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GABAergic polygenic risk for cocaine use disorder is negatively correlated with precuneus activity during cognitive control in African American individuals

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Abstract

Impaired cognitive control has been implicated in cocaine use disorder (CUD). GABAergic treatments have been proposed for CUD. Here we examined relationships between GABAergic genes and neural correlates of cognitive control in CUD. We analyzed two independent African American cohorts: one of >3,000 genomewide-genotyped subjects with substance dependence and another of 40 CUD and 22 healthy control (HC) subjects who were exome-array genotyped and completed an fMRI Stroop task. We used five association thresholds to select variants in the reference cohort, yielding five polygenic risk scores (i.e., CUD-GABA-PRSs) for the fMRI cohort. At $p<0.005$, the CUD-GABA-PRSs, which aggregated relative risks of CUD from 89 variants harboring in 16 genes, differed between CUD and HC individuals in the fMRI sample ($p=0.013$). This CUD-GABA-PRS correlated inversely with Stroop-related activity in the left precuneus in

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Contributors: Drs. Yang and Potenza conceptualized the study. Dr. Gelernter contributed to genetic considerations. Drs. Balodis, Kober, and Worhunsky and Ms. Lacadie contributed to neuroimaging considerations. Dr. Yang generated the initial draft of the manuscript and worked with Drs. Potenza and Gelernter on revisions. All authors contributed to and approved the final manuscript.

CUD (t=−0.58, p_{FWE}<0.05) but not HC participants. Post-hoc seed-based connectivity analysis of the left precuneus identified reduced functional connectivity to the posterior cingulate cortex (PCC) in CUD compared to HC subjects (p=0.0062) and the degree of connectivity correlated with CUD-GABA-PRSs in CUD individuals (t=0.287, p=0.036). Our findings suggest that the GABAergic genetic risk of CUD in African Americans relates to precuneus/PCC functional connectivity during cognitive control. Identification of these GABAergic processes may be relevant targets in CUD treatment. The novel identification of 16 GABAergic genes may be investigated further to inform treatment development efforts for this condition that currently has no medication with a formal indication for its treatment.

Keywords

Cocaine use disorder; cognitive control; GABA; substance-related disorder; Stroop; addictive behaviors; magnetic resonance imaging

INTRODUCTION

Impaired control has been proposed as a central component in models of addiction[1–3]. The Stroop task assesses cognitive control[4]. Neural underpinnings of cognitive-control impairment in cocaine use disorder (CUD) and other substance use disorders (SUDs) have been suggested in Stroop-related fMRI studies[5]. Poor cognitive control may facilitate the development and progression of CUD, contribute to relapse[5], and relate to poorer treatment outcomes[6].

During Stroop performance, regional cognitive-control-related activations in cortical (e.g., ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC)), and subcortical (striatum, thalamus) have been linked to treatment outcomes in CUD[7,8]. With treatment, Stroop-related cortico-striatal activations become less pronounced in individuals with SUDs including CUD, suggesting possible improved neural efficiency after treatment[9,10]. Furthermore, cognitive impairment in CUD relating to Stroop performance may vary according to individual characteristics. For example, among CUD subjects with impaired insight, lower error-induced rostral anterior cingulate cortex (rACC) activity has been associated with more frequent cocaine use and lower levels of emotional awareness[11].

Stroop-related circuits have also been linked to CUD and CUD-related treatment outcomes. CUD patients showed differences in Stroop-related network recruitment, with a fronto-cingular network associated with treatment retention and subcortical and ventral prefrontal networks related to abstinence during treatment[12]. Additionally, a fronto-parietal circuit that included the precuneus was linked to Stroop effects and reaction times differently in CUD and HC subjects[12]. More recent work has suggested a cocaine abstinence network initially identified using task-based reward processing data and more recently extended to Stroop data[13,14] (supplemental materials).

Genetic contributions to CUD are well established (supplementary materials). Cognitive function is also substantially heritable; heritability estimates of cognitive control, inhibitory control, and response inhibition range from 0.38 to 0.60[15–17]. However, little is known

regarding how CUD genetic risk influences brain activity (supplemental material). A study investigating genetic influences of a single nucleotide polymorphism (SNP) at proenkephalin gene (*PENK*) on neural correlates of Stroop performance in CUD and HC subjects found a diagnosis-by-allele interaction that implicated neural responses to errors in the putamen, rACC/OFC, and inferior frontal gyrus, where neural activities were increased in CUD individuals carrying the higher risk allele[18]. Thus, genetic factors linked to CUD may influence brain mechanisms underlying poor cognitive control in CUD. However, such genetic factors have rarely been studied and not with respect to polygenic risk scores (PRSs), a potentially powerful new approach for targeting treatment development efforts for complex disorders[19]. This is particularly relevant for CUD, a complex condition for which no medication has a formal indication.

Augmenting GABAergic function has been proposed as a possible therapy for CUD[20] that may ameliorate cognitive-control deficits[21,22]. GABAergic agents such as topiramate, tiagabine, baclofen, and vigabatrin have shown some promise in CUD treatment[23]. Several lines of evidence support the development of GABAergic agents in treating CUD via restoring GABA system homeostasis and increasing cognitive control[24,25]. Low GABA levels in PFC have been observed in CUD subjects[26]. Cocaine may impact GABAergic systems in the PFC and subcortical regions and thus influence sensitization, craving and relapse processes[27]. Abnormal GABA levels and GABAergic inhibitory circuits have also been linked to impaired cognitive control[28,29], and lower GABA levels have been associated with greater impulsivity and poorer response inhibition[28]. GABAergic disruptions may be partially restored using GABAergic medications[30]. Taken together, data suggest that abnormal GABAergic function may underlie impaired cognitive control in CUD (supplemental materials).

Impaired cognitive control in CUD has been hypothesized to be a consequence of cocaine misuse[27,31]. However, other studies suggest that impaired cognitive control may precede compulsive drug-seeking and drug-taking and accelerate the progression from experimentation to compulsive use[32,33]. Findings among discordant sib-pairs with and without stimulant dependence and unrelated healthy control subjects (HCs) suggest that poor cognitive control may run within vulnerable family members and not directly be caused by chronic drug misuse[34,35]. Thus, pre-existing or genetic factors prior to substance use may contribute to impaired cognitive control in CUD.

Here, we aimed to identify GABAergic PRSs as related to CUD and apply this information in an independent sample to investigate relationships with neural correlates of cognitive control. We chose to focus on African Americans (AAs) because they are disproportionately impacted by CUD, and genetic predispositions are often population-specific. To identify genes of interest, we selected SNP variants mapped to the genes identified in GABAergic pathways and estimated relative risks of SNP variants with respect to CUD from a reference cohort of AAs in a genome-wide association study (GWAS) of CUD[36]. In an independent AA fMRI case-control sample with genotypes from exome microarrays, we computed CUD-related GABAergic PRSs using the relative risks estimated from the reference cohort[37]. The PRS approach has been used to predict disease risk and facilitate interpretation of the genetic architecture of complex diseases[38].

We hypothesized that CUD subjects in the fMRI cohort would, on average, have higher GABAergic PRSs and that higher GABAergic PRSs would be related to lower brain activations during cognitive control processing in regions implicated in cognitive control in CUD (e.g., cingulate, frontal and parietal cortices, precuneus, striatum, and thalamus).

METHODS AND MATERIALS

Subjects and Ethics

Participants were recruited using advertisements and other established methods. The studies were reviewed by ethics committees at the participating universities, written informed consent was obtained after procedures had been fully explained, and procedures were conducted in accordance with the Declaration of Helsinki.

African American Cohort for GABA-PRS (Reference Cohort)—The cohort for determining GABA-PRS included 3,318 AA participants with SUDs (2,482 subjects with cocaine dependence, with relates to moderate to severe CUD in DSM-5), as detailed previously[36].

African American fMRI cohort—The fMRI cohort originally consisted of 67 AA participants (44 CUD, 23 HC) who performed the Stroop task during fMRI as described previously[7,8]. Five participants were excluded from further analysis because of excessive motion or poor image quality (final N=62; See Table 1 for demographic characteristics). Eligibility criteria required that all participants be over 18 years old, with no contraindications for MRI scanning (e.g., no head injuries). Current CUD status (cocaine dependence) was assessed using a Structured Clinical Interview for Diagnosis (SCID) for DSM-IV[39]. Additional information is included in supplemental materials.

Exome-Arrayed Genotyping and Imputation for the fMRI Cohort

DNA was extracted from peripheral blood lymphocytes using the PAXgene Blood DNA Kit (QIAGEN, California USA). All participants in the fMRI cohort were genotyped using the Illumina HumanExome Array 12v1.1. The average genotyping call rate per sample subject was 0.962 for the fMRI cohort, which passed the 95% standard quality threshold for the genotyping call rate[40]. We imputed genotypes for the fMRI cohort by first combining genotypes of the two studied cohorts (fMRI cohort and the reference cohort) and used a high imputation accuracy cutoff (>0.9). Details of the laboratory genotyping and quality control (QC), imputation, pre- and post-imputation QC for data analysis, and the resulting variant distribution are presented in supplementary materials.

Analytic Approach

The analytic approach is depicted in Figure 1.

Gene Ontology Query for the GABA-related Genes and Linkage-Disequilibrium-based SNP Pruning—We queried GABA-related genes from AmiGO2, a set of web-based tools for browsing the Gene Ontology database[41]. We retrieved 101 entities in 43 unique genes from Gene and Gene Product searching for the taxon of *Homo*

sapiens. Correspondingly, 61,114 SNPs (including variants within 3 kb of 3'/5' UTRs) located in the 43 genes were identified for the imputed fMRI sample. Among these SNPs, the post-imputation QC metrics included individuals and SNPs with genotype call rates <98%, Hardy-Weinberg equilibrium p-values $<10^{-5}$, imputation accuracy <0.9, and minor allele frequency (MAF) <1%. The QC resulted in 57,938 SNPs, of which 0.05% was covered in the exome array. To reduce inflated PRSs due to variants in linkage disequilibrium, a linkage-disequilibrium-based SNP pruning procedure in PLINK was implemented to access independent SNPs of association[42]. PLINK is a commonly used and open-source software toolset designed to perform basic and large-scale genetic analyses. Using a sliding window of 50 SNPs and a five-SNP shift at each step, the procedure removed variants in the current window with a variant inflation factor exceeding 2. Finally, 3309 SNPs passed the pruning for further analysis.

Association Analysis for CUD in the Reference Cohort—An association test was conducted in a logistic regression to model the DSM-IV diagnosis of cocaine dependence on each SNP variant (i.e., 3309 SNPs from the pruned set) and included covariates of age, sex, substance dependence on alcohol, nicotine, cannabis, and opioids, and five principal components for adjustment of population stratification[43] using PLINK[42].

GABAergic Polygenic Risk Scores—We computed five PRSs for each individual using SNPs selected according to five nominal p-value thresholds of 0.5, 0.1, 0.05, 0.01, and 0.005 from the association result in the large cohort of individuals with SUDs. Effect directions of SNPs was aligned to indicate risk for CUD. Each PRS was generated by summing all relative risks weighted by the genotype of each SNP for each fMRI participant. We used PLINK to generate risk scores, which were multiplied by 100 to acquire the PRSs.

fMRI Image Acquisition and Analysis—During fMRI, participants completed the Stroop color-word interference test as described previously[44]. Images were acquired using a 3T Siemens Trio magnetic resonance imaging (MRI) system (Siemens AG, Erlangen, Germany). Details of the task, image acquisition, and image preprocessing are described in supplemental materials. A subject-level general linear model was used to estimate brain responses associated with congruent (e.g., the word 'red' in red font) and incongruent (e.g., the word 'red' in blue font) stimuli using robust regression. Neural correlates of the Stroop effect were assessed as differences in neural responses between incongruent versus congruent trials (evaluated using linear t-contrasts) using NeuroElf[45].

Correlations Between Polygenic Risk Score and Brain Activity—Neural correlates (assessed via BOLD signal changes) of responses to incongruent versus congruent stimuli were correlated with PRSs in CUD and HC groups separately. Age was included as a covariate. As CUD individuals self-reported lower education levels than HCs, effects were investigated *post hoc*, as were effects of sex in a stratification analysis. For correlation analyses between CUD-GABA-PRSs and fMRI Stroop effects, we corrected for multiple comparisons at a family-wise-error (FWE) rate of 5% ($p_{FWE}<.05$). Smoothness was estimated from the data, and Monte-Carlo simulation in NeuroElf was used to obtain a combined voxel-wise threshold (of $p<0.01$) and cluster threshold (k=65).

Seed-based Functional Connectivity Analysis—Post-hoc seed-based connectivity of the left precuneus region identified in correlation analyses was performed using BioImage Suite[46]. The time course of the seed in a given participant across all 6 concatenated runs was computed as the average time course across all voxels in the seed. This time course was correlated with that in every other voxel in the brain to create a map of functional connectivity *r*-values between the seed and every other voxel. These *r*-values were transformed to *z*-values using Fisher's transformation, yielding one map for each participant representing the strength of seed-to-whole-brain connectivity. Voxel-wise two-sample *t*-tests were used to compare connectivity between CUD and HC participants. To correct for multiple comparisons, we adopted Monte Carlo simulation using AFNI 3dClustSim (version 16.3.05) on the autocorrelation values of the residuals from the t-test. Results are shown at $p_{FWE}<0.05$ corrected with an initial voxel-level *p*-threshold of $p<0.001$ using a cluster of $k=29$.

RESULTS

GABAergic PRSs

Among the five GABAergic PRSs for the fMRI cohort, only the PRS generated by the *p*-value threshold of 0.005 significantly distinguished CUD from HC subjects ($p=0.013$, Figure 2A). This PRS, designated as CUD-GABA-PRS, was higher in CUD relative to HC subjects (23.47±0.84 versus 22.93±1.08, $p=0.013$). This CUD-GABA-PRS was generated from the association analysis for CUD in the large cohort with 89 SNPs (*p*-value<0.005) from the 3309 SNPs identified in the GABAergic pathways. These 89 SNPs were mapped to 16 genes: *ADORA2A, CNTNAP4, GABARAPL1, GABRA1, GABRB1, GABRB3, GABRG1, GABRP, LHX6, NF1, NLGN1, NLGN2, PLCL1, PRKCE, SLC6A13*, and *USP46*. Details regarding the number of SNPs passing the *p*-value threshold in each gene, gene size, and gene function are presented in supplementary Table S1.

GABAergic PRSs and Stroop-related Measures

Within-group correlation analyses between the CUD-GABA-PRSs and brain activations during Stroop performance identified one cluster in the left precuneus in the CUD group (Figure 2B). The CUD-GABA-PRS was negatively correlated with Stroop-related activation in the left precuneus in CUD subjects ($r=-0.58$; voxel level $p<0.01$, cluster-corrected $p_{FWE}<0.05$, threshold $k=65$) (Figure 2C). This negative correlation was not observed in the HC group ($r=0.054$) (Figure 2C), and the correlation in CUD subjects differed from that in HC subjects ($p<0.05$). The correlation pattern between the CUD-GABA-PRSs and precuneus activity was similar in female ($r=-0.68$) and male ($r=-0.53$) CUD subjects ($p>0.05$; Figure 2D).

Out-of-scanner Stroop performance was also examined. CUD-GABA-PRSs and Stroop-effect magnitudes (i.e., incongruent minus congruent reaction times) were not correlated (Supplementary Figure S1).

Seed-based Functional-connectivity

We conducted a post-hoc functional-connectivity analysis using the left precuneus as a seed in the CUD and HC groups. Differential connectivity to the PCC (Brodmann areas 23 and 31; voxel level $p<0.001$, $p_{FWE}<0.05$, cluster-corrected $k=29$) was identified between CUD and HC subjects (Figure 3A). A pattern of negative functional connectivity between the left precuneus and PCC was observed in HCs and was weaker for CUD than HC subjects (mean connectivity z-scores are −0.015 for CUD and −0.22 for HC ($p=0.0062$; Figure 3B). The functional connectivity was positively correlated with CUD-GABA-PRSs in individuals with CUD ($r=0.29$, $p=0.036$). A non-significant correlation of similar magnitude but in the opposite direction was observed in HC individuals ($r=-0.33$, $p=0.069$; Figure 3C).

DISCUSSION

We identified among AA individuals elevated GABAergic PRSs linked to CUD using genetic variants extracted from genomewide-genotyped data. These PRSs were inversely associated with precuneus activation in an independent AA CUD sample during fMRI Stroop performance. Further, differential precuneus/PCC connectivity was observed between CUD and HC subjects. Our findings suggest that GABA-related genetic factors may relate to neural underpinnings of cognitive control in CUD. These findings provide a foundation for a possible pharmacogenetic strategy for developing treatments for CUD that is relevant for AA people, a group disproportionately impacted by CUD.

Genes Contributing to the CUD-GABA-PRSs

It is a novel finding to identify a CUD-GABA-PRSs. The identified 16 genes that harbor the 89 SNPs for calculating CUD-GABA-PRSs can be divided into two groups based on biological functions. Group-I includes seven genes (*GABARAPL1, GAT2, GABRA1, GABRB1, GABRB3, GABRG1, GABRP*) that are directly involved in encoding members of the GABA-A receptor family ($GABA_AR$) or related GABAergic signaling molecules. Group-II includes nine genes (*ADORA2A, CNTNAP4, LHX6, NF1, NLGN1, NLGN2, PLCL1, PKCE*, and *USP46*) that are involved in various functions regulated by GABA or related to GABAergic functions (Supplemental Table S1). These 16 genes contribute importantly to GABAergic inhibitory signal transduction and executive functioning potentially related to behavioral inhibition (further discussed in suppplemental materials)[47–50].

GABA PRSs and Precuneus Activity in CUD

Precuneus involvement in GABAergic functioning in CUD has been suggested previously[51]. The precuneus is one of three regions with the largest differences in benzodiazepine-induced decrements in whole-brain metabolism in CUD[51]. Stroop-related precuneus activation changes with treatment in CUD[8]. The association between CUD-GABA-PRSs and reduced precuneus activity only in CUD subjects suggests a potential pharmacogenetic effect. The extent to which relates to specific aspects of CUD warrants additional investigation.

Precuneus-PCC Connectivity

We observed Stroop-related precuneus-PCC functional connectivity in CUD subjects. Cognitive control is regulated by numerous brain networks, each containing a set of anatomically distributed regions[52]. The precuneus has been proposed as a central hub of the default mode network[53,54], with specialized hub regions interlinking the parietal and prefrontal regions[53]. PCC activation during Stroop task performance was correlated with longer durations of abstinence in CUD treatment[7]. In the same sample, the precuneus contributed to two circuits (fronto-parietal and fronto-cingular) that were linked to Stroop performance in healthy subjects more so than CUD patients, with the engagement of the latter circuit linked to treatment retention[12].

In concert, the precuneus and PCC have been implicated in the neural substrates of frontoparietal networks associated with attentional control[55–57] and inhibitory control in CUD[12, 58]. However, these networks also involve other regions, and the PCC and precuneus may contribute to multiple networks. For example, the PCC has been implicated in intrinsic cognitive-control networks[59,60].

As we found that higher GABAergic PRSs of CUD were associated with decreased Stroop-related precuneus activity and precuneus-PCC connectivity, further study is needed to understand precise mechanisms underlying these findings with respect to brain functional architecture and prevention and treatment development. Collectively, our results suggest a GABAergic genetic risk for potential deficits in cognitive control in AAs with CUD and altered precuneus-PCC functional connectivity that may relate to such impairments. Further research on the identified 16 GABAergic genes may further reveal potential mechanisms of cognitive controls in CUD and possible treatment targets.

Pharmacogenetic Considerations

Pharmacogenetics consider how genetic factors contribute to the metabolism, response, and/or side effects of a given medication[61]. Pharmacogenetic considerations for CUD are at relatively early stages. In disulfiram treatment of CUD, individuals carrying at least one minor allele in either the *ANKK1* or *DRD2* gene responded better to disulfiram treatment compared to individuals carrying only major alleles[62]. *DBH*, encoding dopamine β-hydroxylase (DβH), is a functional candidate gene for mediating cocaine treatment response, in which the functional regulatory variant rs1611115 reduces DβH enzyme levels[63]. CUD patients with rs1611115*CC genotypes, producing higher DβH enzyme levels, responded to disulfiram treatment[63]. However, among patients carrying the rs1611115*T-allele (CT/TT), there may be better responses to drugs such as doxazosin, an α1-adrenergic antagonist, that may operate by blocking norepinephrine stimulation and reward from cocaine-induced norepinephrine increases[64].

Pharmacogenetic research on CUD treatment has focused on candidate gene approaches on a relatively small scale (N<50 in each treatment group) compared to modern genomewide association analyses. Our current study is not a pharmacogenetic study, but we considered a complex trait approach to investigate genetic factors behind cognitive control. Based on data reviewed in the introduction, we speculate on possible pharmacogenetic mechanisms for

CUD treatment that may involve restoring GABAergic function. We hypothesize that the reported CUD-GABA-PRS may relate to such responses, although this is currently speculative. Further studies are required to examine interactions between the selected GABAergic genes and medications and investigate relationships between the GABA-PRS and responses to medications in CUD treatment.

Strengths and Limitations

Study strengths include the multiple cohorts studied and tested across multiple methods, the large cohort used to define the CUD-GABA-PRSs and an independent fMRI-scanned cohort. Further, inclusion of solely AA participants reduces race-related variance and minimizes potential false-positive findings in that a mixture of African and European American samples could create confounding results based on population stratification[65]. Limitations include the small size of the fMRI cohort; thus, findings should be considered preliminary. In fMRI analyses, since years of education years were not correlated with Stroop-related effects (r=0.068, p=0.598), education levels were not controlled in whole-brain correlations with PRSs. However, the main effect was found only in CUD individuals and was not affected by group differences in education. The voxel-wise p threshold we set was relatively lax (p<0.01), When adopting a more stringent voxel-wise threshold (p<0.001), the cluster appeared in the same left precuneus region; however, it did not survive the whole-brain-correction threshold, and should thus be considered cautiously. Another limitation is that the GABA-related genes could also have non-GABAergic functions. For example, one of the identified GABA-related genes, *ADORA2A* encodes the adenosine A2A receptor, which forms a heteromer with dopamine receptors[66]. Other limitations include the studies' cross-sectional nature (precluding causal inferences), identified precuneus voxels including both white and gray matter, and possibility of HCs having lifetime cocaine use. Also, given the focus on AA subjects, future studies involving other racial or ethnic groups are warranted to examine generalizability of the findings. We used a data-driven whole-brain analysis to investigate our neuroimaging hypotheses. Alternate approaches (e.g., region-of-interest approaches) could be used in future studies to investigate potential roles of specific brain areas (e.g., frontal and striatal regions) with respect to relationships between genetic factors and neural correlates of cognitive control in CUD. We also did not use Bonferonni corrections when considering the 5 CUD-GABA-PRS thresholds, consistent with prior studies[67].

Conclusions

We demonstrated that GABAergic PRSs relate to Stroop-related precuneus activity and connectivity in CUD by integrating two independent AA cohorts assessed through large-scale genetic screening and brain imaging. The findings extend pre-clinical reports of cocaine-related alterations in GABAergic neural function[27,68], demonstrating for the first time GABAergic genetic links to neural correlates of cognitive control for individuals with CUD. Given that neural correlates of cognitive control have been linked to treatment outcomes for CUD, the findings suggest that GABAergic mechanisms may warrant further study in CUD treatment, particularly among AA populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest:

The authors report no conflicts of interest with respect to the content of this manuscript. Dr. Potenza has: consulted for and advised the Addiction Policy Forum, Game Day Data, AXA, Idorsia and Opiant/Lakelight Therapeutics; received research support from the Mohegan Sun Casino and the National Center for Responsible Gaming (now the International Center for Responsible Gaming); consulted for legal and gambling entities on issues related to impulse-control and addictive disorders; given academic lectures in grand rounds, CME events, and other clinical/scientific venues; and generated books or chapters for publishers of mental health texts. Dr. Gelernter is named as a co-inventor (with Dr. Henry Kranzler) on the PCT patent application #15/878,640 entitled: “Genotype-guided dosing of opioid agonists,” filed January 24, 2018. Dr. Kober has provided consultation for Invidior, Inc. The other authors report no disclosures. The views presented in this manuscript represent those of the authors and not necessarily those of the funding agencies.

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- GABA polygenic risk scores (PRSs) for cocaine use disorder (CUD) differ between cases and controls.
- GABA PRSs relate inversely with Stroop neural correlates in the left precuneus in CUD.
- Seed-based connectivity identified reduced precuneus-to-posterior-cingulate connectivity in CUD.

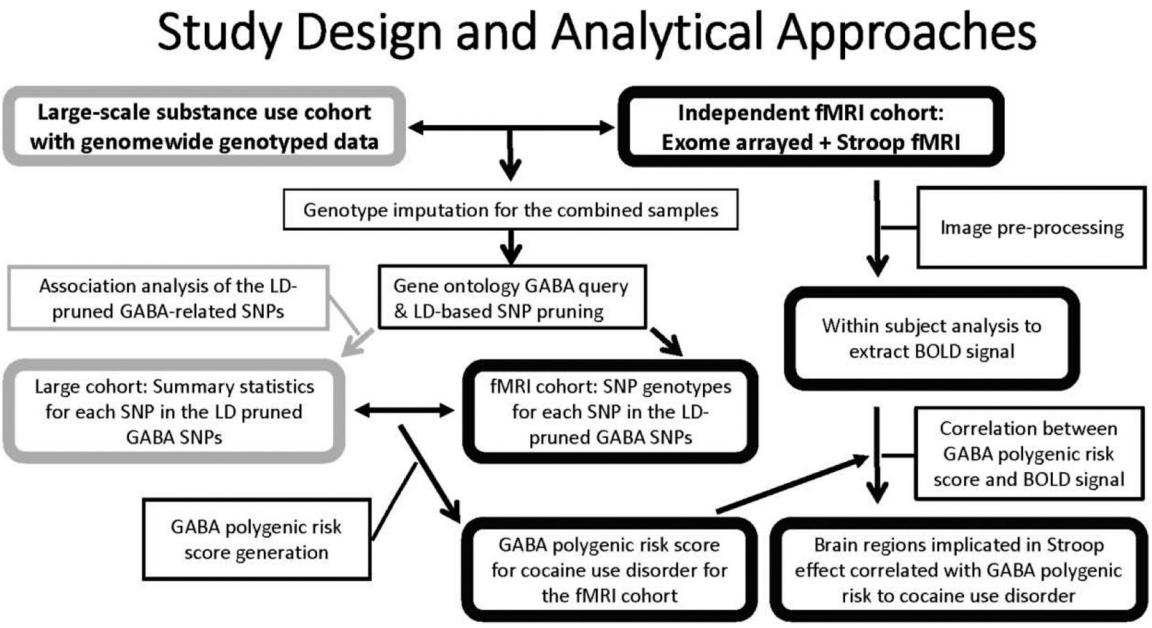

Figure 1.

Flow of the analytical approach investigating the GABAergic polygenic risk score (PRS). Rounded rectangles indicate the observed data or derived statistics. Rectangles indicate the analytical approach. The large-scale substance use cohort with genomewide genotypes was combined with the independent and exome-arrayed fMRI cohort for genotype imputation. The imputed genetic variants which belong to the gene ontology GABA query set were selected and further gone through the LD-based SNP pruning before the association analysis to generate the summary statistics for each SNP in the LD pruned GABA SNPs. Borrowing the summary statistics from the large cohort, GABA polygenic risk scores for CUD for the fMRI cohort were generated. On the other hand, the fMRI cohort with the Stroop task had image pre-processing and within-subject analyses. Correlation analyses between BOLD signal and GABA polygenic risk scores were conducted to identify brain regions implicated in the Stroop effect correlated with the GABA polygenic risk for CUD. GABA, gamma-aminobutyric acid; GWAS, genomewide association study; fMRI, functional magnetic resonance imaging; LD, linkage disequilibrium; SNP, single nucleotide polymorphism; BOLD, blood-oxygen-level-dependent.

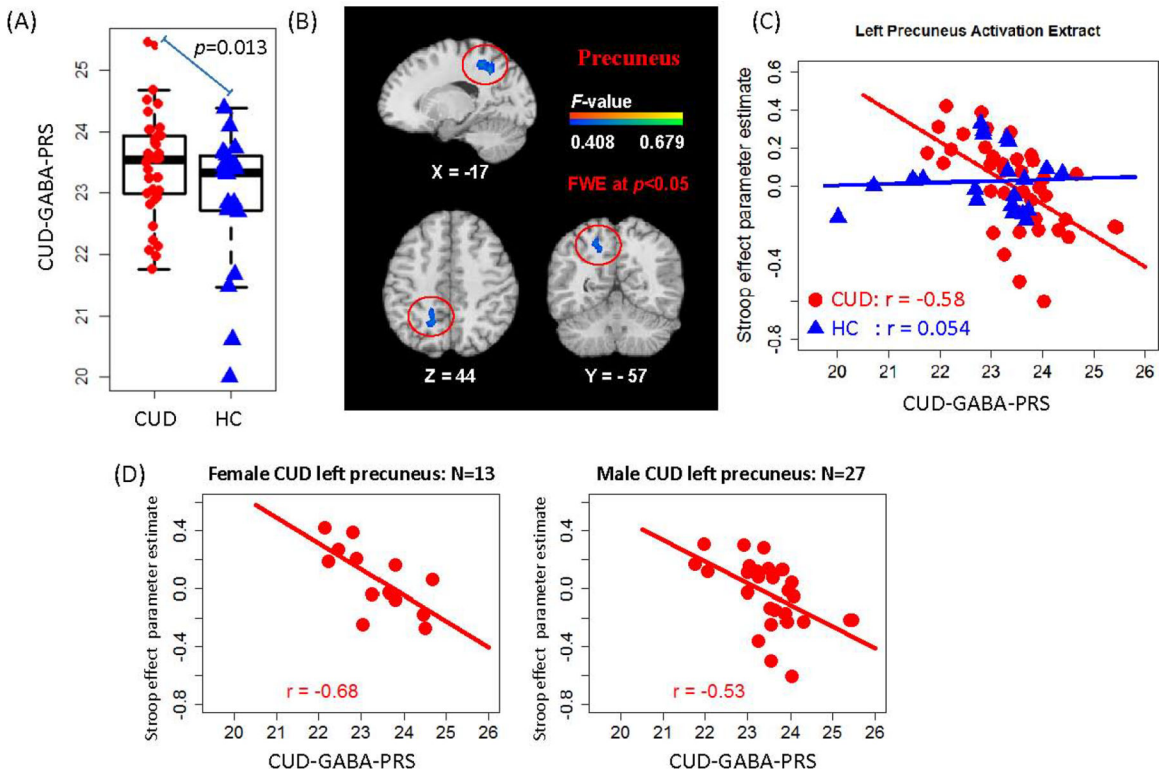

Figure 2.

GABA polygenic risk scores (CUD-GABA-PRSs) and correlated brain activations during Stroop performance. (A) Boxplot of the CUD-GABA-PRSs in the individuals with cocaine use disorder (CUD) and healthy control (HC) participants. Boxplots (in black) are overlaid with scatter plots. (B) Correlation analyses between CUD-GABA-PRSs and the neural correlates of the Stroop effect (incongruent > congruent) identified a cluster in the left-precuneus in the CUD group. All contrast maps are thresholded (k=65) at a voxel-level of p<0.01 two-tailed and family-wise-error-corrected at p<0.05. (C) Scatter plot of the peak activation extraction of the left precuneus at Talairach (x, y, z)=(−18,−45,48) correlated with CUD-GABA-PRSs in CUD and HC participants. (D) Within-sex scatter plots of the correlations of CUD-GABA-PRSs and the Stroop-effect-related activation in the left precuneus in individuals with CUD.

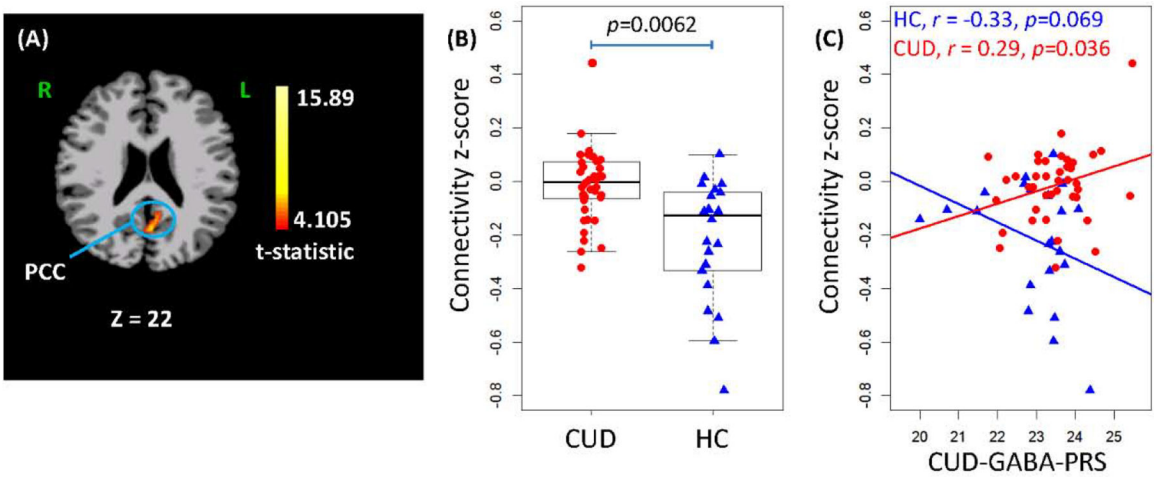

Figure 3.

(A) A seed-based connectivity analysis identified differential connectivity between the precuneus seed and the posterior cingulate cortex (PCC) between individuals with cocaine use disorder (CUD) and healthy control (HC) participants. Findings are reported at $p_{FWE}<0.05$ with a voxel-level $p<0.001$ using a cluster of $k=29$. (B) Boxplots of the connectivity z-scores in CUD and HC groups are shown. Boxplots are overlaid on scatter plots (difference between CUD versus HC individuals, $p=0.0062$). (C) Relationship between the connectivity z-scores and the GABAergic polygenic risk scores (CUD-GABA-PRSs). Correlations $r=0.29$ ($p=0.036$) in individuals with CUD ($p=0.036$), and $r=-0.33$ in HC individuals ($p=0.069$).

Table 1.

Characteristics of the fMRI Cohort

	Cocaine Use Disorder	Healthy Control	*p*-value
N	40	22	
Male (%)	67.5	36.4	<0.05
Age (mean/sd)	43.5/5.5	31.9/9.7	<0.01
Education years (mean/sd)	11.9/1.3	14.9/1.6	<0.01
Years of cocaine use (mean/sd)	13.4/7.6		
Age of cocaine first use (mean/sd)	22.5/8.1		