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Altered power spectra in antisocial males during rest as a function of cocaine dependence: A network analysis

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Abstract

Abnormalities in the spectral power of offenders' neural oscillations have been noted within select Resting-State Networks (RSNs); however, no study has yet evaluated the influence of cocaine dependence, drug use severity, and psychopathic traits on these abnormalities. To this end, the present study compared rest-related power spectral characteristics between two groups of offenders (with and without a DSM-IV-TR cocaine-dependence diagnosis) and a non-offender control group. Results indicated that both offender groups presented with *lower low frequency power* ratio (LFPR) scores (i.e. across all RSNs) than non-offenders. These differences in LFPR scores were found to be due to both higher high-frequency power (0.15-0.25 Hz; within seven of eight investigated networks) and decreased low-frequency power (0.01-0.10 Hz; within six of eight investigated networks) in both offender groups compared to non-offenders. Thus, both cocaine-dependent and non-dependent offenders displayed consistently abnormal neural oscillations, suggesting that these oscillatory abnormalities could serve as a broad neurobiological marker of offender status. Offenders' LFPR levels correlated with lifetime years of cocaine use, but not with the level of psychopathic traits. These findings supplement our knowledge of the influence of substance use on resting-state activity in offenders; moreover, they provide further indication of the importance of evaluating shared/unique variance associated with drug use and antisocial personality traits.

Keywords

ICA; psychopathy; cocaine use; offenders; resting-state; fMRI

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Conflict of interest statement

None of the material included in our research article has been published previously, and it is not under consideration in another journal. All the coauthors have contributed significantly to this study and agree on the content and authorship of the manuscript. Isabelle Simard conceptualized and designed the study, analyzed and interpreted the data, as well as drafted the article and gave final approval of the version hereby submitted. William J. Denomme and Matthew S. Shane both contributed to the analysis and interpretation of data, critically revised the manuscript and gave final approval of the version submitted, additionally Dr. Shane acquired the data. None of us have conflicts of interest related to this study.

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1. Introduction

The spectral dynamics of resting-state networks (RSNs), which can be assessed through the evaluation of frequency oscillations across the power spectrum, have been hypothesized to underlie the synchronicity of rest-related activity in RSNs (Baria et al., 2011; Thompson & Fransson, 2015; Yaesoubi et al., 2017), and to provide generalized insights into the development and maintenance of healthy brain function (Pizoli et al., 2011). A typical normalized resting-state spectral profile consists of peak activity within low-frequencies (< 0.10 Hz), with sharply decreased activity occurring within mid- (0.10-0.149 Hz), and particularly within high-frequencies (0.15-0.25 Hz; Allen et al., 2011; Kalcher et al., 2014). A higher proportion of low-frequency activity at rest is believed indicative of a more stable, functional network (Biswal et al., 1996), whereas a higher proportion of high-frequency activity at rest has been linked to instability of network activity (Buzsáki & Draguhn, 2004; Salvador et al., 2008; but see DeRamus et al., 2020). Consistent with this view, considerable work has associated decreased low-frequency activity (Cauda et al., 2009; Garrity et al., 2007; Han et al., 2011; Malinen et al., 2010; Wang et al., 2016; Xu et al., 2014; Yu et al., 2014) and/or increased high-frequency activity (Cauda et al., 2009; Malinen et al., 2010; Otti et al., 2013; Sambataro et al., 2017) with numerous neurological and psychiatric disorders, including schizophrenia, chronic pain, bipolar disorder, major depressive disorder and amnesic mild cognitive impairment. The consistency and breadth of this body of work suggests that aberrant spectral patterns may serve as a common underlying feature of a wide variety of psychiatric disorders.

To date, only a handful of studies have reported on spectral dynamics within offender populations, and work has almost exclusively been conducted within adolescent samples (Liu et al., 2014; Thijssen et al., 2017; Zhou et al., 2015). Zhou and colleagues (2015) reported decreased *fractional amplitude of low frequency fluctuation* (fALFF) within adolescent offenders' bilateral amygdala/hypothalamus, right lingual gyrus, left cuneus and right insula. More recently, Thijssen and colleagues (2017) demonstrated that more prolonged cannabis use related to decreased low-frequency power within the Default-Mode Network (DMN), Executive Control Network (ECN) and sensory networks of adolescent offenders (more extended history of alcohol use also related to decreased low-frequency power within the right frontoparietal, salience, dorsal attention and sensory networks). Finally, the only study to have investigated spectral abnormalities within an adult offender sample to date (though the mean age of the sample was still only 20; Liu et al., 2014) reported reduced low-frequency fluctuations within the right orbitofrontal cortex, left temporal pole, right inferior temporal gyrus and left cerebellum of 32 offenders with antisocial personality disorder compared to 35 healthy controls. The consistency of these findings does provide preliminary support for the existence of spectral abnormalities in offending populations. However, the relative sparseness of the field, the small sample sizes employed, and the predominant focus on adolescent offenders does significantly limit the ability to form firm conclusions.

One distinct possibility is that offenders' oscillatory abnormalities are due to their generally higher levels of substance use disorders (SUD), which can reach prevalence rates as high as 74% (Peters et al., 1998) or even 95% (Kouri et al., 1997), and which are well-established to

impart long-lasting changes to neural integrity (e.g. Barrós-Loscertales et al., 2011; Cisler et al., 2013; Ma et al., 2015; Beard et al., 2019). Indeed, a growing body of work has begun reporting spectral disturbances within substance-dependent populations (Ide et al., 2016; Jiang et al., 2011; Wang et al., 2013), including evidence of increased thalamic fALFF (Ide et al., 2014) and decreased power spectrum scale invariance (i.e. weaker autocorrelation and signal persistence) in various frontoparietal regions (Ide et al., 2016) in cocaine dependent individuals. Similar results have been reported in heroin-dependent individuals within a variety of frontal, temporal, occipital and parietal regions (Jiang et al., 2011; Wang et al., 2013) in heroin dependent individuals. It should be noted, however, that the vast majority of this work has not been conducted within an offender population. Thus, important gaps remain regarding the extent to which dependence status underpins spectral abnormalities in offender populations.

To this end, the present study sought to evaluate the integrity of resting-state power spectral dynamics within two groups of offenders (those who do and do not meet DSM-IV diagnosis for cocaine-dependence) and within a control group without offending behavior. Resting-state networks were identified using Independent Component Analysis (ICA), and power spectral dynamics were evaluated within and between the three study groups. Based on the handful of studies conducted within offender samples, and on the work conducted to date within substance-using populations, we predicted decreased low-frequency activity and increased high-frequency activity (resulting in decreased *low frequency power ratio* (LFPR; the ratio of the integral of low-frequency activity to the integral of high-frequency activity, see Allen et al., 2011) in both offender groups compared to the non-offender controls. Identifying such power spectra disruptions in offenders could indicate incoherence in baseline neural activity in this population. Additionally, we sought to explore the extent to which network-related disruptions in offenders were characteristic of all RSNs or were instead specific to only certain resting-state networks. To this end, exploratory analyses compared/contrasted oscillatory patterns within each identified RSN, to evaluate for the existence of global versus network-specific effects.

Another possibility is that offenders' abnormal spectral patterns are due to their generally higher levels of antisocial traits, which have also been linked to substantive neural abnormalities, including decreased amygdalar and frontal activity (Blair, 2010; Poepl et al., 2019; Umbach et al., 2015), as well as increased fronto-insular cortex activity (Poepl et al., 2019). As a complicating factor, antisociality and substance abuse are themselves highly comorbidity (as high as 90% comorbidity by some estimates; Smith & Newman, 1990), making dissection of SUD/antisociality distinctions extremely difficult to parse. As this parcellation is a particular focus of work in our laboratory, we also conducted subsequent exploratory regression analyses to evaluate the extent to which SUD participants' spectral patterns could be explained as a function of either their drug-use severity or their psychopathic personality. To our knowledge, no work has yet investigated these issues as they pertain to spectral power in adult offenders; thus, while exploratory, results may provide preliminary insights that can help guide future progress into this underrepresented area.

2. Methods

2.1 Participants

One hundred and twelve right-handed male participants were recruited as part of a larger project focused on identifying various biomarkers of cocaine use disorders. Offenders were recruited through active recruitment at New Mexico probation/parole offices, temporary employment agencies, alcohol/drug treatment centers, and through print/online ads. Non-offenders were recruited solely through print/online ads. Offenders met initial screening criteria if they were on probation/parole, were 18-55 years of age, had a felony-level conviction history, did not self-report psychotic disorders or use of antipsychotic medications, and matched fMRI acquisition criteria (e.g. no metal in the body, no history of major head trauma, no pregnancy, right-handedness). Subsequent screening excluded for lifetime history of a psychotic disorder (one exclusion), major depressive disorder within the last six months, current use of antipsychotic medications (9 exclusions), and full IQ estimates < 70. Non-offenders were matched on important demographic variables to the extent possible, but self-reported having no criminal record. Following all screening mechanisms, 102 participants were included in final analyses (37 Cocaine-Dependent, 47 Non-Dependent and 18 non-offenders; see Table 1 for full demographics). This study was approved by the Research Ethics Board of the University of New Mexico. Participants provided written informed consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2 Clinical/Forensic Assessments

2.2.1 SCID-I/P—The Structured Clinical Interview for DSM-IV-TR (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2002) was used to evaluate participants for Axis I and II disorders. Interviews were videotaped and conducted by highly trained Master's level research personnel, under the guidance of a senior SCID trainer (R.C.; see acknowledgements).

2.2.2 Psychopathic traits—Offenders were assessed for psychopathic traits via a semi-structured Psychopathy Checklist-Revised (PCL-R) interview (Hare, 2003), videotaped and conducted by highly-trained research personnel (trained by M.S.). Subsequent file reviews were not possible; thus, participants were scored 0 to 2 on each of the 20 PCL-R items based on the clinical interview alone (see Denomme et al., 2018, 2020; Forth et al., 1996; Kosson et al., 1997 for evidence of the validity of this approach).

2.2.3 Cocaine use—The number of years of regular drug use was evaluated using a modified Addiction Severity Index - Expanded (ASI-X; McLellan et al., 1992), administered orally by a trained examiner. As offenders were recruited based on cocaine abuse/dependency diagnoses, total years of Lifetime Cocaine Use (LCU) was included in relevant analyses throughout this study.

2.2.4 Drug use—Following administration of the ASI-X, composite scores of total drug use (other than cocaine) were calculated by summing the total years of use of drugs that corresponded to two categories: Major drugs (i.e. methamphetamines, opiates/analgesics,

heroin) and Minor drugs (i.e. alcohol, cannabis, nicotine, hallucinogens and inhalants). Thus, for example, if a participant used cannabis for 3 years, hallucinogens for 5 years and nicotine for 5 years, their Minor drug use score was calculated as 13 years. In addition, a ‘Total drug use’ score was calculated as the sum of major + minor drug use. These drug use scores were included as covariates in supplementary regression analyses, to examine whether reported results were specific to cocaine use, or instead generalized to other drugs of abuse.

2.2.5 WAIS-III—Full-scale intelligence quotient was approximated using the vocabulary and matrix reasoning scales of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III).

2.3 Data acquisition

Resting-state data was acquired using a 3T Magnetom Trio Tim Siemens scanner at the Mind Research Network (MRN). Participants kept their eyes open and directed at a fixation cross. The 5.5 minutes acquisition was performed using a fast gradient-echo EPI sequence. Imaging parameters were as follows: TR = 2000ms, TE = 29ms, FA = 75°, matrix = 63 x 63, slices = 33 acquired in an ascending interleaved fashion, slice thickness = 3.5 mm, FOV = 240mm x 240mm and voxel size = 3.8 x 3.8 x 3.5mm.

2.4 Preprocessing

Resting-state data was preprocessed using SPM12. Data was motion-corrected using INRIAAlign (Freire et al., 2002). Realignment was handled using a distance cut-off of 2.5, with data coregistered with a full-width-at-half-maximum (FWHM) of 8mm. Slice timing correction was applied using the 16th slice as reference. Data was then normalized using the SPM5 EPI template; the mean image was used for parameter estimation. Finally, data was smoothed using a 10mm Gaussian kernel. No participant presented movement above 5mm. Hence, after preprocessing, all participants were included in analyses.

2.5 Independent Component Analysis (ICA)

Following preprocessing, ICA was performed on all 102 participants using the GIFT toolbox (GroupICAT v4.0b, <https://trendscenter.org/software/>) following well-established methodology (Allen et al., 2011). The spatial group ICA (GICA) was set to identify a high number of components (75) using the Infomax algorithm. To ensure the stability of the estimation, the Infomax ICA algorithm was repeated in *Icasso* 20 times. Two GICA back-reconstruction steps were performed to produce subject-specific spatial maps (SMs) and time courses (TCs); results were subsequently scaled to z-scores.

The ICA analysis yielded 75 components, constructed by grouping individual voxels that were synchronously activated during rest. Components were manually classified into two groups: resting state and noise. Components were classified into resting-state based on the methodology recommended by Allen et al. (2011): component t-maps showed activity in grey matter areas, activity peaks between 0.01-0.08 Hz followed by flat activity in high frequencies, a low to high-frequency ratio higher than 4, and a cluster stability index (I_q) of at least 0.80. Components displaying spectral activity non-typical of resting-state networks (i.e. activity outside of grey matter, a flat power spectrum, or power spectrum with an

activity peak in high-frequency) were classified as noise. One-sample t-tests were performed using SPMstats in GIFT to create SPM12 compatible t-maps. Activity peaks in each component were visually inspected, identified using PickAtlas 3.0.5 (Maldjian et al., 2003), matched with key regions of known resting-state networks using the 90 fROIs Atlas (Shirer et al., 2012), and classified into the corresponding RSN category.

Following component selection (Allen et al., 2011), 34 components (from the original 75) were selected as representing valid BOLD activity. Following network categorization based on the 90 fROIs atlas (Shirer et al., 2012), these 34 components were categorized into one of DMN, ECN, Posterior Salience (PS), Visual, Basal Ganglia (BG), SMN, Language (LG) and Auditory (AU) networks (see Figure 1).

2.6 Spectral Analyses

Power spectra were computed for each participant using spectral group comparison analyses in GIFT. Following the widely used process for categorizing frequency bands (Allen et al., 2011; Bryant et al., 2016), power spectra data were pooled into three bins representing low- (< 0.10 Hz), mid- (0.10 to 0.149 Hz) and high-frequency (0.15 to 0.25 Hz) activity. Analyses focused exclusively on the low and high frequency bands, as both the function and dynamics of mid-frequency activity are significantly less characterized in the broader clinical literature. Spectral data for each participant was then extracted for further analysis in SPSS 22.

2.7 Data Analytic Strategy

A 3 (Group) x 2 (Bins) x 8 (Network) omnibus ANOVA was used to evaluate all higher-order effects, followed by targeted comparisons used to evaluate specific hypothesized effects. This analytic strategy provides the greatest granularity with regard to the nature of spectral distributions in offenders, and thus served as our primary analytic pipeline. However, because the literature tends to focus predominantly on low-frequency centered metrics (e.g. ALFF, fALFF, LFPR) as a single predictive metric, we also report differences in LFPR scores, which have previously been used as a predictor in a clinical setting (see Yu et al., 2013).

In addition, hierarchical regression models were employed, using interview-based PCL-R scores, LCU, and their interaction as regressors, to explore the potential influence of psychopathic traits and LCU on power spectra integrity. These models were run with and without lifetime use of other substances as covariates in the model, to ensure that reported effects were specific to lifetime cocaine burden rather than the burden of other comorbid substances. Results of these analyses can be found in the supplementary material Sections 7 to 12.

3. Results

3.1 Demographics

As can be seen in Table 1, rates of comorbid psychiatric disorders were generally low, with no prevalence differences between offender groups, $\chi_s = 1.97, 0.03$). Interview-based PCL-

R scores ($M = 20.79$) were closely in line with previously published norms collected through interview + file review methods in offender populations (Hare, 2003).

One-way ANOVA identified group differences in LCU, ($F = 28.79$, $p < 0.001$), with the Dependent group ($M = 7.00$, $SD = 6.66$) showing higher LCU than either the Non-Dependent ($M = 0.47$, $SD = 1.67$; $t = -5.82$, $p < 0.001$) or Non-Offender ($M = 0.33$, $SD = 1.29$; $t = 5.89$, $p < 0.001$) groups. As expected, the Dependent group ($M = 23.19$, $SD = 6.57$) also manifested higher PCL-R scores than the Non-Dependent group ($M = 18.90$, $SD = 7.43$; $t = -2.76$, $p < 0.05$; Non-Offenders did not receive the PCL-R interview). No main effect of IQ was identified; however, the Dependent group ($M = 35.11$, $SD = 8.36$) was somewhat older than the Non-Dependent ($M = 32.13$, $SD = 9.3$; $t = -1.52$, $p > 0.05$), and Non-Offender ($M = 30.87$, $SD = 9.27$; $t = 3.32$, $p < 0.05$) groups. Analyses reported within were reported without controlling for age, as the well-established collinearity between age and LCU (Wagner & Anthony, 2002) may influence validity/interpretability of age-controlled models. However, we also provide age-controlled results in Section 1 of Supplementary Materials.

Correlational analyses indicated that PCL-R scores were positively correlated with negatively correlated with IQ ($r = -0.26$, $p = 0.02$), and uncorrelated with age ($r = -0.01$, $p = 0.95$), whereas LCU was positively correlated with age ($r = 0.45$, $p < 0.001$), but uncorrelated with IQ ($r = -0.11$, $p = 0.27$). LCU and PCL-R scores showed a modest positive relationship ($r = 0.26$, $p = 0.02$).

3.2 Spectra analyses

The omnibus ANOVA identified a main effect of Group, $F(2, 99) = 9.92$, $p < 0.001$, with pairwise comparisons indicating that Dependent ($M = 0.83$; $SD = 0.05$) and Non-Dependent ($M = 0.83$; $SD = 0.05$) groups showed similar overall power spectra, $p = 1.00$, that were both higher than Non-Offenders ($M = 0.79$; $SD = 0.07$; both $ps < .05$). Main effects of Network, $F(7, 99) = 8.13$, $p < 0.001$, and Bin $F(1, 99) = 1116.57$, $p < 0.001$, were also observed, with the low frequency bin ($M = 1.15$; $SD = 0.08$) showing higher overall power than the high-frequency bin ($M = 0.56$; $SD = 0.10$). These main effects were influenced by significant Group x Bin, $F(2, 99) = 6.19$, $p = 0.003$, and Network x Bin, $F(7, 99) = 13.20$, $p < 0.001$, interactions. The Group x Network, $F(14, 99) = 1.39$, $p = 0.15$, and Group x Bin x Network, $F(14, 99) = 0.94$, $p = 0.63$, interactions did not reach significance.

As no interactions with Network were found, we collapsed mean spectral values across all networks and evaluated for group differences in low-/high-frequency bins via Bonferroni-corrected pairwise comparisons. As can be seen in Figure 2 (see also Section 2 of Supplementary materials), while the two offender groups did not present with differences across either low or high frequency bins, several differences were observed between these groups and the Non-Offender group. Specifically, both offender groups showed significantly decreased low-frequency power spectra compared to Non-Offenders (Dependent Offenders: $t = -3.29$, $p(\text{Family Wise Error (FWE)}) = 0.002$; Non-Dependent Offenders: $t = -2.26$, $p(\text{FWE}) = 0.03$), and significantly increased high-frequency power compared to Non-Offenders (Dependent Offenders: $t = 4.25$, $p(\text{FWE}) < 0.001$; Non-dependent Offenders: $t = 3.24$, $p(\text{FWE}) = 0.002$). As may be expected, given the pattern of low/high frequency

activity reported, both Dependent Offenders ($M = 5.83$, $SD = 2.94$; $t = -2.29$, $p(FWE) = 0.03$) and Non-Dependent Offenders ($M = 5.64$, $SD = 3.13$; $t = -2.38$, $p(FWE) = 0.03$) presented with significantly decreased LFPR in comparison to Non-Offenders ($M = 10.76$, $SD = 8.91$; see Figure 3).

3.3 Exploratory network analyses

The non-significant interactions with Network suggested that observed differences in spectral power occurred similarly across all RSNs. To more formally evaluate the extent to which this was true, we compared LFPR between our three participant groups within each of the eight RSNs. As displayed in Figure 4, the two offender groups presented with highly similar spectral profiles within each RSN (all p s > 0.05), which differed from the Non-Offender group's frequency profiles within several RSNs. Most consistent was an increase in high-frequency power, which was characteristic of five of the Dependent groups' RSNs, and seven of the Non-Dependent groups' RSNs. On the other hand, reductions in low-frequency power were identified within six of the Non-Dependent group's RSNs, but only one of the Dependent group's RSNs (the DMN; see Section 3 of Supplementary materials for results of higher order effects). Together, this led to significantly reduced network-specific LFPR scores compared to Non-Offenders in a highly overlapping set of four of the Dependent group's RSNs (DMN, ECN, LG and AU), and four of the Non-Dependent group's RSNs (DMN, ECN, LG and BG; see Section 4 of Supplementary materials).

3.4 Exploratory contributions of LCU and psychopathy

Exploratory regression models evaluating the influence of LCU and/or interview-based PCL-R scores on LFPR were conducted separately for Dependent and Non-Dependent groups, as LCU levels showed a quite restricted range within the Non-Dependent group. In the Dependent group, only LCU negatively predicted Total LFPR, while PCL-R and the LCU x PCL-R interaction were unproductive (see Section 5 of Supplementary materials for detailed results). Importantly, this negative relationship with LCU was identified within seven of the eight investigated RSNs (see section 6 of Supplementary materials); moreover, these findings were only minimally affected by the inclusion of 'major', 'minor' or 'total' substance use metrics as model covariates (see section 2.2.4 for definitions of major/minor/total substance use). Thus, LCU appeared to serve as a broad-spectrum marker of spectral imbalance in the cocaine-dependent offenders that could not be attributed to the use of comorbid substances.

Figure 5 displays a plot of LCU and overall LFPR within the Dependent offenders. As can be seen, this relationship was curvilinear and negatively-skewed, $r = -0.39$, $p = 0.016$; see the best-fit line in Figure 5), with data populating only three of four quadrants. Of potential importance, visual inspection of the data suggests that all offenders who presented with LCU levels > 10 years showed lower LFPR scores (i.e. less than 6), while all offenders with LFPR > 8 reported LCU levels < 8 years. To formalize these observations, we used k-means clustering to evaluate the efficacy of both 2-cluster and 3-cluster models. Results indicated that the 2-cluster model (Silhouette coefficient = 0.62, Calinski-Harabasz index = 78.76, Davies-Boulding index = 0.50) performed better than the 3-cluster model (Silhouette coefficient = 0.45, Calinski-Harabasz index = 66.58, Davies-Boulding index = 0.82). Given

the modest sample size, the precision of this solution should be considered preliminary; however, previous guidance on the use of clustering techniques suggests that a minimum of 30-40 participants per variable (in line with the present study) is sufficient to provide adequate reliability (Clatworthy et al., 2007; Dalmaijer et al., 2020; Dolnicar et al., 2014).

Similar regression models undertaken within the Non-Dependent group showed no significant relationships. Nor were any relationships revealed when regression models were conducted across the entire offender sample. However, two caveats: First, it should be reiterated that the range of LCU scores in the Non-Dependent group were significantly restricted, making interpretation of these null results with cocaine difficult. Second, supplementary analyses indicated that 'minor' and 'total' drug use metrics (see section 2.2.4 for definitions) did correlate negatively with LFPR in the Non-Dependent participants (see Sections 7 to 12 of Supplementary materials).

4. Discussion

The primary aim of our study was to investigate the integrity of rest-related spectral power in antisocial offenders with and without DSM-IV diagnoses of cocaine dependence. Our results indicated broadly disrupted neural oscillations within both offender groups, compared to a group of non-offender controls. Indeed, both offender groups showed reduced low-frequency power, and increased high-frequency power, compared to the Non-Offender group. In total, these spectral disruptions led to lower global LFPR levels in both offender groups within seven of the eight investigated RSNs. Work of this nature is currently sparse; however, the current results are consistent with a handful of studies that have reported spectral abnormalities in a variety of offender populations, including adult offenders with antisocial personality disorder (Liu et al., 2014), and adolescent offenders with antisocial tendencies (Thijssen et al., 2017; Zhou et al., 2015). These results expand on this previous work by suggesting that the observed abnormalities may a) represent a pervasive disturbance characteristic of a majority of RSNs, and b) be largely independent of cocaine dependence status.

4.1 Interpretations of spectral abnormalities in offenders

An understanding of the role of low- and high-frequency activity during rest remains in its infancy; however, several interpretations have been offered. The traditional view posits low-frequency activity during rest as a marker of neural efficiency, and high-frequency activity during rest as indicative of increased 'neural noise' (Biswal et al., 1995). In line with this view, the decreased LFPR levels in both offender groups may be interpreted as indicative of neural inefficiencies. Importantly, our results extend previous findings by suggesting that disruptions in offenders are not network-specific, but rather extend broadly to a majority of rest-related neural activity disruptions.

Other research, relying more on task-related activity (i.e. non-rest), suggests that high-frequency activity may play an active, functional role in network dynamics (see Baria et al., 2011; Craig et al., 2017; Gohel & Biswal, 2015). For instance, Baria and colleagues (2011) reported that high-frequency activity often related to increased BOLD response within cortical regions involved in higher-level cognitive processes (i.e. OFC, temporal cortex). In

contrast, the low-frequency activity often related to BOLD response within subcortical regions involved in lower-level processes (i.e. posterior precuneus, posterior cingulate). Moreover, Craig and colleagues (2017) observed that high-frequency activity in the DMN was strongly engaged during cognitively demanding tasks. These results suggest that in the DMN, at least, high-frequency activity may play an as-yet-undetermined functional role (Craig et al., 2017). Though speculative, through this lens, our results could suggest the increased engagement of resource-demanding activity during rest in offenders.

Interestingly, some research has linked variation in spectral activity to variation in the synchrony/coherence across disparate neural regions (Anderson et al., 2014; Biswal et al., 1995; Di et al., 2013). For instance, Anderson and colleagues (2014) found a positive relationship between low-frequency amplitudes and local connectivity across the brain. Similarly, low-frequency fluctuations have been associated with connectivity within the motor network during rest (Biswal et al., 1995) and ALFF values (calculated between 0.01 and 0.08 Hz) were strongly related to connectivity strength within and between various RSNs/ROIs (Di et al., 2013). One possibility then is that our result of altered power dynamics in offenders could underpin disruptions in functional connectivity. This interpretation is consistent with numerous reports of connectivity disruptions in offenders (Contreras-Rodríguez et al., 2015; Hoppenbrouwers et al., 2014; Jiang et al., 2017; Leutgeb et al., 2016) and cocaine users (Geng et al., 2017; Ide et al., 2016; Martins et al., 2018; McCarthy et al., 2017; Prichep et al., 2002). Hence, our results demonstrating that both offender groups present decreased LFPR in the DMN, ECN, and language networks in comparison to non-offenders could be indicative of functional connectivity disruptions in these networks.

4.2 Implications for Dependence

Interestingly, both offender samples showed similar oscillatory differences compared to the non-offender controls; moreover, no between-group differences were observed between the Cocaine-Dependent and Non-Dependent Offenders. Thus, all offenders appeared to show common atypical neural oscillations that were largely independent of their drug dependence status. While these results could be seen as running somewhat counter to reports of spectral disruptions in cocaine-dependent (Ide et al., 2016, 2014) and heroin-dependent (Jiang et al., 2011; Wang et al., 2013) individuals, it should be noted that these previous studies were conducted within non-offender samples (and showed a combination of increased and decreased fALFF levels). This distinction may be important, should an aspect of the offender lifestyle itself underpin the observed spectral abnormalities. For instance, we note a handful of studies that have connected neural/cognitive abnormalities to environmental factors such as early life adversity (Dismukes et al., 2015; Kolla et al., 2014), and incarceration itself (Gendreau et al., 1972; Johnson et al., 2015; Umbach et al., 2018). It would be interesting for future research to evaluate the effects of these environmental factors on spectral integrity and/or other neural features.

The results from the present findings will require additional confirmation, optimally with larger samples of participants. However, if the results hold, it would be interesting to consider the potential for targeting abnormal oscillatory patterns in offender populations as

treatment/rehabilitative targets. To our knowledge, no fMRI-based power spectra treatment protocols have been tested within offending populations, however, an EEG-based protocol has shown preliminary efficacy reducing aggression and impulsivity in violent offenders through regulation of frequency dynamics (Konicar et al., 2015). Clearly only so much should be made of this at present; however, the finding does serve as an early demonstration that oscillatory disruptions can be remedied, and that this change can have an impact on downstream behavioral/cognitive constructs in offenders.

4.3 Influence of LCU and/or PCL-R scores on spectral abnormalities in offenders

While we identified no differences in spectral dysfunction between the Dependent and Non-Dependent offender groups, the length of lifetime cocaine use (but not interview-based PCL-R scores) was negatively predictive of spectral dysfunction within the Dependent group. One possibility then is that it is not dependence status, but rather the lifetime drug burden, that is most relevant to the degree of spectral dysfunction in offenders. These findings partially replicate a recent report regarding the detrimental influences of drug use on spectral integrity in antisocial adolescents (Thijssen et al., 2017), but serve as the first demonstration of this effect within adult offenders. In contrast, neither LCU nor PCL-R scores predicted the magnitude of spectral dysfunction in the Non-Dependent group. Given the restricted range of LCU in the Non-Dependent group, it would be premature to read too much into these group differences. However, one possibility deserving of future consideration is that drug use severity may serve as an important predictor of dysfunction only after it reaches a certain threshold, whereas other (as of yet unidentified) factors (e.g. personality traits, early life adversity, length of incarceration) could serve more explanatory roles in individuals with less substance use/abuse problems. Consistent with this interpretation, supplementary analyses indicated that some metrics of noncocaine drug use (ie. 'minor' and 'total' drug use), which the Non-Dependent group did show measurable levels of, did correlate with LFPR. At the least, these results further highlight the need for increased work that treats the offender population as a heterogeneous group, with unique, if overlapping, risk factors.

5. Limitations

Several limitations are important to note. First, as the highest identifiable frequency in a power spectrum is equal to $\frac{1}{2}$ the sampling rate (Weik, 2001), the upper-bound limit for the observable frequencies of the time series was limited to < 0.25 Hz given the 2 sec TR. However, high-frequency activity has been shown to contribute to network activity up to 1.4 Hz when using a shorter TR of less than 500 ms (Boubela et al., 2013). A faster TR should be used in future work to investigate the contribution of all ranges of high-frequency activity to resting-state activity in offenders. Second, while our reliance on male-only data will provide the greatest comparison to the extant literature, generalization to female offenders should be undertaken with caution. Particularly given reports of significant differences between male/female offenders (Colins et al., 2017; Rogstad & Rogers, 2008), a future evaluation within a sample of offending women will be crucial. Third, in light of the non-significant effects with PCL-R scores, we should note that our assessment of psychopathy entailed an interview-only process that did not include subsequent file review. While this assessment process has been previously accepted (e.g. Forth et al., 1996; Kosson et al.,

1997), and has elicited valid, significant findings in several previous imaging studies (Denomme et al., 2018, 2020; Arbuckle & Shane, 2016; Shane & Groat, 2018), it does not follow official PCL-R scoring guidelines (Hare, 1991). Thus, the possibility that differences in scoring methodologies are responsible for the null findings should not be completely overlooked. Finally, we note that participants' LCU scores correlated moderately-to-highly with their age in our sample. This is hardly unexpected, however, the inherent collinearity between substance use burden and age does complicate the ability to dissect their influence on rest-related neural activity (see supplementary analyses for results that control for age, but these should be interpreted with caution given due to this collinearity). That said, the fact that LCU only correlated with LFPR in the Dependent group (where LCU variance was sufficient to reliably interrogate the effect) suggests that LCU, and not age, wielded the important influence in our dataset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Offenders present lower whole-brain rest-related *low-frequency power ratio (LFPR)* compared to non-offenders
- Offenders present increased high- and decreased low-frequency power in various RSNs
- LFPR in cocaine-dependent offenders correlates with lifetime years of cocaine use
- Dependence status does not influence power spectra profiles in offenders
- Oscillatory abnormalities could serve as a neurobiological marker of offender status

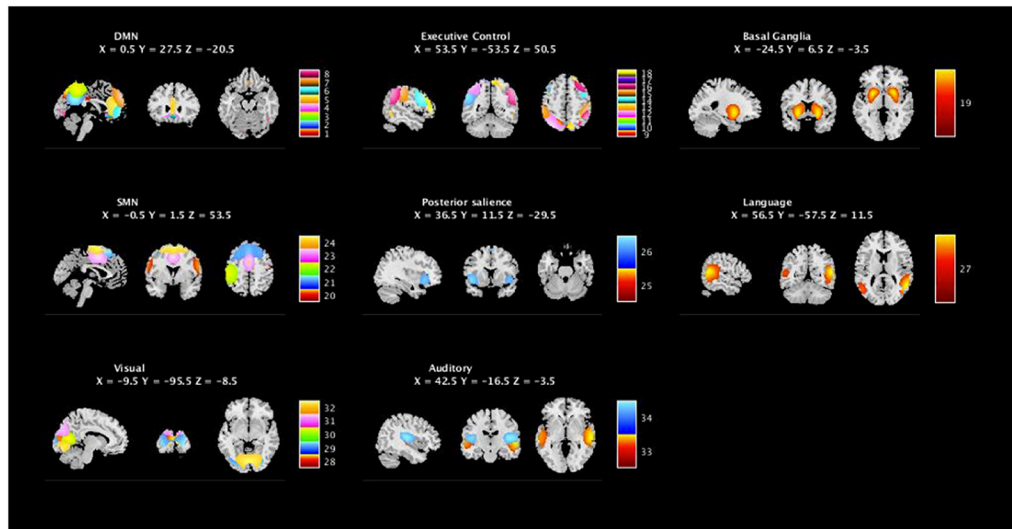


Figure 1. Network classification of valid resting-state components

Resting-state component classification yielded 34 components of interest. RSN classification, using the peak of activity of the components, allowed us to categorize those components in 8 RSNs: Default mode (DMN), Executive Control (ECN), Basal Ganglia, Sensorimotor (SMN), Posterior Salience, Language, Visual and Auditory networks. $p(\text{FWE}) < 0.05$

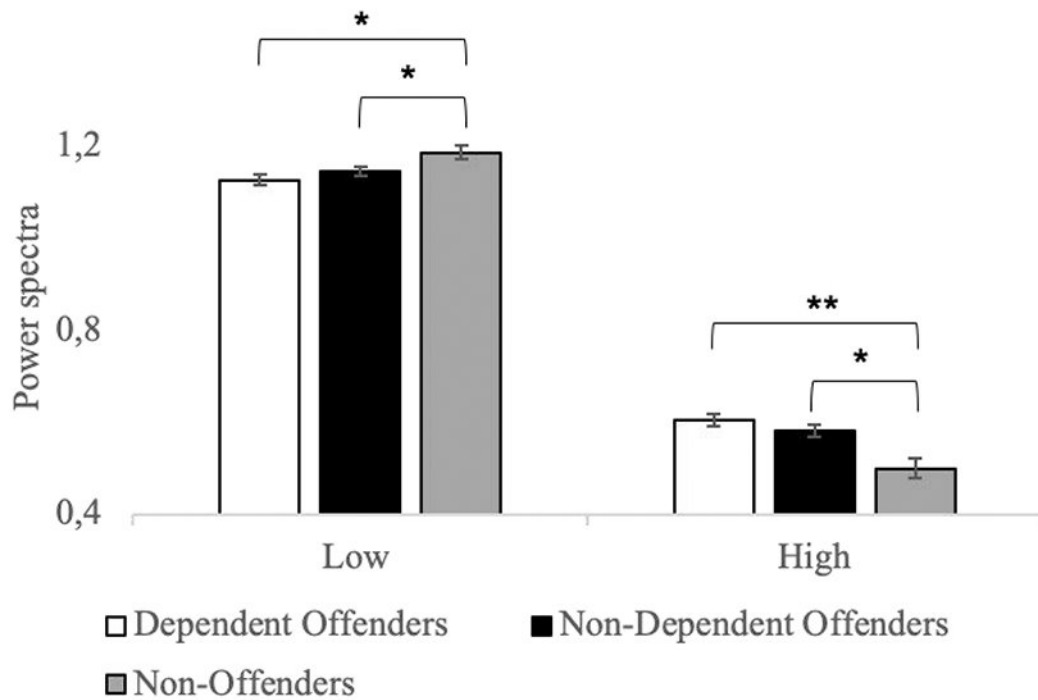


Figure 2. Mean power spectra differences between groups during the overall resting-state activity

Mean power spectra differences in the low-, mid- and high-frequency bins between Dependent Offenders (white), Non-Dependent Offenders (black), and Non-Offenders (grey) during overall resting-state activity. Dependent and Non-Dependent Offenders exhibited an overall lower activity amplitude during low-frequency activity and a higher activity amplitude during high-frequency activity in comparison to Non-Offenders. However, no significant differences were observed between the two Offender sub-groups in any of the frequency bins.

* $p(FWE) < 0.05$ ** $p(FWE) < 0.001$, error bars = SEM

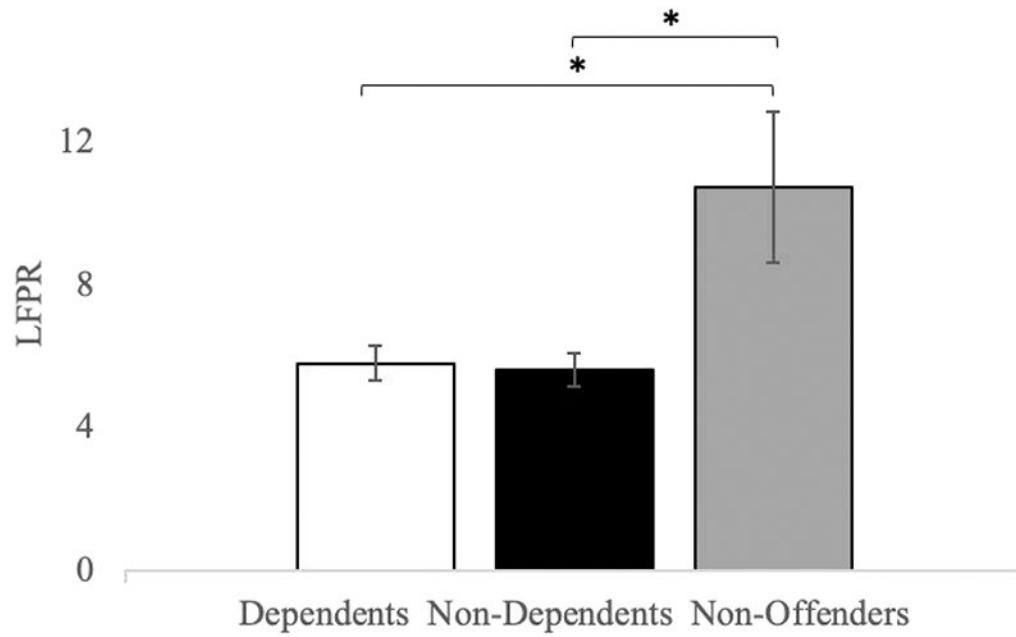


Figure 3. LFPR differences between groups across all networks

Mean differences in LFPR between Dependent Offenders, Non-Dependent Offenders and Non-Offenders during overall resting-state activity (i.e. across all networks). Both Offender sub-groups displayed significantly lower LFPR in comparison to Non-Offenders; however, no differences were observed between Dependent and Non-Dependent Offenders.

* $p(\text{FWE}) < 0.05$, error bars = SEM

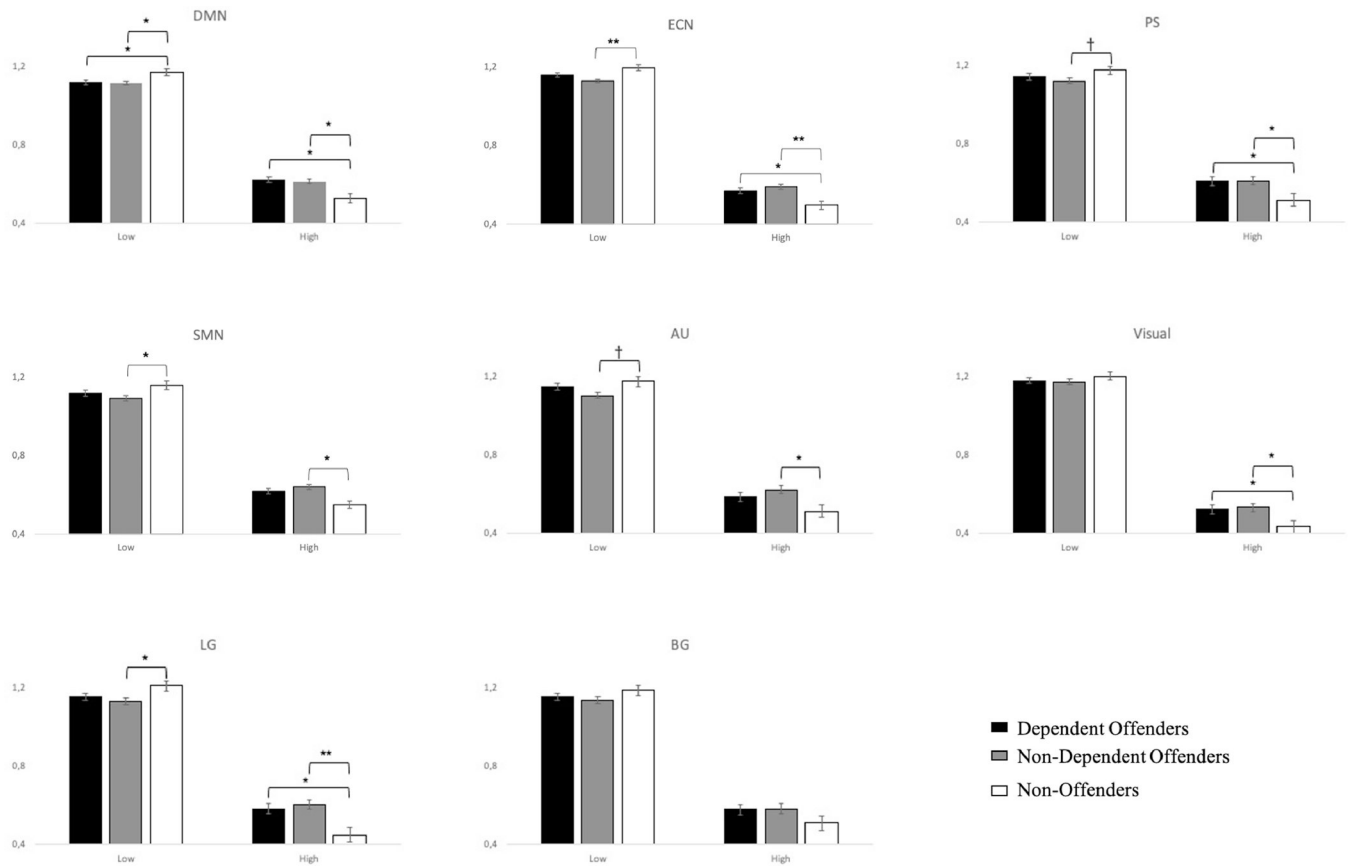


Figure 4. Pairwise comparisons in power spectra between groups in each RSN
 Mean power spectra differences between Dependent Offenders, Non-Dependent Offenders and Non-Offenders in the low- and high-frequency bins in each RSN during rest.
 † $p(FWE) < 0.10$ * $p(FWE) < 0.05$ ** $p(FWE) < 0.001$, error bars = SEM

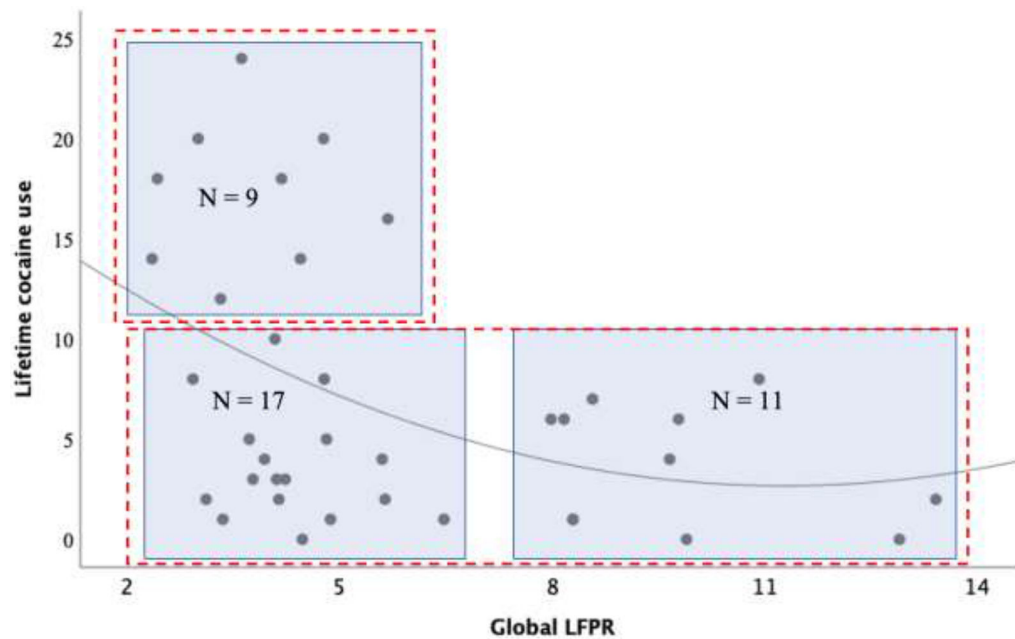


Figure 5. Relationship between lifetime cocaine use and global LFP in the Dependent Offender group

The negative curvilinear relationship between lifetime cocaine use and LFP during overall resting-state activity in Dependent Offenders. The red dotted-lined rectangles represent a 2-cluster representation of the relationship between LCU and LFP with 9 Dependent Offenders presenting LCU > 10 and LFP < 7, as well as 28 with LCU < 10 and ranging LFP. The blue rectangles represent a 3-cluster representation between LCU and LFP with 9 Dependent Offenders presented LCU > 10 years with a LFP < 7, 17 with LCU < 10 years and LFP < 7, 11 with LCU < 10 years and LFP > 7, while no Dependent Offenders presented a LCU > 10 years and LFP > 7.

Table 1

Participant demographics

	O (N = 84)		DO (N = 37)		NDO (N = 47)		NO (N = 18)		Group differences (t scores)	
	Mean Range SD	N	Mean Range SD	N	Mean Range SD	Mean Range SD	O vs NO	DO vs NO	NDO vs NO	DO vs NDO
Age	33.44 20-59 8.97		35.11 22-56 8.36		32.13 20-59 9.30	30.87 18-50 9.27	2.63 *	3.32 *	1.90	-1.52
IQ	105.76 77-137 11.84		106.03 80-137 11.74		105.55 77-131 12.04	112.60 89-131 12.50	-1.99 *	-1.77	-1.93	-0.18
ASI-X										
LCU	3.35 0-24 5.61	7	7 0-24 6.66		0.47 0-10 1.67	0.33 0-5 1.29	4.48 **	5.89 **	0.31	-5.82 **
Major Drugs	4.51 0-31 6.87		6.38 0-31 7.24		3.04 0-29 6.26					1.58
Minor Drugs	21.55 0-74 16.25		27.05 1-61 14.82		17.21 0-74 16.15					1.05
PCL-R										
Total	20.79 4-34 7.34		23.19 12-34 6.57		18.90 4-34 7.43					-2.76 *
Factor 1	7.32 2-15 3.51		8.09 2-14 3.21		6.71 2-15 3.64					-1.81
Factor 2	12.09 2-20 4.09		13.38 3-20 3.83		11.08 2-19 4.05					-2.66 *
SCID										
GAD		1		1						
MDD		7		4						

Demographic data on age, IQ, Lifetime Cocaine Use (LCU), Major Drug use (combining years of use of methamphetamines, opiates/analgesics, heroin), Minor Drug use (combining year of use of alcohol, cannabis, nicotine, hallucinogens and inhalants), PCL-R and SCID diagnosis (i.e. General Anxiety Disorder (GAD) and Major Depression Disorder (MDD)) reported separately for Dependent Offenders (DO), Non-Dependent Offenders (NDO) and Non-Offenders (NO). Group differences between Offenders (O), DO, NDO and NO were evaluated via between-group t-tests.

* $p < 0.05$

** $p < 0.001$