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Neuroplastic effects of changes in cocaine use intensity on resting-state functional connectivity of the brain: a longitudinal study

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Abstract

Background: Chronic cocaine use is associated with physical, neuropsychiatric, and social consequences. While cocaine-induced neuroplasticity is well-studied in animal models, less is known about recovery of the human brain after prolonged exposure. This longitudinal functional MRI (fMRI) study therefore examined whether (1) whole-brain and fronto-striatal resting-state functional connectivity (rsFC) are modulated by reduced cocaine use and (2) baseline fronto-striatal rsFC predicts future cocaine intake in individuals with chronic cocaine use (ICCU).

Methods: We analysed rsFC data from 32 ICCU (15 sustained users [SU], 17 decreased users [DU]) and 38 matched cocaine-naive controls (CNC) collected at baseline and long-term follow-up (median interval: 10.3 months). Whole-brain rsFC was compared between ICCU and CNC and fronto-striatal rsFC was examined within ICCU subgroups. Additionally, we tested whether baseline rsFC predicted future cocaine use and intensity or craving.

Results: At TP1, no striatal-prefrontal rsFC differences emerged between SU and DU. At TP2, SU exhibited widespread whole-brain hyperconnectivity versus CNC and stronger striatal rsFC (pallidum/nucleus accumbens to superior frontal gyrus; caudate anti-correlation to inferior frontal gyrus) versus DU (rm-ANCOVA, $p<0.05$, cluster-corrected). Baseline TP1 striatal-prefrontal rsFC significantly predicted TP2 cocaine use ($R^2=0.892$; caudate fronto-striatal connectivity surviving FDR correction), whereas the craving model showed high in-sample fit ($R^2=0.975$) but no single seed survived FDR correction.

Conclusion: Our findings indicate that altered rsFC in ICCU reflects widespread network disruption, while rsFC changes partially normalize toward control-like patterns with reduced cocaine use. Finally, fronto-striatal rsFC might be useful to predict cocaine use trajectories for individualized treatment of cocaine use disorder.

Introduction

Cocaine remains one of the most widely used illegal substances, with approximately 18 million people worldwide and 2.2 million in the United States reporting lifetime use (https://library.samhsa.gov/product/2023-nsduh-report/pep24-07-021). Recent data from a study including ~20,500 adults show a significantly greater mortality risk among those reporting lifetime cocaine use[1]. Additionally, cocaine and methamphetamine are both proposed to cause long-term changes to the brain's dopaminergic pathways contributing to the high addictive potential of these substances[2, 3].

Structural magnetic resonance imaging (MRI) studies have shown that chronic cocaine use (CCU) affects several brain regions, particularly those involved in reward processing and executive control[4, 5]. Yet, mega-analyses of individuals dependent on one of five substances (alcohol, nicotine, cocaine, methamphetamine, and cannabis), found subcortical volumetric alterations driven by alcohol dependence but not cocaine or other substance dependences[6, 7]. Functional MRI (fMRI) studies of cue-induced BOLD signal changes revealed that CCU increased activity in the nucleus accumbens (NAc), basal forebrain, and ventral tegmental area, while decreasing activity in the amygdala and medial prefrontal cortex[8-10]. These regions are highly interconnected[11], forming key nodes of the brain's reward circuitry, and their dysfunction is thought to underlie many of the cognitive and emotional impairments in individuals with CCU (ICCU)[12, 13]. Beyond task-based fMRI, resting-state functional connectivity (rsFC) analysis has shown that ICCU exhibit reduced rsFC between visual and motor cortices after acute cocaine administration[14] and impaired frontostriatal connectivity in chronic use[15]. Furthermore, reduced interhemispheric prefrontal (e.g. anterior insular cortex [AIC] or anterior cingulate cortex [ACC]) rsFC has been shown in currently abstinent ICCU[16] compared to non-using participants. Other studies highlighted reduced functional connectedness in ICCU compared to controls[17-22]. Specifically, a disruption in the balance between reward and executive control networks has been linked to heightened impulsivity in ICCU[23]. Furthermore, mesocorticolimbic circuits—particularly those involving the ventral tegmental area, NAc, amygdala and hippocampus—show altered rsFC in ICCU[21]. Abnormalities in the putamen have also been observed during attentional tasks in abstinent ICCU[24]. Moreover, it was seen that striatal and pallidal activity correlated with craving and addiction severity, particularly during a monetary reward task[24]. Other areas of the reward system, such as the caudate nucleus, have shown reduced activity during working memory tasks in ICCU compared to controls[25]. While reward circuit dysfunction is well documented, less is known about how different intake patterns (decreased vs. sustained use) dynamically affect rsFC. Evidence in ICCU suggests differences in inhibitory control depending on abstinence duration[26]. More recent use of cocaine was characterized by altered fronto-temporal, subcortical, and visual network efficiency. In addition, a similar FC pattern characterized impaired inhibitory control performance within ICCU. It has also been reported that neural connectivity can predict craving intensity in cocaine use disorder and gambling disorder[27]. Specifically prefrontal connectivity to regions known to be involved in working memory and autobiographical memory processing seems important in predicting craving. Recent rsFC studies confirm cerebellar dysconnectivity[28] and triple-network alterations[29] in high- vs low-use CUD subgroups[30], yet longitudinal trajectory divergence remains unexamined.

Longitudinal prefronto-striatal connectivity changes have been reported only in rats[31], where escalated intake altered caudate-putamen to AIC rsFC during abstinence. Although cortical structural integrity in ICCU covaries with cocaine use intensity[32], no human study has examined longitudinal rsFC changes tracking natural cocaine use trajectories (decreased vs sustained intake). Increased striatal–dorsolateral prefrontal cortex rsFC correlates with recent cocaine use[15, 33], but whether fronto-striatal rsFC predicts future use remains unknown. We therefore investigated longitudinal rsFC divergence between ICCU with decreased (DU) vs sustained (SU) cocaine use and cocaine-naïve controls (CNC) matched for age, sex, and education. We hypothesized DU would show normalized rsFC toward CNC while SU would develop persistent hyperconnectivity, mirroring rat abstinence normalization findings[34]. We further hypothesized that striatal-prefrontal rsFC would be modulated by cocaine use intensity and predict future trajectories, based on mesocorticolimbic dysfunction[21], reward network alterations[24], and longitudinal trajectory divergence in rats[31].

Methods

Participants

ICCU (*n*=43) were recruited from inpatient and outpatient units at the University Hospital of Psychiatry Zurich and affiliated institutions[32], as part of the large-scale Zurich Cocaine Cognition Study (ZuCo^{2}St)[35, 36]. CNC participants (*n*=42), matched for age, education (school years), and sex, were recruited through online advertisements. Inclusion criteria for the ICCU group required participants to report cocaine as their primary substance of choice, with a consumption of >0.5 g per month and an abstinence duration of <6 months. Exclusion criteria were a history of a neurological disorder and any DSM-IV Axis I psychiatric disorders other than cocaine, cannabis, nicotine, alcohol abuse/dependence, attention deficit hyperactivity disorder (ADHD), or past depressive episodes. Based on changes in hair cocaine concentration, ICCU participants were classified either *DU* (i.e., “Decreaser”, n=17) or *SU* (i.e., “Maintainer/Increaser”, n=15), using the a priori criteria established in our previous MRI study[32]. Participants were categorized as DU if thy showed (i) an absolute decrease in cocaine hair concentration of at least 500 pg/mg from baseline to follow-up and (ii) a relative decrease of ≥10% in the robust parameter $\text{cocaine}_{\text{total}}$ (= cocaine + benzoylecgonine + norcocaine)[37] hair concentration compared with baseline[38]. SU participants included those who did not change or increased their consumption based on $\text{cocaine}_{\text{total}}$ levels. One participant meeting the DU criteria was nevertheless assigned to the SU group due to a $\text{cocaine}_{\text{total}}$ value at follow-up >27.8 ng/mg, consistent with prior evidence indicating that dependent users exhibit average $\text{cocaine}_{\text{total}}$ hair concentrations of 27.8 ng/mg[36, 39]. Craving was assessed using the brief

version of the Cocaine Craving Questionnaire (CCQ), a 10-item adaptation of the CCQ-Now[40]. Each item was rated on a 7-point scale (1 to 7), yielding a higher total score of 10 to 70, with higher scores indicating stronger craving.

CNC exclusion criteria included any current or past DSM-IV Axis I psychiatric disorder (except nicotine dependence), neurological disorder, or use of illegal substances more than 15 times in their lifetime or within 6 months prior to study start (excluding cannabis).

All participants were instructed to abstain from illegal substances for ≥72 h and from alcohol for 24h before testing. Urine toxicology was used to verify self-reports. If available, 6-cm hair strands were collected from the occiput to estimate substance use over the previous six months. Hair samples were analysed using liquid chromatography-tandem mass spectrometry[41] to confirm regular cocaine use (cocaine hair concentration>500 pg/mg)[42] and verify cocaine as the primary drug of choice. Recent work demonstrates that hair concentration predicts cocaine dependency with high sensitivity and specificity[39], supporting its validity for classifying dependent *versus* non-dependent users. The study was approved by the Ethics Committee of the Canton of Zurich (No. E-14/2009, Amendment 1) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Psychopathological assessment

A trained psychologist conducted a structured clinical interview to assess DSM-IV Axis I diagnoses[43]. Substance use was evaluated with the Interview for Psychotropic Drug Consumption[44]. Smoking habits were assessed using the Fagerström Test for Nicotine Dependence[45]. Trait impulsivity and ADHD symptoms were measured with the Barratt Impulsiveness Scale[46] and the ADHD Self-Rating Scale[47], respectively. Depressive symptoms were assessed using the Beck Depression Inventory (BDI)[48]. Verbal intelligence was estimated using a standard German vocabulary test[49].

MRI data acquisition

MRI was collected at baseline (TP1) and follow-up (TP2) with a time interval ranging from 3-53.4 months (median interval: 10.3 months; no significant group differences between ICCU and CNC: p=0.59, two-sample t-test); or between ICCU subgroups: p=0.97 two-sample t-test, see Table 1). All scans were acquired on a 3T whole-body MR system (Achieva, Philips Healthcare, Best, The Netherlands, upgraded to dStream) equipped with 80 mT/m gradients and a 32-channel receive-only head coil. Functional MRI were acquired with a spin-echo echo-planar imaging (EPI) sequence (repetition time (TR)=2 s, echo time (TE)=35 ms, flip angle=82°, field of view (FOV)=220×220 mm², 32 contiguous transverse slices, voxel resolution=2.75×2.75 mm, slice thickness=4 mm, acquisition matrix=80×80,

and 300 dynamics (10 min)). Slices were aligned along the anterior-posterior commissure based on a T1-weighted midline sagittal scout. T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient-echo sequence (1-mm isotropic).

MRI data pre-processing

Data were processed in CONN toolbox (CONN 22a; www.nitrc.org/projects/conn)[50]. Structural images were segmented into grey matter, white matter, and cerebrospinal fluid maps using the SPM12 (Wellcome Trust, UK) 'New Segment' function[51]. fMRI preprocessing included realignment (head motion correction, see below), centering to the anterior commissure, slice-timing correction (ascending), outlier detection, and scrubbing using ARtifact Detection Tools (ART) during a dedicated denoising step[52, 53], normalization to MNI space, and spatial smoothing with a 6-mm FWHM Gaussian kernel, resulting in 2×2×2 mm³ resampled images. Head motion was estimated using six dimensions (translation and rotation). All fMRI images were denoised using a principal component-based noise correction method (CompCor) which improves selectivity, sensitivity, and inter-scan reliability[54]. During the denoising step, a band-pass filter (0.01–0.1 Hz) was applied to remove linear drift and high-frequency noise. For each participant, scrubbing values as well as 24 realignment parameters (including first-order derivates and quadratic effects) (Friston et al., 1996) and time series from segmented (using the SPM12 'New Segment' option) white matter and cerebrospinal fluid (probabilistic) maps were included as regressors of no interest to reduce noise and non-neuronal signal. In addition, following Power et al. (2012), translation and rotation values were calculated (outside CONN) on a 50 mm radius spherical surface for each participant and scan[53]. These were used to estimate the mean frame-wise displacement (FD) with standard deviation. Cut-off values for data exclusion were set to 0.2 mm[55], as even small magnitudes of motion (< 0.05 mm) can introduce artifactual impacts on the data[56]. Mean FD was included as covariate for all statistical analyses (see below).

fMRI analyses

We examined whole-brain (region-to-region) rsFC at TP1 and TP2 in two designs: between participant groups (ICCU vs. CNC) and within substance user groups (DU vs. SU), using cerebral and subcortical areas of the AAL atlas[57, 58] and major resting-state networks (Default Mode, Salience, Frontoparietal, Sensorimotor, Visual, Language, and Dorsal Attention networks)[59]. Cerebellar regions were not included, as those regions were not fully covered spatially in all participants (i.e., 55 AAL ROIs and 19 RSN nodes were analysed). Further, seed-to-frontal rsFC was examined within ICCU groups using a bilateral frontal mask encompassing the superior frontal-, middle frontal-, lateral orbitofrontal-, and medial orbitofrontal gyri as well as the ACC[32]; four bilateral seed

regions were used: ventral striatum (1: NAc, 2: pallidum) and dorsal striatum (3: putamen, 4: caudate nucleus).

Statistical analysis

Statistical analyses on demographic data were performed with SPSS (IBM, version 29.0). To test normality of participants' characteristics and clinical readouts, histograms, Q–Q plots and Shapiro–Wilk tests were applied. For normal distributed data, independent t-tests (two-tailed) were used for group comparison. For not normally distributed data (i.e., cocaine hair concentrations at TP1 and TP2; Kolmogorov-Smirnov Test: $p \leq 0.05$), non-parametric Mann-Whitney U tests were used for group comparison. For binary variables, χ^2 tests were used.

Whole-brain rsFC analyses comprised two repeated-measures ANCOVAs (rm-ANCOVAs). The between-group rm-ANCOVA included the factors Group (CNC, ICCU) and Time (TP1, TP2), plus covariates of age, mean FD, and interval (months between TP1/TP2), to test longitudinal group differences. Statistical significance was determined at the voxel level (FDR-corrected[60] $p < 0.05$), with additional cluster-level correction ($p < 0.05$, based on multi-voxel omnibus testing). Significant main or interaction effects were followed by post hoc two-tailed t-tests (FDR-corrected) for bidirectional contrasts at each TP. An exploratory analysis compared CNC and ICCU subgroups at TP2 to test whether lower cocaine use yielded CNC-like rsFC patterns.

The second rm-ANCOVA included factors Group (DU, SU) and Time (TP1, TP2) and the same covariates as described above, to assess longitudinal (whole-brain) within-patient group differences. Significant (FDR-corrected at $p_{voxel} < 0.05$, $p_{cluster} < 0.05$) main or interaction effects were followed by post hoc t-tests (two-tailed) for bidirectional contrasts at each TP.

Within the ICCU group, we examined seed-to-voxel fronto-striatal (reward) rsFC differences (within DU vs. SU and between timepoints) at both TPs. An rm-ANCOVA tested rsFC from the four seed regions (ventral/dorsal striatum), with factors Group (SU, DU) and Time (TP1, TP2) and identical covariates. Significant main or interaction effects were followed by seed-specific post hoc t-tests (FDR-corrected) for bidirectional contrasts at each TP.

To test whether TP1 fronto-striatal (four seeds) rsFC predicts cocaine use and craving intensity (CCQ score) at TP2, we used linear mixed-effects models (fitlme; MATLAB R2024b). Separate models predicted cocaine use intensity or craving intensity (dependent variables), with all four seed rsFC values as simultaneous fixed effects and subject ID as a random intercept. Beta coefficients (β) represent the estimated change in the outcome (e.g., grams cocaine use) per 1-unit increase in each rsFC predictor (z-scored Fisher z),

holding other fixed effects constant—positive β indicates greater use/craving with stronger connectivity, while negative β indicates less. Model performance was quantified via coefficient of determination (R^2) between predicted/observed values. Fixed-effect uncorrected p-values underwent FDR correction across the four predictors; both uncorrected and FDR-adjusted significance levels were reported. Multicollinearity among the seed rsFC predictors was assessed by calculating pairwise correlations and Variance Inflation Factors.

Results

Data quality

Of the original sample (n=85), all underwent structural MRI, but three ICCU and four CNC lacked resting-state fMRI data[32]. From the remaining 38 CNC and 40 ICCU, eight ICCU were excluded due to poor data quality (excessive head motion, mean FD>0.2 mm) or missing cocaine hair data at ≥1 TP. Analyses thus included 32 ICCU and 38 CNC (final n=70).

Mean (±SD) FD across TPs did not differ between ICCU and CNC (t-test p=0.74; ICCU: 0.13 ±0.05; CNC: 0.14 ±0.11), or between SU and DU (p=0.62; SU: 0.13 ±0.05; DU: 0.17 ±0.22), indicating no group differences in head motion. Within-group TP1–TP2 comparisons were also non-significant (ICCU: p=0.07; CNC: p=0.79). All group mean FDs remained below the 0.2 mm threshold. Regarding the linear mixed-effects model, none of the correlations exceeded 0.7, and Variance Inflation Factors indicated that multicollinearity did not significantly inflate the model estimate.

Demographic and clinical values

No between-group differences were found for age, sex, education, handedness, or intracranial volume (ICV; all $p > 0.05$; Table 1). As expected, ICCU participants showed significantly lower verbal IQ ($p < 0.01$, d=0.6) and higher ADHD and depression scores, alcohol and nicotine intake, and MDMA hair concentrations (all $p < 0.05$; Table 1 for details)

Whole brain rsFC analysis

Between-group rm-ANCOVA revealed significant main effects of Group ($F(1,67)=4.6$, FDR-corrected $p<0.05$) and a Group × Time interaction ($F_{(1,67)}=9.1$, FDR-corrected $p<0.001$). Post hoc t-tests (FDR-corrected) showed:

TP1 (CNC>ICCU): ICCU exhibited weaker rsFC in frontal connections (ACC–rostral prefrontal cortex; **Figure 1A**); ICCU showed stronger limbic–frontal connectivity

(subcallosal cortex–inferior/orbitofrontal gyri).
TP2 (ICCU>CNC): ICCU demonstrated stronger caudate–occipital pole rsFC (not shown).
TP2 subgroups: CNC showed stronger left rostral prefrontal–right AIC/frontal operculum rsFC vs. DU (**Figure 2A**); SU exhibited hyperconnectivity across frontal–temporal–parietal regions vs. CNC (**Figure 2B**).

Within-substance-user rm-ANCOVA yielded main effects of Group ($F_{(1,33)}$=7.9, p<0.01), Time ($F_{(1,33)}$=6.0, p<0.05), and interaction of both ($F_{(1,33)}$=7.6, p<0.01). Post hoc tests revealed:
TP1 (DU vs. SU): DU showed higher rsFC between bilateral inferior temporal gyri and right sensorimotor network–parietal operculum (**Figure 3A**).
TP2 (SU>DU): SU exhibited widespread hyperconnectivity (frontal–hippocampal, frontal–visual; **Figure 3B**).

Seed-to-frontal rsFC analysis (ICCU only)

Seed-based rm-ANCOVA (across four striatal regions) revealed a main effect of Time ($F_{(1,27)}$=8.2, FDR-corrected p<0.01; medial frontal cluster) and a Group × Time interaction ($F_{(1,27)}$=6.5, FDR-corrected p<0.05; lateral frontal cluster). Post hoc tests (FDR-corrected) revealed:
TP1: No rsFC differences between SU and DU across seeds.
TP2: Pallidum rsFC was stronger in SU vs. DU to left superior frontal gyrus (**Figure 4A**). NAc showed stronger positive rsFC in SU to right frontal pole/superior frontal gyrus (**Figure 4B**). Caudate nucleus exhibited stronger negative rsFC in SU to left inferior frontal gyrus (**Figure 4C**).

Prediction analysis

The rsFC (TP1) of the four striatal seeds to prefrontal regions significantly predicted cocaine use (R^2=0.892) and craving (R^2=0.975) at TP2 (**Figure 5**).

Cocaine use model: Caudate to supplementary motor area and superior frontal gyrus was FDR-significant (p_{uncorr}=0.0089, q_{FDR}=0.036, **Figure 6A**); NAc to ACC showed nominal significance (p_{uncorr}=0.0297, q_{FDR}=0.059, **Figure 6B**). Pallidum and putamen were non-significant (p_{uncorr}≥0.246, q_{FDR}≥0.328).

Craving model: no seeds survived FDR correction (minimum q_{FDR}=0.972).

Discussion

In this longitudinal preliminary rsFC study, we identified four key findings: 1. At TP1, ICCU showed weaker frontal rsFC and exhibited limbic–frontal hyperconnectivity when

compared to controls; 2. At TP2, individuals with sustained or increased cocaine use (SU) demonstrated widespread hyperconnectivity compared to controls and individuals with decreased cocaine use (DU); 3. Within ICCU, seed-based (pallidum/NAc/caudate) rsFC differentiated individuals with sustained/increased cocaine use (SU) from decreasing users (DU) at TP2; 4. Caudate TP1 rsFC predicted intensity of cocaine use at TP2.

These findings, which we consider preliminary because of the limited sample size, largely align with our hypotheses that cocaine reduction modulates rsFC and that reward-circuit rsFC predicts future use intensity, though some prior studies report null or inconsistent rsFC group differences in early-stage CUD or recently abstinent users[61-63]. Specifically, our findings provide robust (adjusted for age, mean FD, and TP1–TP2 interval) evidence of dynamic group differences and time-dependent large-scale network reconfiguration, particularly involving fronto-striatal/frontoparietal systems. Omnibus rm-ANCOVA Group and Group × Time effects across ROIs demonstrate non-static rsFC alterations, consistent with state-dependent network models in addiction[64, 65].

Subtle ICCU–CNC differences at baseline likely reflect early-stage functional homogeneity characteristic of mild-moderate CUD, aligning with previous neuroimaging studies in the addiction field showing progressive network disruption with chronicity[66,67]. This baseline homogeneity enabled detection of divergent trajectories: SU developed pervasive hyperconnectivity, while DU showed partial normalization. Clinically, these findings may delineate a potential early intervention window during which striatal–prefrontal circuits remain relatively intact, supporting adaptive control mechanisms before more entrenched network over-engagement develops with persistent use.

Specifically, at TP2, SU exhibited widespread hyperconnectivity relative to both CNC and DU (within-ICCU), spanning frontal–temporal–parietal regions. This extends prior CUD work documenting hypo- and hyperconnectivity in frontoparietal/mesocorticolimbic circuits linked to impaired cognitive control[68] and maladaptive salience processing[69]. Unlike CNC (stronger ACC–rostral PFC coupling at TP1), SU at TP2 showed broad rsFC increases, likely reflecting failed network segregation of executive, salience, and sensory systems following persistent cocaine exposure[67].

Persistent cocaine use appears to 'lock' brain networks into hyperconnected configurations, particularly frontal–posterior (parietal/visual) circuits, amplifying drug-related internal states and external cues[28, 29]. Frontoparietal hyperconnectivity may signal inefficient control, where elevated coupling correlates with symptom severity/maladaptive responding in SUDs, not improved performance[15, 69]. Thus, SU rsFC may index an over-engaged but ineffective control system failing to normalize[15, 69].

The comparison of SU vs. DU at TP2 highlights functional relevance: DU showed restricted changes (temporal/sensorimotor connectivity) with frontoparietal reduction, paralleling prefrontal grey matter recovery during sustained abstinence; SU maintained extensive association cortex hyperconnectivity[33].

Whole-brain analysis at TP2 revealed SU hyperconnectivity (vs. CNC) spanning sensorimotor network, central/parietal opercula, planum temporale, Heschl's gyrus, posterior middle temporal gyrus, SMA, AIC, and inferior frontal gyrus extending to temporal/occipital regions, while CNC>DU differences remained spatially circumscribed. This SU/DU divergence (relative to CNC) aligns with models of successful stimulant reduction involving frontostriatal/frontoparietal normalization alongside preserved memory network integrity. SU hyperconnectivity (vs. DU) spanned hippocampus, parahippocampal cortex, fusiform gyrus, plus frontal/temporal/parietal regions (Figure 3), indicating diffuse network over-engagement[67, 69]. Clinically, SU hyperconnectivity may represent a neural vulnerability signature – elevated co-activation without functional specialization for adaptive control – consistent with abstinence-related reversal of attentional bias to cocaine drug cues[70].

Seed-to-frontal analyses within ICCU revealed fine-grained striatal–prefrontal alterations. SU showed stronger positive pallidal/NAc rsFC to superior/medial frontal regions at TP2, while caudate–inferior frontal rsFC became more negative (Figure 4), consistent with parallel cortico-striatal loops in addiction[71]. Enhanced ventral striatal (NAc/pallidum)–medial frontal coupling likely reflects heightened reward/motivational integration into control regions, promoting drug-seeking decisions during persistent use[72, 73].

Conversely, stronger caudate–inferior frontal anticorrelations in SU suggest a decoupling of dorsal striatal habit circuitry from lateral prefrontal regions crucial for inhibitory control and flexible behavior[72, 74]. Such a pattern aligns with evidence that reduced or imbalanced frontostriatal connectivity contributes to impaired response inhibition and compulsive drug use[69, 75]. The absence of SU–DU differences at TP1 but clear pallidal/NAc/caudate divergence at TP2 supports the view that short-term cocaine use trajectories between TP1 and TP2 shape striatal–frontal network architecture over time, with sustained use reinforcing maladaptive loop dynamics.

The SU network phenotype combines widespread cortico-cortical hyperconnectivity with dysregulated striatal–frontal coupling (ventral hyper- vs. dorsal hypo-connectivity), over-integrating frontal networks while compromising reward/habit gating. Notably, with no systematic treatment between TPs, this spontaneously amplifies drug salience and impairs lateral suppression in persistent users, mechanistically explaining naturalistic cocaine use persistence[73].

The prediction analyses add an important translational dimension by demonstrating that rsFC of striatal seeds to prefrontal regions at TP1 explained a large proportion of variance in cocaine use and craving at TP2. The very high model R□ values for both outcomes indicate that baseline frontostriatal connectivity carries substantial prognostic information about short-term clinical trajectories, in line with emerging work using resting-state neuromarkers to forecast treatment response[76] and relapse risk in CUD[77, 78]. Within this multivariate framework, the caudate seed showed an association with later cocaine use when connected to SMA and SFG, highlighting dorsal frontostriatal circuits as particularly relevant for behavioral outcomes. This aligns with prior reports that caudate–frontal rsFC during rest predicts relapse in stimulant users[77] and individuals at risk[78].

Functionally, stronger caudate coupling with medial/superior frontal motor-control areas may index a habitual, stimulus–response shift in drug-taking, where behavior becomes less goal-directed and more automatized[72, 79]. The nominal NAc–ACC association is neurobiologically plausible, given the ACC's role in reward prediction error and conflict monitoring[80, 81]. Even though this seed did not survive FDR correction, the NAc-ACC pattern aligns with the literature, showing ventral striatal–ACC connectivity relates to craving intensity, affective dysregulation, and continued use risk[69]. The absence of significant single-seed predictors for craving after correction, despite excellent model fit, suggests craving reflects distributed connectivity patterns across striatal-prefrontal-insular-default mode networks not fully captured by our ROI set.

From a clinical and methodological standpoint, these findings support connectivity-based prognostic markers for CUD risk stratification. Caudate–frontal and NAc–ACC rsFC models could guide individualized interventions targeting frontostriatal circuits via e.g. repetitive transcranial magnetic stimulation[82, 83]. Future studies should validate these effects in larger cohorts, extend follow-up beyond TP2, and test rsFC mediation of cocaine use trajectories.

Overall, the present results indicate that natural cocaine use trajectories between TP1 and TP2 are mirrored by distinct patterns of large-scale network organization, with sustained users showing widespread frontoparietal hyperconnectivity and maladaptive striatal–frontal coupling, and decreased users displaying comparatively attenuated alterations. The strong prognostic value of early frontostriatal rsFC underscores the potential of resting-state neuromarkers for precision medicine approaches in CUD, while also highlighting the need for mechanistic work to disentangle when hyperconnectivity reflects compensatory *versus* detrimental processes.

Limitations

Key subcortical regions (ventral tegmental area and substantia nigra) omitted from our frontal mask limit insight into dopaminergic and regulatory contributions to ICCU rsFC alterations. Dopamine receptor density also influences ventral attention/default mode networks[84], beyond our ROI coverage. Multimodal approaches combining structural and functional data could reveal latent cocaine-related impairments[85]. Future ICCU studies should expand ROIs, incorporate diffusion imaging[86], and test craving incubation[87-89]. The ICCU subgroup sample size is small—reflecting characteristic high attrition and adherence challenges in this population—which increases the risk of Type II error and limits the generalizability of the subgroup and prediction findings, even though this remains one of the few longitudinal ICCU neuroimaging studies to date. Missing interim (between TP1 and TP2) hair data precludes incubation testing, though 6-month pre-TP samples and covarying the TP interval strengthen SU/DU classification beyond self-report and urine. Frontostriatal seeds and clusters were defined within the same cohort used for the prediction analyses, so the reported in-sample R values likely overestimate true predictive performance and require replication in an independent sample. Dichotomizing cocaine-use change into SU and DU enhances interpretability but may reduce statistical efficiency, particularly given the modest subgroup size.

Conclusion

Baseline rsFC shows promise for stratifying natural cocaine use trajectories, with caudate-prefrontal connectivity serving as a predictor of future use intensity. Here, in one of the first human studies to demonstrate divergent longitudinal rsFC trajectories (SU hyperconnectivity vs DU normalization) without intervention, we establish resting-state neuromarkers for precision stratification in early CUD, informing targeted early intervention timing and individualized treatment.

Declarations

Author’s contribution

LM: analysis, interpretation of data for the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

DMC: analysis, acquisition, interpretation of data for the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

SH: analysis, acquisition, interpretation of data for the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

EJEE: acquisition, interpretation of data for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

MK: acquisition, interpretation of data for the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

KHP: acquisition, final approval of the version to be published, agreement to be accountable for all aspects of the work.

PS: acquisition, final approval of the version to be published, agreement to be accountable for all aspects of the work.

MRB: acquisition, final approval of the version to be published, agreement to be accountable for all aspects of the work.

ES: conception or design of the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

MH: drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

BBQ: conception or design of the work, interpretation of data for the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work.

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Disclosures

The authors declare that they have no known competing financial interest. KHP is currently an employee of Boehringer Ingelheim Switzerland.

Data Availability Statement

The data associated with this publication can be shared upon reasonable request.

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Table 1

Table 1 is available in the Supplementary Files section.

Figures

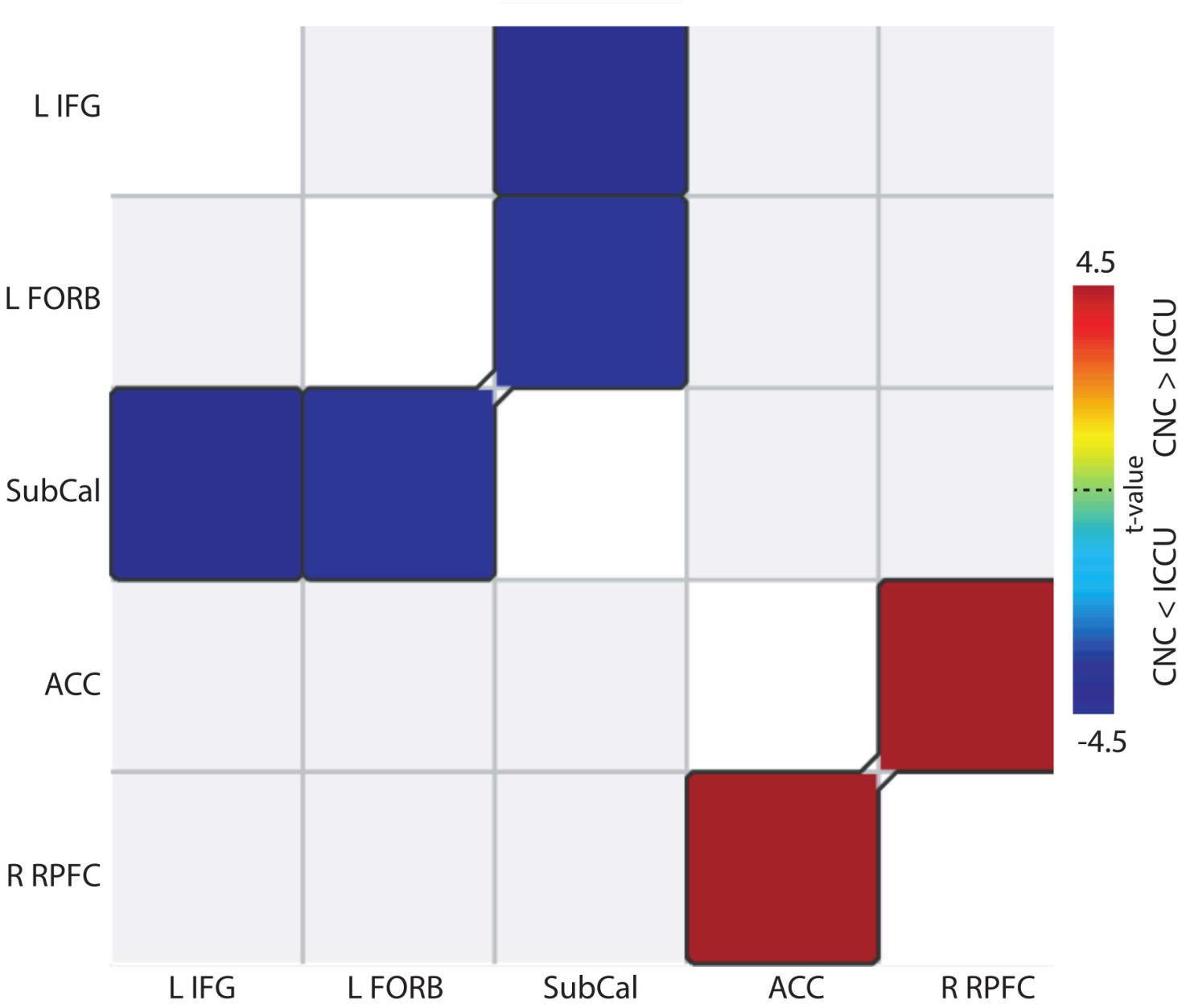


Figure 1

TP1 differences in rsFC between cocaine-naive controls (CNC) and individuals with chronic cocaine use (ICCU). Results are displayed at $p_{voxel} < 0.05$ FDR comparison correction with an additional cluster-level correction at $p_{cluster} < 0.05$ (with adjustment for participants' age, mean FD, and months between TP1 and TP2). *Abbreviations*: ACC = anterior cingulate cortex, FORB = frontal orbital cortex, IFG = inferior frontal gyrus, L = left hemisphere, R = right hemisphere, RPFC = rostral prefrontal cortex, SubCal = subcallosal cortex. Black lines marking significant clusters (cluster boundaries), i.e., sets of ROIs that are significantly connected to each other after thresholding.

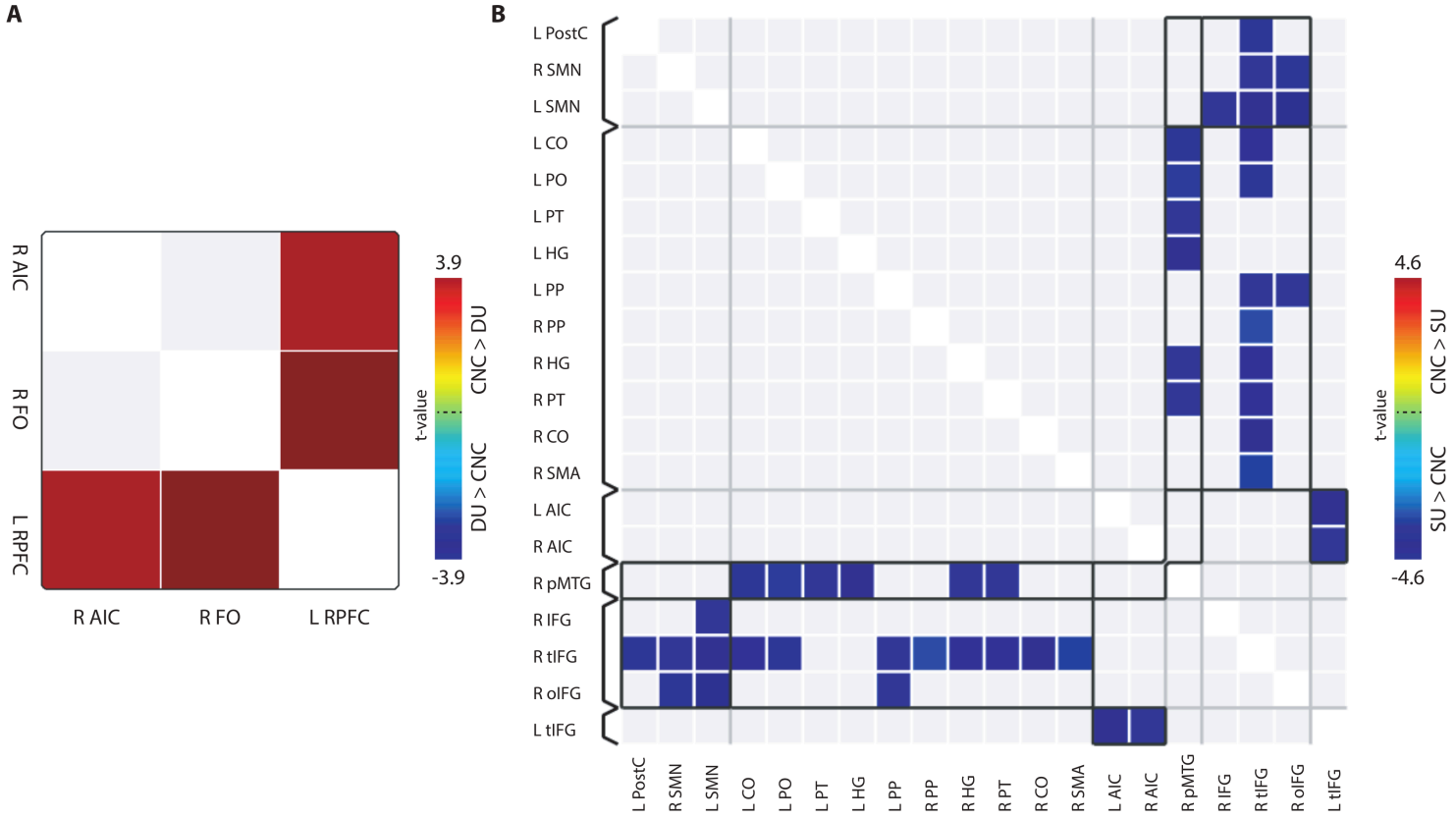


Figure 2

Whole brain rsFC connectivity differences at TP2 between CNC and ICCU subgroups. **A** CNC vs. DU, **B** CNC vs. SU at TP2. Results are displayed at $p_{voxel} < 0.05$ FDR comparison correction with an additional cluster-level correction at $p_{cluster} < 0.05$ (with adjustment for participants' age, mean FD, and months between TP1 and TP2). *Abbreviations:* AIC = anterior insular cortex, CO = central operculum, HG = Heschl's gyrus, IFG = inferior frontal gyrus (t = temporal, o = occipital), L = left hemisphere, pMTG = posterior middle temporal gyrus, PO = parietal operculum, PP = planum polare, PT = planum temporale, R = right hemisphere, SMA = supplementary motor area, SMN = sensori-motor network. Black lines marking significant clusters (cluster boundaries), i.e., sets of ROIs that are significantly connected to each other after thresholding.

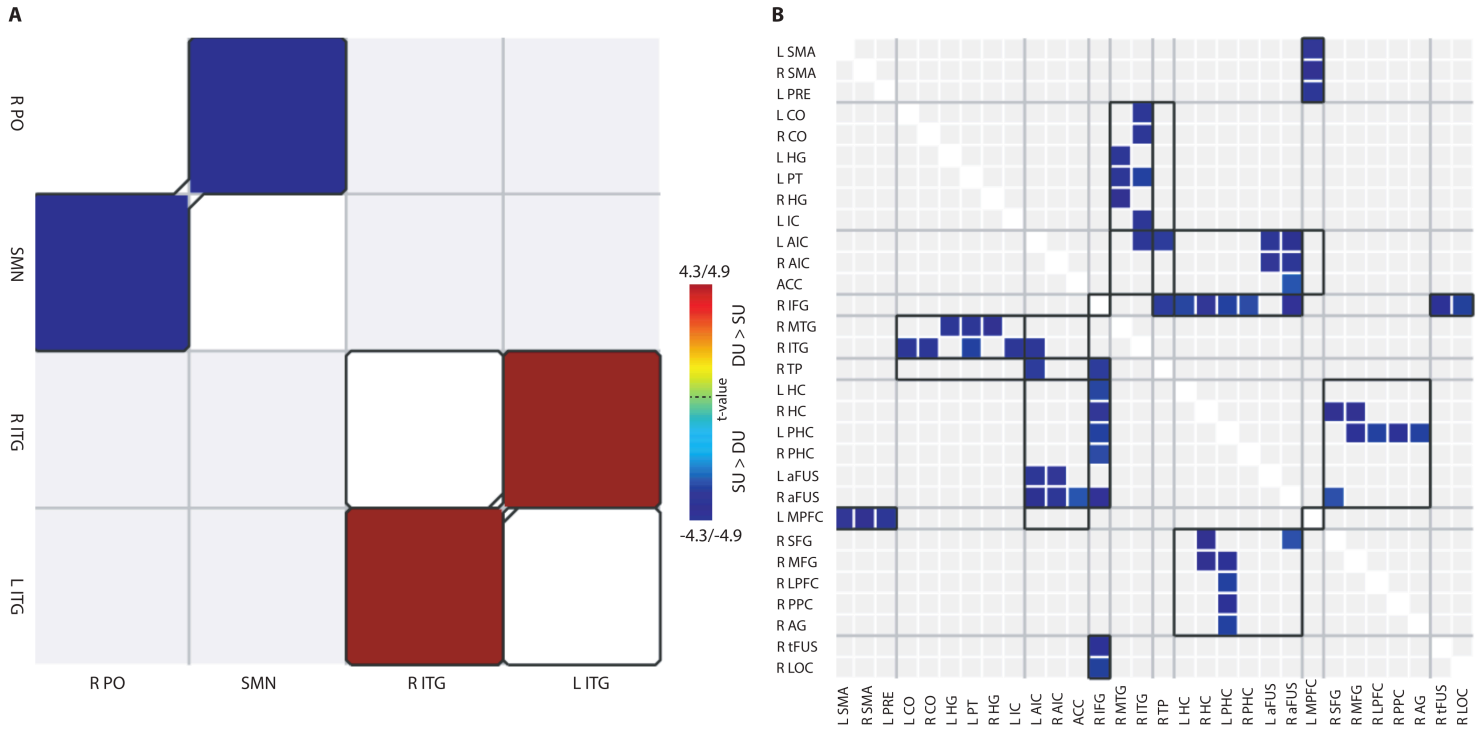


Figure 3

Whole brain rsFC connectivity differences between ICCU groups. **A** TP1, **B** = TP2. Results are displayed at $p_{voxel} < 0.05$ FDR comparison correction with an additional cluster-level correction at $p_{cluster} < 0.05$ (with adjustment for participants' age, mean FD, and months between TP1 and TP2). *Abbreviations*: ACC = anterior cingulate cortex, aFUS = anterior fusiform, AG = angular gyrus, AIC = anterior insular cortex, CO = central operculum, FUS = fusiform, HC = hippocampus, HG = Heschl's gyrus, IFG = inferior frontal gyrus, ITG = inferior temporal gyrus, L = left hemisphere, LIC = left inferior cortex (context-specific), LOC = lateral occipital cortex, LPFC = lateral prefrontal cortex, MFG = middle frontal gyrus, MPFC = medial prefrontal cortex, MTG = middle temporal gyrus, PHC = parahippocampal cortex, PO = parietal operculum, PPC = posterior parietal cortex, PRE = precentral gyrus, PT = planum temporale, R = right hemisphere, SFG = superior frontal gyrus, SMA = supplementary motor area, SMN = somato-motor network, SU = sustained users, tFUS = temporal fusiform, TP = temporal pole. Black lines marking significant clusters (cluster boundaries), i.e., sets of ROIs that are significantly connected to each other after thresholding.

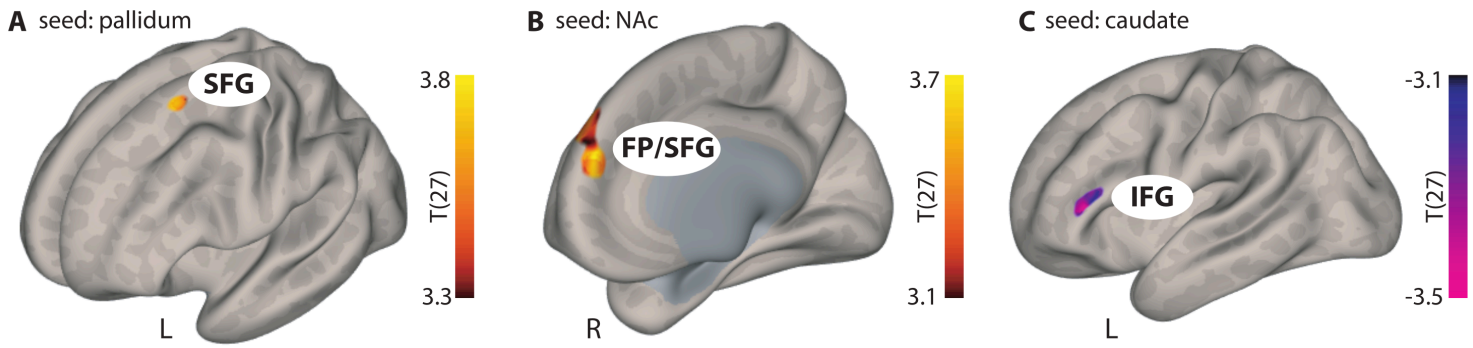


Figure 4

Illustration of how striatal seed regions (pallidum, NAc, caudate) differentiate successful cocaine reduction (DU) from sustained use (SU) at follow-up (TP2). The rm-ANCOVA revealed main Time effects (medial frontal clusters) and Time × Group interactions. No TP1 group differences emerged across seeds. At TP2, results show:

A Pallidum rsFC: SU > DU to left superior frontal gyrus.
B NAc rsFC: SU > DU to right frontal pole/superior frontal gyrus.
C Caudate rsFC: SU > DU (stronger anti-correlations) to left inferior frontal gyrus.

Abbreviations: DU = drug use reducers, ICCU = individuals with cocaine use disorder, NAc = nucleus accumbens, rsFC = resting-state functional connectivity, SU = sustained users.

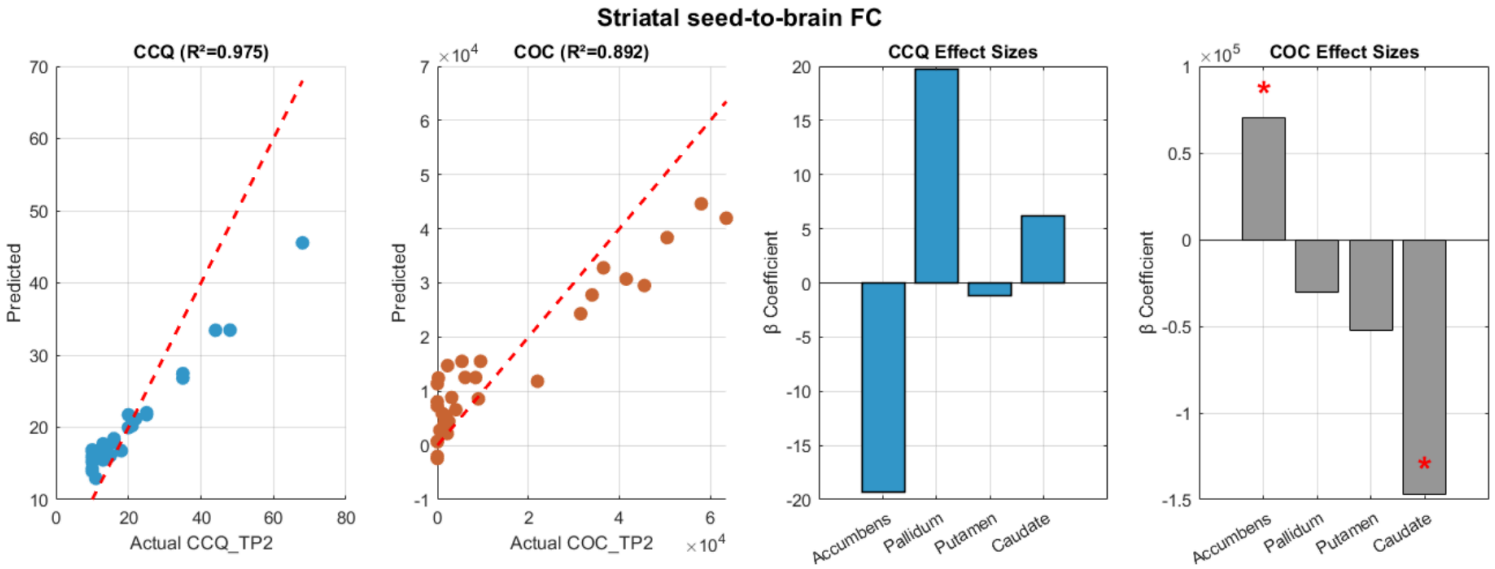


Figure 5

Results of the linear mixed-model effects. Visualization included: scatterplots comparing predicted and observed outcomes for craving (CCQ) and cocaine use intensity (COC) annotated with R^2 (panels on the left) and bar plots (panels on the right) illustrating

standardized β coefficients for each of the four seed regions. Significant ($p < 0.05$) effects denoted by color-coded asterisks.

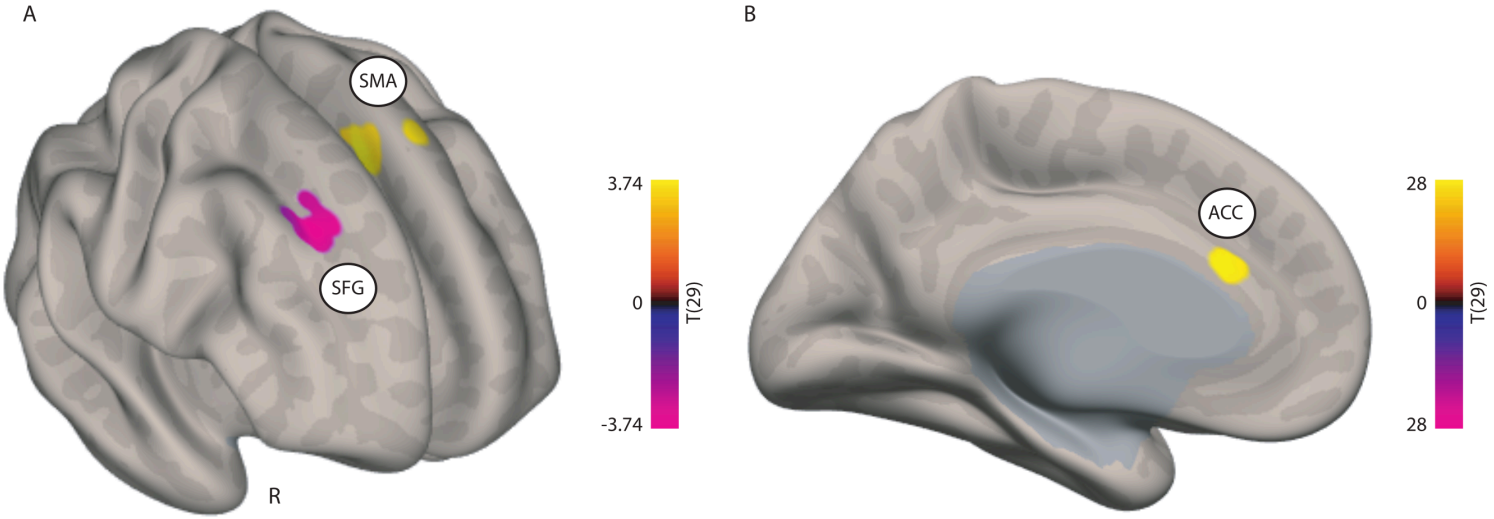


Figure 6

TP1 striatal-prefrontal rsFC predicts TP2 cocaine use outcomes in ICCU participants.

A Caudate rsFC at TP1 predicts cocaine use at TP2 ($p < 0.05$, FDR correct).
B NAc rsFC at TP1 predicts cocaine use at TP2 ($p < 0.05$, uncorrected).

Abbreviations: ACC = anterior cingulate cortex, SFG = superior frontal gyrus, SMA = supplementary motor area.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx