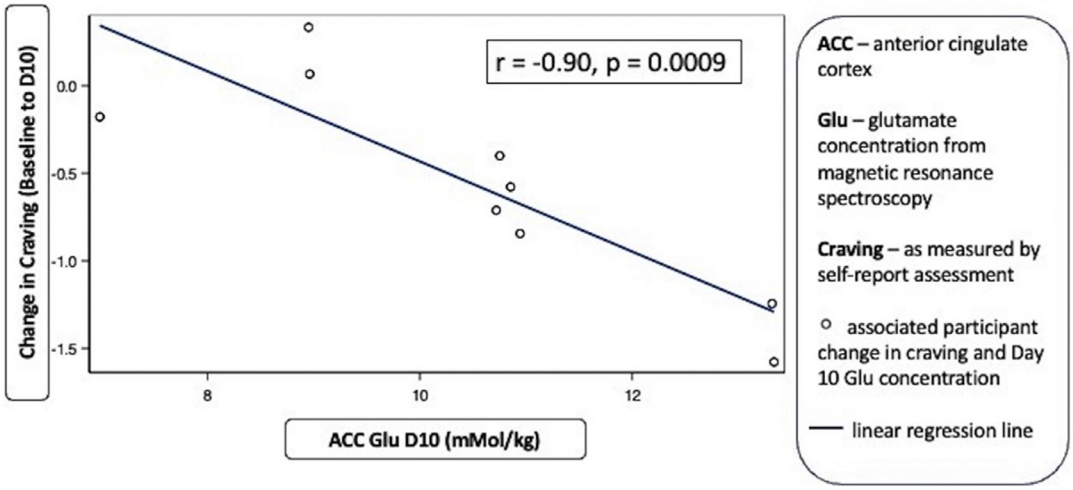

Figure 1. Increased Day 10 ACC Glu is associated with decreased craving with CLAV treatment. Strong inverse correlation between change in cocaine craving and ACC Glu concentration from baseline to Day 10 ($r = -0.90$, $P = 0.0009$).

was positioned in the dorsal ACC. Images of the baseline voxel position of the ACC in sagittal, axial, and coronal planes were used to maximize consistency of voxel placement in subsequent scans.

The Tarquin software package (http://tarquin.sourceforge.net) was used to estimate the concentrations of Glu and Glx in the ACC. After data preprocessing (including removal of residual water signal, eddy current correction, and phase estimation), Tarquin uses linear combination model fitting to fit a linear combination of its model spectral signals (32 molecules, including small metabolites, lipids, and macromolecules) to the MRS data and calculate the concentration of each metabolite. Absolute quantification of Glu and Glx metabolites in units of mmol/kg wet weight of brain tissue was performed by scaling the metabolite signal to the water signal in the voxel and correcting the voxel water concentration for the relative amounts of grey and white matter (GM and WM) and cerebrospinal fluid (CSF) in the ACC voxel.[19] The voxel fractions of GM, WM, and CSF were obtained by segmentation of the T1-weighted structural image using FSL (fsl.fmrib.ox.ac.uk). Glu concentrations were corrected for effects of transverse T2 relaxation.

Statistical approach

Regions of the highest FC change with the RSNs of interest (SN and ECN) were identified in the between-subjects' comparisons of RSN FC analysis. The regional mean FC *z*-score was calculated for each subject and session and used for further correlational analyses. The relationships between ACC Glu concentrations, craving scores, and regional FC *z*-scores were assessed using robust nonparametric correlation coefficients that did not require normality of the data. Because of the exploratory nature, data distribution, and small size of the study ($n = 9$), Spearman correlation coefficients were reported and *P* values less than 0.10 were considered statistically significant. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for all the data analyses.

Results

Subjects: Nine adult participants with DSM-5 severe COC dependence completed the study. All participants received CLAV (double-masked) after a minimum of 7 days of abstinence. Three PBO participants were excluded from analyses due to insufficient power to serve as an adequate control group. Participants were predominantly middle-aged (median = 54.2 years, range = 28–61.5 years), male (6 M, 3 F), and identified as Black ($n = 6$). Subjects used COC for an average (SD) of 22.1 (12.1) years (median = 24, range = 1.5–34.5 years).

High ACC Glu was associated with decreased COC craving at Day 10

ACC Glu concentration was assessed during rsfMRI/MRS scans at 5 time points. On Day 10, the median (med) ACC Glu level was 10.75 mMol/kg (range 6.99–13.34 mMol/kg) compared with the baseline med Glu level of 10.17 mMol/kg (range 4.39–13.43 mMol/kg), with a med change of +0.58 mMol/kg (range −0.09 to 2.6 mMol/kg) at Day 10. Overall, craving decreased during the study with med CCQ scores of 2.84 (range 1.67–4.36) at baseline, 2.44 (range 1.40–4.11) at Day 6, and 2.13 (range 1.27–3.78) at Day 10. Notably, higher ACC Glu levels at Day 10 were strongly associated with greater decrease in COC craving ($r = -0.90$, $P = 0.0009$, $n = 9$) (Figure 1 and Figure 3).

CLAV increased FC in addiction-related RSNs

At Day 6, FC of SN with the supplementary motor area (SMA) was increased (Figure 2A). At Day 10, FC of ECN with the left insula and right caudate nucleus was increased (Figure 2B).

Low baseline Glu was associated with increased FC in addiction-related RSNs

Both SN and ECN demonstrated an association between low baseline ACC Glu and increased FC at Days 6 (SN, 750 mg dose) and 10 (ECN, 1000 mg dose) as discussed in Figure 3.

SN CLAV 750 mg

Lower baseline ACC Glu was associated with higher FC of SN with the SMA ($r = -0.82$, $P = 0.007$) at Day 6 (750 mg dose). Greater change in Glx from Day 0 to 6 was associated with greater increase in FC from Day 0 to 6 ($r = 0.68$, $P = 0.042$).

ECN CLAV 1000 mg

Lower baseline ACC Glu was associated with a greater increase in ECN FC with the left insula and caudate nucleus ($r = -0.667$, $P = 0.050$) at Day 10 (1000 mg dose).

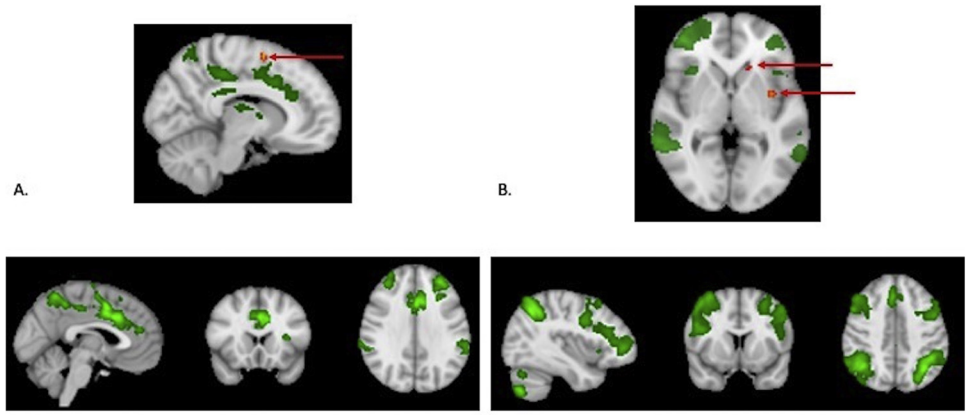

Figure 2. CLAV-increased FC in subjects with low baseline Glu in both Salience Network (Day 6) and Executive Control Network (Day 10). Resting state networks depicted in green, regions of increased connectivity depicted in red/orange. (A) Salience network regions (top: paracingulate gyrus, precuneus, lateral occipital cortex; left: anterior cingulate cortex, precuneus; middle: ACC; right: angular gyrus, ACC, frontal pole) show increased connectivity with supplementary motor area (top) following 6 days of CLAV treatment, CLAV dose 750 mg/day. (B) Executive control network regions (top: frontal pole, anterior insula, middle temporal gyrus; left: angular gyrus, precentral gyrus, middle frontal gyrus, frontal pole; middle: middle frontal gyrus, inferior frontal gyrus, middle frontal gyrus, right: paracingulate gyrus, middle frontal gyrus, angular gyrus) show increased connectivity with left insula and caudate nucleus (top) following 10 days of CLAV treatment, CLAV dose 1000 mg/day.

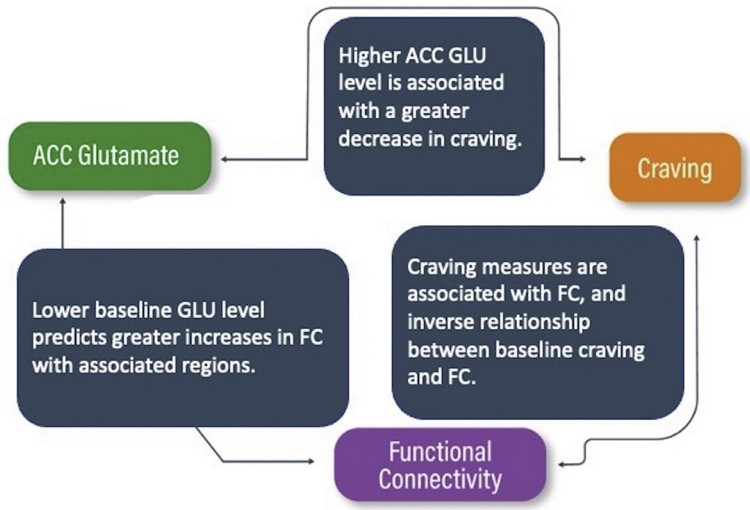

Figure 3. CLAV-mediated reciprocal relationships between ACC Glu concentration, FC, and cocaine craving.

Craving was associated with CLAV-mediated changes in FC

SN CLAV 750 mg, Day 6

Lower baseline craving was associated with higher SN FC with the SMA at Day 6 ($r = -0.617$, $P = 0.077$).

SN CLAV 1000 mg, Day 10

Greater craving change from baseline to Day 6 predicted higher SN FC with SMA at Day 10 ($r = 0.633$, $P = 0.067$). In addition, craving changes were correlated with SN FC changes from baseline to Day 10 ($r = 0.633$, $P = 0.067$).

ECN CLAV 750 mg, Day 6

Lower baseline craving was associated with higher ECN FC at Day 6 (750 mg CLAV) ($r = -0.700$, $P = 0.036$). Lower baseline craving was also associated with greater change in FC ($r = -0.650$, $P = 0.058$) from baseline to Day 6. Thus, those with low baseline craving had the highest FC and greatest changes in FC at the 750 mg dose in the ECN. The associations between low baseline craving and increased FC were not seen at Day 10, at the higher dose (1000 mg, data not shown).

ECN CLAV 1000 mg, Day 10

After 10 days of CLAV treatment high ECN FC with insula and caudate was strongly associated with decreased COC craving ($r = -0.833$, $P = 0.005$). ECN FC at Day 10 was inversely associated with COC craving at Day 6 ($r = -0.700$, $P = 0.036$). Those with the lowest COC craving at Day 6 had the highest FC at Day 10.

Discussion/Conclusion

This is the first published study investigating the brain actions of CLAV, a GLT-1 activator, in COC-dependent people using resting state fMRI and MRS.

Participants who attained high ACC Glu levels after CLAV treatment had strong decreases in craving (Figure 3). Reversing craving, or the desire to use COC, is considered a cornerstone of preventing COC relapse and maintaining abstinence. With CLAV treatment, ACC Glu concentrations might be considered as a potential biomarker of treatment effect on COC craving. While ACC Glu measurements during medication treatment are an impractical biomarker in the clinical setting, identification of a research biomarker can help in the discovery of a clinically useful biomarker of efficacy targeted toward decrease or abstinence in COC use.

People who chronically use COC have low levels of rostral ACC glutamate concentrations.[20] In this study, CLAV-treated COC users responded with increased ACC Glu concentrations and reduced COC craving. CLAV increases GLT-1, an astrocytic glutamate transporter.[6] One possible mechanism for increased ACC Glu is that CLAV treatment, through GLT-1, increases Glu transport to astrocytes. Glu is then rapidly converted to glutamine and transported to neurons for regeneration of neuronal Glu for synaptic release, thus accelerating the glutamate/glutamine cycle for glutamatergic neurotransmission. Ceftriaxone (CTX), another beta-lactam that enhances GLT-1 expression, upregulated expression of a key glutamine transporter, 9SNAT1, and glutaminase activity in mice.[21] CTX enhanced glutamine levels, which was transported into the neuron and was converted into Glu. CTX increased glutamate assembly in the neuron, which could then increase total glutamate concentration. CLAV, as a similar beta-lactam, could also increase activity of a key glutamate transporter to increase Glu levels, neurotransmitter cycling, and glutamatergic activity.

Our pilot study shows that 10 days of CLAV is associated with changes in RSN connectivity in two important brain networks implicated in addiction and that these changes are associated with decreased craving.

Individuals with lower baseline ACC glutamate responded to CLAV treatment with increased FC of two addiction-associated networks, the SN and the ECN (Figure 3), with brain regions implicated in craving control. In a study of another glutamatergic modulating medication, N acetylcysteine (NAC) in people with CUD, 2 days of NAC treatment was associated with increased FC of the dorsolateral prefrontal cortex (DLPFC) to the nucleus accumbens (NAc) during a cue-induced craving session. There was no relationship of FC to NAc Glu levels.[22]

In people with nicotine use disorder, 3.5 days of NAC treatment was associated with increased frontostriatal RSN FC.[23] Brain Glu levels were not measured. In our study with CLAV, the inverse relationship between FC and baseline glutamate in the SN and ECN suggests that CLAV is particularly effective in changing RSN connectivity in COC-dependent individuals who exhibit diminished glutamate levels.

Both salience and ECNs are critical to maintaining addictive behavior and represent two of the three large-scale brain networks in the “Triple Networks” important in maintaining substance use disorders.[24,25]

The SN mediates the incentive or reward associated with the stimulus. COC-associated stimuli orient the cortex to propel drug-seeking and taking.[26] At Day 6, the 750 mg dose, lower baseline COC craving was associated with higher FC with the SMA, part of the SN.[27] The SMA is the part of the cortex that regulates motor function. One interpretation might be that people with low baseline craving respond to CLAV treatment with increased motor control over drug-seeking/taking at either Day 6 of CLAV treatment or the CLAV dose of 750 mg/day.

The ECN mediates cognitive flexibility, decision-making, and attention.[26] Greater FC of the ECN was seen with the left insula and caudate nucleus after CLAV treatment. The insula detects salient events and initiates appropriate processing for control.[24] The left insula is part of the SN.[27] Greater ECN FC was associated with decreased COC craving, suggesting that one mechanism for down-regulation of craving is through improved executive control and decreased interest in COC. In a study (from China) in people with methamphetamine (Meth) use disorder, 4 weeks of transcranial magnetic stimulation (TMS) at the left DLPFC was associated with increased FC between the L-DLPFC and the inferior parietal lobe regions included in the ECN (FC $r = -0.53$, $P = 0.028$).[28] Decreased Meth craving was noted. Thus, in a TMS intervention to treat a different stimulant use disorder, improved ECN FC was associated with decreased craving.

Addiction science needs useful biomarkers indicating therapeutic effects. Both MRS ACC glutamate levels and rsfMRI FC changes are promising to be informative in this pilot study of CLAV in participants with CUD. Strengths include strong methods, supervised medication intake, dose escalation design, and the lack of substance use in an inpatient setting. Limitations include the small sample size and a PBO control group of insufficient size for comparison.

Though this was a pilot study, the data contribute to an understudied research area regarding pharmacological treatment of CUD, particularly related to effects on brain network connectivity changes. This study provides evidence supporting CLAV as an effective treatment for CUD with data supporting improved executive function and decreased craving in those who achieve high ACC glutamate levels. CLAV is attractive as a therapeutic medication for COC abuse because of its long safety record as part of the human antibiotic Augmentin. Future directions include outpatient studies that investigate CLAV’s usefulness for relapse prevention and abstinence initiation.

Declaration of competing interest

The authors declare the following financial or nonfinancial interests which may be considered as potential conflicts of interest: MFM receives support from Braeburn Pharmaceuticals (Plymouth Meeting PA). All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Author Contributors

MFM, NRB, and HLPK conceptualized and designed the study. HLPK acquired the data and was assisted by RC. JM, HLPK, MFM, RC, DY, MIW, XL, and NRB contributed to data analysis and interpretation. JM, RC prepared the manuscript under the direction of MFM and NRB. All authors reviewed and approved the final manuscript before publication.

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