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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - SHORT COMMUNICATION

Association between cognitive performance and *SYT1*-rs2251214 among women with cocaine use disorder

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Abstract
The SNP rs2251214 of the SYT1 gene was recently associated with externalizing phenotypes, including ADHD and cocaine use disorder (CUD). Here, we investigated whether *SYT1*-rs2251214 could also be implicated with cognitive performance variations among women with CUD. Results showed that G homozygous ($n=146$) have lower cognitive performance in the Stroop, Trail Making and Matrix Reasoning tests compared with A-allele carriers ($n=64$), suggesting that rs2251214 may influence the severity of cognitive impairments in CUD.

Keywords SNARE complex · Cocaine addiction · Substance use disorders · Stimulants · Cognition

Introduction

Cocaine use disorder (CUD) is associated with cognitive deficits. A meta-analytic review comprising 1452 CUD patients and 1411 controls demonstrated deficits across 8 cognitive domains with larger effect sizes related to attention, impulsivity, learning/memory, working memory and inhibitory control (Potvin et al. 2014). Such impairments remain stable during the first months of abstinence, although evidence suggests improvements in cognition of CUD patients after sustained abstinence (Mahoney 2019). Cognitive dysfunction in CUD has been shown to be closely linked to negative clinical outcomes, such as lack of treatment adherence, as well as with higher relapse rates (Nuijten et al. 2016; Sofuoglu et al. 2016). However, genetic factors influencing the effects of chronic cocaine use on cognition are not fully understood.

The SNARE (soluble *N*-ethylmaleimide-sensitive fusion protein attachment protein receptors) complex plays a key role in the brain by controlling neurotransmitter release (Ramakrishnan et al. 2012). Synaptotagmin I (SYT1) is a synaptic vesicle protein that functions as a calcium sensor and is a main regulator of the SNARE complex. Convincing preclinical data have shown that SYT1 expression correlates with cognitive measures and neuronal function in rodents (Balietti et al. 2018; Jia et al. 2010; Chen et al. 2013; Zhang et al. 2017; Yu et al. 2018). Recently, human genome-wide association studies (GWAS) have identified associated SNPs on *SYT1* gene with personality traits as neuroticism (Luciano et al. 2018), and with educational attainment and cognitive performance (Lee et al. 2018). Furthermore, a recent GWAS of 300,486 non-demented individuals found that *SYT1* is among many genes influencing general cognitive ability (Davies et al. 2018).

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A specific variant, *SYT1*-rs2251214, was recently associated with methylphenidate treatment response variability in ADHD (da Silva et al. 2018) and with the susceptibility to develop CUD (da Silva et al. 2019) in candidate gene studies. However, the role of *SYT1*-rs2251214 in cognitive phenotypes of substance use disorders remains to be elucidated. Therefore, in this study, we investigated whether *SYT1*-rs2251214 could also be implicated with cognitive performance variations among women with CUD.

Materials and methods

Participants

This cross-sectional study was performed in female patients with CUD undergoing treatment in an inpatient detoxification unit of a public hospital in Southern Brazil. Hospitalization for drug detoxification is one of the treatment options available in the public health-care system in Brazil. Included participants ($n = 210$) met the following criteria: (1) age of 18–60 years; (2) diagnosis of CUD according to Structured Clinical Interview for DSM-5 (SCID) (American Psychiatric Association 2010); (3) self-report of smoked or snorted cocaine as the most harmful substance with regard to drug-related problems; (4) absence of psychotic syndromes and other severe medical condition. The current research was approved by the Ethical Committee of the enrolled institutions, and all of the participants provided written informed consent.

Study procedures and cognitive assessment

The detoxification treatment takes 21 days and participants were invited to take part in the study during the first 3 days after treatment enrollment. Participants were treated in an inpatient abstinence-controlled environment, so they had no access to alcohol, nicotine or other drugs. Prescribed symptomatic cocaine detoxification protocol was applied during treatment, including neuroleptics, analgesics, antidepressants and mood stabilizers. Benzodiazepines were not prescribed.

Within the first week, clinical characteristics of participants were assessed through the Addiction Severity Index 6 (ASI-6) (Kessler et al. 2012; Cacciola et al. 2011). The ASI-6 is a semi-structured interview and it was used to assess recent substance use (e.g., cocaine, alcohol, cannabis and tobacco), as well as lifetime problems in the following domains: psychiatric, alcohol, legal, medical, employment, and family and social support. The presence of polysubstance use was defined as having consumed ten or more times other substances during the last 30 days before treatment enrollment.

The battery of tests was designed to assess multiple cognitive components, including verbal knowledge, reasoning, verbal fluency, inhibition, cognitive flexibility, visual attention, processing speed and selective attention. To reduce any possible bias in cognitive tasks due to abstinence symptoms, the cognitive battery was administered individually over two sessions, when participants were no longer in the acute phases of drug withdrawal (defined as the first 72 h of abstinence, Potvin et al. 2014). No sedative medication was administered for 24 h before cognitive assessment.

The first session was carried out approximately 10 days after participant's enrollment in the treatment program. In this session, the vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) (Heck and Trentini 2009) was used to assess verbal knowledge, and the Matrix Reasoning subtest of the WASI was used to assess reasoning capabilities. No participants had early treatment discharge at this point, resulting in a sample size of 210 for these analyses.

The second session was performed approximately 15 days after treatment enrollment. The Trail Making Test B assessed cognitive flexibility, visual attention and processing speed (Campanholo et al. 2014), and the Stroop Color–Word Interference Test—Golden Version measured the domains of selective attention and inhibitory control (Zimmermann et al. 2015). The Verbal Fluency task assessed phonemic and semantic verbal fluency (Bertola et al. 2014). Sixteen participants had early treatment discharge, resulting in a sample size of 194 for these analyses. Patients were voluntarily included in the treatment program, thus they were allowed to request early discharge.

Genotyping

DNA extraction from peripheral blood was performed by salting out as described in Lahiri and Nurnberger (1991). *SYT1*-rs2251214 was genotyped by TaqMan allelic discrimination assay (Applied Biosystems StepOne Real-Time PCR System) according to the manufacturer's suggested protocol. Approximately, 10% of the sample was re-genotyped, aiming quality control, and no genotyping inconsistencies were found.

Statistical analyses

Data were tested for normality of distribution by Shapiro–Wilk test. The demographic, clinical and cognitive measures were examined using Chi-squared tests, or independent *t* tests comparing groups with CUD subdivided according to *SYT1*-rs2251214. Heterozygotes and homozygotes for the minor allele were assembled and compared to homozygotes for the major allele (A-carriers versus GG). For each cognitive task, the dominant genetic model

was tested using SNPassoc R package (version 1.9-2). We tested for possible confounders; however, none of the variables tested (Table 1) was included as a covariate since they were not associated with both the study factor and outcomes (Cordell 2009).

Results

Demographic and clinical data are depicted in Table 1. No significant differences were detected on these measures between A-carriers versus GG. Overall means of cognitive measures are depicted in Table 2. Association analyses showed an effect of *SYT1*-rs2251214 on Matrix Reasoning score ($p=0.011$), on Stroop score ($p=0.019$) and on Trail Making Test B score ($p=0.042$). GG genotype was associated with lower performance in these cognitive tests among women with CUD. No significant effects of *SYT1*-rs2251214 on the remaining cognitive measures were observed.

Table 2 Overall means of cognitive measures and parameters of the association analyses

Outcome	GG mean (SE)	A-carriers mean (SE)	*p* value
Vocabulary	37.42 (1.02)	38.25 (1.19)	0.637
Matrix Reasoning	15.12 (0.51)	17.52 (0.77)	0.011
Stroop	26.29 (0.80)	29.69 (1.27)	0.019
Trail Making	153.8 (5.91)	133.5 (7.80)	0.042
Verbal Fluency	39.37 (1.03)	40.92 (1.35)	0.416

Data presented in mean and standard error. Vocabulary score was the sum of points in the test. Matrix Reasoning score was the number of correct answers in the test. Stroop score was the number of correct colors named during 45 s in the color–word condition. Trail Making score was the time needed to finish test B. Verbal Fluency score was the sum of the words produced in each stage of the task and a final score that represented the sum of all of the words produced during the task

Discussion

In this study, we showed that *SYT1*-rs2251214 GG was associated with lower cognitive performance in reasoning, selective attention, inhibitory control, cognitive flexibility, visual attention and processing speed domains compared with A-carriers. These cognitive domains have a key role in behavioral adaptation and self-control among substance abusers (Sullivan et al. 2018). Although CUD is associated with cognitive impairments per se, this finding indicates that *SYT1*-rs2251214 may also influence the severity of cognitive impairments among female cocaine users. Moreover, it is possible that the cognitive alterations associated with this SNP may contribute to increase the risk for the development of CUD, considering the association between *SYT1*-rs2251214 GG genotype and CUD found in a previous case–control study (da Silva et al. 2019). This hypothesis corroborates the idea that cocaine users may present cognitive deficits predating the onset of cocaine use (Spronk et al. 2013).

Table 1 Demographic and clinical data of groups with CUD subdivided by *SYT1*-rs2251214 genotype

	GG ($n=146$)	A-carriers ($n=64$)	Statistics	*p* value
Age (years)	30.75 (8.2)	30.18 (7.0)	$t=0.48$	0.627
Educational level			$\chi^2=1.01$	0.200
Did not enroll high school	76.1% ($n=108$)	69.4% ($n=43$)		
Enrolled or finished high school	23.9% ($n=34$)	30.6% ($n=19$)		
Ethnicity			$\chi^2=1.04$	0.194
White	31.3% ($n=46$)	38.5% ($n=25$)		
Non-white	68.7% ($n=101$)	61.5% ($n=40$)		
Recent polysubstance chronic use				
Alcohol	25.0% ($n=37$)	24.6% ($n=16$)	$\chi^2=0.04$	0.549
Cannabis	18.9% ($n=28$)	21.5% ($n=14$)	$\chi^2=0.19$	0.394
Tobacco	96.5% ($n=141$)	96.8% ($n=62$)	$\chi^2=0.28$	0.867
Addiction Severity Index 6 scores				
Alcohol	48.41 (9.5)	48.58 (10.3)	$t=0.14$	0.888
Psychiatric	49.34 (8.9)	50.26 (9.1)	$t=0.84$	0.400
Medical	48.61 (8.6)	48.53 (8.0)	$t=0.06$	0.945
Legal	53.01 (8.1)	52.06 (7.2)	$t=0.96$	0.338
Employment	37.83 (3.9)	38.46 (4.46)	$t=1.27$	0.204
Family and social support	39.68 (8.4)	38.44 (9.0)	$t=1.16$	0.246
Psychiatric medication use (daily)	19.6% ($n=29$)	21.5% ($n=14$)	$\chi^2=0.10$	0.439

Data presented in mean and standard deviation, or percentage and number of participants

Indeed, this SNP has been associated with neuropsychiatric disorders in which reduced cognitive and executive functioning performance are key features. The G allele of rs2251214 was associated with ADHD susceptibility (Cupertino et al. 2017) and more recently with methylphenidate poor treatment response, specifically in the domains of inattention and oppositional defiant symptoms (da Silva et al. 2018). This SNP had also an effect on the age at onset of impairment due to ADHD and other externalizing disorders (Cupertino et al. 2017). Although the molecular mechanisms by which rs2251214 could affect cognition are still unknown, preclinical evidence supports the role of *SYT1* on brain functioning given that CRISPRi tools that silence *SYT1* also impaired the balance between inhibitory and excitatory synapses (Zheng et al. 2018).

This study should be interpreted in the context of some limitations. First, considering that participants were recruited by convenience sampling in a women's psychiatric unit, we cannot generalize these findings to male samples. Second, participants with CUD also presented a history of alcohol, tobacco and cannabis use, which might interfere in cognitive performance as well. Despite that individuals with drug addiction commonly report the consumption of multiple drugs (Aharonovich et al. 2005; Viola et al. 2014), the frequency of polysubstance use was similar among GG and A-carriers. Third, this study had a small sample size; however, it is important to highlight the difficulty in performing multiple levels of assessment (e.g., cognitive, clinical and genetic) in individuals with CUD. Future studies with larger samples and addressing the molecular effects of *SYT1*-rs2251214 on cognition and substance use disorders are warranted.

These findings fit well with a growing body of evidence, including GWAS findings, showing that SNPs in genes implicated with neurotransmitter release are important factors accounting for cognition and externalizing phenotypes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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