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Serotonin transporter gene promoter polymorphism predicts relationship between years of cocaine use and impulsivity

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Summary

This study investigated the relationship between the *serotonin transporter* gene (*SLC6A4*) *5-HTTLPR* genotypes, cocaine-dependence, and impulsivity. Ninety-eight healthy control and 243 treatment-seeking, cocaine-dependent subjects from the greater Houston area were evaluated between February 2007 and April 2012. Subjects signed an informed consent. Medical and drug use histories [ASI (McLellan *et al*., 19980)], demographics, impulsivity [BIS-11 (Patton *et al*., 1995)], psychiatric disorders [DSM-IV (SCID-I) (First *et al*., 1996)], and 10 ml of blood for DNA isolation were collected. This study was approved by the local IRBs at the medical centers of the University of Texas, Baylor College of Medicine, and the Veterans Affairs Research and Development Committee.

DNA was genotyped for the low-expressing S' and high-expressing L' triallelic *5-HTTLPR* polymorphism (Hu *et al*., 2006). There were 59, 117, and 67 S'S, L'S', L'L' cocaine-dependent subjects, respectively, and 24, 45, and 29 controls, respectively. Cocaine-dependent subjects used cocaine for an average of 14.5 years and 16.1 days in last 30 days. Data analyses were conducted in SAS 9.2 (SAS Institute Inc., Cary, NC) and significance set as $P < 0.05$ (one-tail) for *a priori* hypotheses (Keppel and Wickens, 2004). We hypothesized that the S'-allele carrier subjects would be more impulsive. Differences were observed in age ($P<0.01$), sex ($P<0.01$), population structure (Kosten, et al., 2013 ($P<0.05$),

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Conflict of Interest

None.

and educational level (P<0.01) between control and cocaine-dependent groups. Therefore, analyses were adjusted for age, sex, ethnicity, and educational level.

The general linear model revealed a group (cocaine-dependent versus control) × *5-HTTLPR* (L'L' genotype versus S' allele carriers [L'S'+S'S' genotypes combined]) interaction ($F_{1,323}$=4.87, P=0.028), suggesting that the relationship between impulsivity and *5-HTTLPR* genotype in cocaine-dependent subjects was different from that in controls. *Post hoc* analysis showed that S' allele cocaine-dependent carriers had significantly lower BIS-11 total scores (71.3±1.6) than did those with the L'L' genotype (74.9±2.0) (P<0.05), while controls showed no difference in BIS-11 total scores as a function of genotype (L'L': 56.0±2.7; L'S'/S'S': 59.5±2.0). The cocaine-dependent subjects had higher BIS-11 total scores (73.1±1.7) than did the controls (57.6±2.3; P<0.0001).

There was a group × *5-HTTLPR* genotype interaction ($F_{1,323}$=6.31, P=0.012) for the nonplanning BIS-11 subscore. S'-allele cocaine-dependent carriers had significantly lower BIS-11 nonplanning subscores (28.7±0.7) than those with the L'L' genotype (31.3±0.9) (P<0.01), a relationship not observed in the controls (S'-allele carriers: 22.5±0.9; L'L' genotype: 21.2±1.2). For the BIS-11 motor and attentional subscores, the group × *5-HTTLPR* genotype interactions were not significant.

A *5-HTTLPR* × years of cocaine use interaction ($F_{1,232}$=4.22, P=0.04) was found for the BIS-11 total scores of the cocaine-dependent subjects. The BIS-11 total score was positively associated with years of cocaine use for S'-allele carriers (r=0.26, P=0.0006, Pearson's correlation analysis), but not for L'L' genotype subjects (r=0.02, P=0.87). For the BIS-11 subscores, the *5-HTTLPR* × years of cocaine use interactions were not significant. For the BIS-11 total score and subscores, the *5-HTTLPR* × days of cocaine use in last 30 days interactions were not significant.

Understanding genotype and dependence in moderating impulsivity may help in the development of effective treatments.

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