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Research report

Effects of an opioid (proenkephalin) polymorphism on neural response to errors in health and cocaine use disorder

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HIGHLIGHTS

- Opioid genetics can help clarify addiction phenomenology.
- We tested functional and structural correlates of a select proenkephalin gene.
- Addiction group differences were accentuated in those with the riskier genetic variant.
- Results provide an intermediate phenotype that can be targeted for further study.

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ABSTRACT

Chronic exposure to drugs of abuse perturbs the endogenous opioid system, which plays a critical role in the development and maintenance of addictive disorders. Opioid genetics may therefore play an important modulatory role in the expression of substance use disorders, but these genes have not been extensively characterized, especially in humans. In the current imaging genetics study, we investigated a single nucleotide polymorphism (SNP) of the protein-coding proenkephalin gene (*PENK*: rs2609997, recently shown to be associated with cannabis dependence) in 55 individuals with cocaine use disorder and 37 healthy controls. Analyses tested for *PENK* associations with fMRI response to error (during a classical color-word Stroop task) and gray matter volume (voxel-based morphometry) as a function of Diagnosis (cocaine, control). Results revealed whole-brain Diagnosis × *PENK* interactions on the neural response to errors (fMRI error > correct contrast) in the right putamen, left rostral anterior cingulate cortex/medial orbitofrontal cortex, and right inferior frontal gyrus; there was also a significant Diagnosis × *PENK* interaction on right inferior frontal gyrus gray matter volume. These interactions were driven by differences between individuals with cocaine use disorders and controls that were accentuated in individuals carrying the higher-risk *PENK* C-allele. Taken together, the *PENK* polymorphism—and potentially opioid neurotransmission more generally—modulates functioning and structural integrity of brain regions previously implicated in error-related processing. *PENK* could potentially render a subgroup of individuals with cocaine use disorder (i.e., C-allele carriers) more sensitive to mistakes or other related challenges; in future studies, these results could contribute to the development of individualized genetics-informed treatments.

1. Introduction

Error processing is a core executive function that allows for successful identification and correction of discrepancies between an intended and executed response [1,2]. In health, the neural correlates of error-related processing typically encompass a network of regions of the medial prefrontal cortex (PFC) including the

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anterior cingulate cortex (ACC) [3–5]. Despite this common neural signature, error-related processing is also modulated by individual differences [6–9]. That is, certain individuals or groups may differ in the frequency with which they commit errors, and/or in the reactivity they show upon committing such errors. One important individual difference is the presence of a substance use disorder (SUD), a psychopathology marked by pervasive and disruptive neurocognitive disruptions (e.g., in error-related processing) that modulate the severity and course of the disease [10–19]. Our goal in the current study was to explore whether error-related processing in SUD is further modulated by another potentially important individual difference: opioid system genetics [specifically, a single nucleotide polymorphism (SNP) of the protein-coding proenkephalin gene (*PENK*: rs2609997)].

The opioid system forms a crucial component of the brain's reward circuit and importantly contributes to SUD symptomatology [20,21]. Preclinical work has largely shown that knocking out proenkephalin—alone or in combination with related neuropeptides—reduces motivation, drug reward, and drug self-administration behavior [22–24]. In human SUD, opioid neurotransmission has been examined with positron emission tomography (PET). For example, [^{11}C] carfentanil has been used to image mu opioid receptor binding in smokers [25–27], and in abusers of heroin [28], alcohol [29–31], and cocaine [32–35]. More proximally to the current goals, *PENK* gene variants that have a functional relationship with gene expression levels have been associated with increased risk for marijuana use disorder [36] and opioid use disorder [37,38]. In contrast, *PENK* was not associated with alcohol dependence [39], and a postmortem study of alcohol-dependent individuals and controls did not reveal differences in *PENK* expression [40]. These studies collectively provide some suggestive evidence that *PENK* is associated with a substance abuse phenotype, highlighting this SNP as a potentially interesting candidate for further study. However, the specific role of the gene in SUD remains unclear.

Here, we used an imaging genetics approach to test for *PENK* associations with fMRI response to error (during a classical color-word Stroop task) and gray matter volume as a function of cocaine use disorder (CUD) diagnosis. The C-allele of *PENK* SNP rs2609997, associated with increased *PENK* expression compared with the T/T genotype, has been characterized as the "riskier" allele because of its association with increased negative emotionality and a higher prevalence of cannabis abuse [36]. Nevertheless, because the literature on the functional effects of this particular *PENK* SNP—and, indeed, of *PENK* in general—is minimal, the findings of the current study can add crucial new information to the field by clarifying the neurobiological and psychological implications of carrying this C-allele. More specifically, uncovering this kind of intermediate imaging phenotype can provide important clues about this gene's operation vis-à-vis SUD [41]. Our decision to focus on CUD in the context of *PENK* was informed by prior research showing that *PENK* mRNA expression is impaired in monkeys that self-administered cocaine [42] and in humans who used cocaine [43], and that variants of this gene have been linked to other addictive disorders [36]. Our decision to focus on errors in the context of *PENK* was informed by prior research showing that *PENK* mRNA is expressed in limbic brain regions (e.g., amygdala) [36], relevant to a Stroop task insofar as these regions participate in the assigning of negative valence to errors and other negative action outcomes [44]. More importantly, *PENK* is also expressed in regions of the PFC [40,45–48], of core relevance for performing Stroop tasks (recently reviewed in [49]). In the current study, participants performed an event-related color-word Stroop task while undergoing functional magnetic resonance imaging (fMRI) [50]; we have previously used this task to evaluate error-related processing in CUD [51–53]. During these same scanning sessions, structural MRI was also collected. We hypothesized that the "riskier" C-allele of the *PENK* SNP rs2609997 (i.e., compared with the less risky T/T genotype) (A) would be associated with more frequent and severe cocaine use; and (B) would accentuate group differences between CUD and controls in structure and responsiveness to error in limbic and PFC brain regions as indicated by significant whole-brain CUD × *PENK* interactions in these respective measures.

2. Methods

2.1. Participants

Fifty-five CUD and 37 healthy controls, recruited through advertisements, local treatment facilities, and word of mouth, participated in this research; all provided written informed consent in accordance with the local Institutional Review Board. Some of these participants have been included in prior imaging genetics studies in our lab, but these studies have always included different genes and/or different neural probes, and accordingly have reported activations in different brain regions [54–56]. More specifically, we previously reported on polymorphisms of the dopamine transporter (*DAT1*) [54] and the protein-coding monoamine oxidase A gene (*MAOA*) [55,56] while participants performed a *drug-word* inhibitory control task during fMRI [54], viewed unpleasant images during EEG [55], or simply while they underwent structural MRI scans [56]. For these reasons, overlap in variance with the current study is likely minimal. Exclusion criteria for the current study were: (A) history of head trauma or loss of consciousness (>30 min) or other neurological disease of central origin (including seizures); (B) abnormal vital signs at time of screening; (C) history of major medical conditions, encompassing cardiovascular (including high blood pressure), endocrinological (including metabolic), oncological, or autoimmune diseases; (D) history of major psychiatric disorder, with some exceptions (for both groups: nicotine dependence; for CUD: comorbidities of known high co-occurrence including other SUD, major depression, and/or post-traumatic stress disorder [57,58]); (E) pregnancy as confirmed with a urine test in all females; (F) contraindications to the MRI environment; (G) except for cocaine in CUD participants, positive urine screens for psychoactive drugs or their metabolites (amphetamine or methamphetamine, phencyclidine, benzodiazepines, cannabis, opiates, barbiturates and inhalants) (note that although participants were permitted to have a current comorbid SUD as described below, participants who tested positive for other drugs indicating active use were excluded from all study procedures in the lab); (H) current evidence of intoxication from alcohol or any illicit drug. Protection against acute intoxication (alcohol and other drugs including cocaine) was afforded by our trained research staff, which has extensive experience with recognizing signs of intoxication in individuals with CUD (note that cigarette smoking was not restricted to avoid possible confounding effects on the fMRI results of cigarette withdrawal).

Participants underwent a comprehensive diagnostic interview, which consisted of: (A) Structured Clinical Interview for DSM-IV axis I Disorders [59]; (B) Addiction Severity Index [60], a semi-structured interview instrument used to assess history and severity of substance-related problems in seven problem areas (medical, employment, legal, alcohol, other drug use, family-social functioning, and psychological status); (C) Cocaine Selective Severity Assessment Scale [61], measuring cocaine abstinence/withdrawal signs and symptoms (i.e., sleep impairment, anxiety, energy levels, craving, and depressive symptoms) 24 hours within the time of interview; (D) Severity of Dependence Scale [62]; and (E) Cocaine Craving Questionnaire [63]. This interview identified the following cocaine-related diagnoses in CUD participants: current cocaine