COMT Genotype, Gambling Activity, and Cognition

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Jon E. Grant[1]

Sarah A. Redden[1]

Eric W. Leppink[1]

Brian L. Odlaug[2]

Samuel R. Chamberlain[3]

[1]Department of Psychiatry & Behavioral Neuroscience
University of Chicago, Chicago, IL, USA

[2]Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[3]Department of Psychiatry, University of Cambridge, UK; & Cambridge and Peterborough NHS Foundation Trust (CPFT), UK

Address correspondence to:
Jon E. Grant, JD, MD, MPH
Professor, Department of Psychiatry & Behavioral Neuroscience
University of Chicago
Pritzker School of Medicine
5841 S. Maryland Avenue, MC 3077
Chicago, IL 60637
Phone: 773-834-1325; Fax: 773-834-6761; Email: jongrant@uchicago.edu

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ABSTRACT

Neuropsychological studies of adults with problem gambling indicate impairments in many cognitive areas. Catechol-O-methyltransferase (COMT) plays a unique role in the regulation of dopamine in the prefrontal cortex and has been proposed to play a role in the cognitive dysfunction of problem gambling. This study examined adults with varying levels of gambling behavior to determine whether COMT genotype was associated with differences in gambling symptoms and cognitive functioning. 260 non-treatment-seeking adults aged 18-29 years with varying degrees of gambling behavior provided saliva samples for genotyping COMT val158met (rs4680). All subjects underwent clinical evaluations and neurocognitive assessment of decision-making, working memory, and impulsivity. The Val/Val genotype was associated with the largest percentage of subjects with gambling disorder (31.8%), a rate significantly different from the Val/Met (13.2%) group (p=0.001). The Val/Val group was also associated with significantly more gambling disorder diagnostic criteria, greater frequency of gambling behavior, significantly worse cognitive performance on the Cambridge Gamble Task (risk adjustment and delay aversion) and the Spatial Working Memory task (total errors). This study adds to the growing literature on the role of COMT in impulsive behaviors by showing that the Val/Val genotype was associated with specific clinical and cognitive elements among young adults who gamble, in the absence of differences on demographic measures and other cognitive domains. Future work should consider using COMT genotyping to track whether certain genotypes predict which young people will develop gambling disorder or other impulsive behaviors over time.

Key words: dopamine; COMT; planning; cognition; impulsivity; gambling

Introduction

Problem gambling represents a significant public health problem characterized by persistent and recurrent maladaptive patterns of gambling and is associated with impaired functioning (Hodgins et al., 2011). Problem gambling-related impairment may impact on every aspect of a person's life and many feel ill equipped to cope (Thon et al., 2014).

Neuropsychological studies of adults with problem gambling indicate impairments in many cognitive areas including inhibition, working memory, decision-making, cognitive flexibility, and executive planning (Ledgerwood et al, 2012; Goudriaan et al, 2006). Dopamine is a neurotransmitter that regulates cognitive functions dependent on the fronto-striatal circuitry, and dopamine dysregulation has been suggested as playing a key role in a range of impulsive behaviors, particularly those related to inhibitory control and decision making (Malloy-Diniz et al., 2013). The catechol-O-methyltransferase (COMT) enzyme plays a unique role in the regulation of dopamine in the prefrontal cortex (Tunbridge et al., 2004) and has been proposed to be a potential target for the treatment of cognitive dysfunction in a number of psychiatric illnesses, especially those characterized by high rates of impulsivity (Scheggia et al., 2012). A recent pharmacological treatment study for problem gambling found that the COMT inhibitor, tolcapone, improved gambling behavior and that this improvement was associated with enhanced fronto-parietal brain activation during planning (Grant et al., 2013).

In the frontal lobes, COMT is the enzyme largely responsible for the inactivation of synaptic dopamine (Tunbridge et al., 2004). A common functional polymorphism in the COMT gene, the Val substitution at codon 158 [rs4680 (val158met)], results in a ~40% increase in enzymatic activity and thereby reduces cortical dopamine levels (Lotta et al., 1995). Carriers of the Val allele exhibit less efficient prefrontal neural signaling and relative deficits in executive

cognitive functioning (Diaz-Asper et al., 2008; Dumontheil et al., 2010). Therefore, individuals homozygous for the Val allele are expected to have decreased levels of dopamine in comparison to individuals with two met alleles and should exhibit greater problems with executive functioning and impulsivity.

Studies of healthy control subjects, however, have demonstrated mixed results with respect to COMT genotype, cognitive performance, trait impulsivity, and impulsive behaviors. In an early study, the Met allele was predictive of enhanced performance on the Wisconsin Card Sorting test, and more efficient physiological responses in the prefrontal cortices (Egan et al., 2001). Another study found that Met subjects outperformed Val subjects on an N-Back working memory task (Farrell et al., 2012), while the same research group also found that the COMT polymorphism affected functional connectivity of the brain in the resting state (Tunbridge et al., 2013). One study found no differences between COMT genotype groups on a battery of 19 cognitive tasks including cognitive flexibility, memory, and visual processing (Dennis et al., 2010). A later study, however, found that health controls homozygous for the met allele demonstrated better performance on a cognitive task of executive functioning (Trail-Making Test) (Wishart et al., 2011). Other studies have shown that healthy control subjects homozygous for the Met allelic variant exhibited better performance on tasks of working memory and the Wisconsin Card Sorting Task compared to subjects homozygous for Val (Malhotra et al., 2002; Rosa et al., 2004). Conversely, van Den Bos and colleagues (2009) found that healthy control female subjects who were Met/Met homozygous chose more disadvantageously on the Iowa Gambling Task than subjects homozygous for valine (Val/Val). Similarly, a study of 82 healthy volunteers found that those with a Met/Met genotype had higher impulsivity scores on the Barratt Impulsiveness Scale compared to either Val/Met or Val/Val subjects (Soeiro-De-Souza et

al., 2013). Clinically, a study of 139 healthy controls found that COMT met/met homozygotes were more likely to be at-risk gamblers and mild problem drinkers compared to Val/Val homozygotes (Guillot et al., 2014). To further complicate the picture, a small genome-wide association study from the national community-based Australian Twin Registry did not find an association between COMT rs4680 and disordered gambling in 1312 twins (Lind et al. 2013). One potential explanation for discordant results in relation to cognition and the COMT polymorphism is that different optimal levels of dopamine are required for different cognitive functions; there may be a 'trade off' with higher dopamine (as seen with the Met variant) being associated with relatively superior improvement in some domains, with relative impairments in others. This suggestion would fit with an inverted 'U' model of executive functioning (e.g. Robbins & Arnsten, 2009; Kehagia et al., 2013).

Unlike previous studies examining COMT genotyping in healthy controls and seeking to explain impulsive behaviors, this study sought to examine COMT genotypes in a large sample of individuals with varying levels of gambling behavior to determine whether COMT genotype was associated with differences in gambling phenomenology and cognitive functioning. We hypothesized that those Val/Val homozygote gamblers, compared to Met carriers, would exhibit greater problem gambling severity, relative impairment in spatial working memory, relative impairment in decision-making, and no differences with respect to response inhibition (since the latter appears to be under noradrenergic control) (Bari and Robbins, 2013).

Material and Methods

Subjects

Participants comprised non-treatment-seeking young adults aged 18-29 years, recruited as part of an ongoing longitudinal study of impulsive behaviors. Subjects who had gambled at least five times during the preceding 12 months (i.e. a proxy for some baseline level of gambling behavior and impulsivity) responded to media announcements in two large metropolitan areas, and were compensated with a $50 gift card to a local department store for their participation. Inability to understand/undertake the procedures and to provide voluntary, written informed consent were exclusionary criteria. Since we sought to examine a naturalistic sample of people reflective of the broader population, subjects with psychiatric and substance use comorbidity, as well as those subjects currently taking psychotropic medications, were all allowed to participate.

The study procedures were carried out in accordance with the most recent version of the Declaration of Helsinki. The Institutional Review Board of the University of Chicago approved the study and the informed consent procedures. After all study procedures were explained and subjects had the opportunity to ask questions, subjects provided voluntary written informed consent.

Assessments

Raters assessed each subject using the Structured Clinical Interview for Gambling Disorder (SCI-GD), a nine-item instrument assessing symptoms of Gambling Disorder: a score of 0 reflected ‘low risk’, a score of 1-3 was consistent with ‘at risk’ gambling, and a score of ≥4 fulfilled the diagnostic criteria for gambling disorder. The SCI-GD is a modification of the DSM-IV based Structured Clinical Interview for Pathological Gambling (SCI-PG) (Grant et al., 2004) but omits the illegal acts criterion as it is no longer included in the DSM-5.

In addition, subjects were asked about frequency of gambling behavior, money lost gambling, and they completed the Yale-Brown Obsessive-Compulsive Scale Modified for Pathological Gambling (PG-YBOCS), which is a clinician-administered instrument that assesses thoughts, urges and gambling behavior over the seven days preceding assessment (Pallanti et al., 2005).

Subjects undertook a detailed interview incorporating clinical and cognitive evaluations. Occurrence of psychiatric conditions was evaluated using the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998), and the Minnesota Impulsive Disorders Interview (MIDI) (Grant, 2008). The former examines mainstream psychiatric conditions (e.g., depression), while the latter is tailored to detect impulse control disorders, namely binge-eating disorder, kleptomania, trichotillomania, intermittent explosive disorder, pyromania, compulsive buying, and compulsive sexual behavior.

Participants undertook the following cognitive paradigms at baseline, using a touch-screen computer in conjunction with the Cambridge Neuropsychological Test Automated Battery (CANTABeclipse, version 3, Cambridge Cognition Ltd, Cambridge, UK). Task order was fixed (indicated by order of task descriptions below). Cognitive testing took up to 50 minutes to complete and was done in one continuous session. The cognitive domains of interest were selected because they have been particularly strongly implicated in the pathophysiology of gambling problems, and we focused on spatial working memory, decision-making, and response inhibition (Clark, 2010; Van Holst et al., 2010).

Aspects of decision-making were examined using the Cambridge Gamble Task (CGT) (Lawrence et al., 2009). There were four practice trials followed by eight blocks of nine trials. At the start of each block, the ‘cumulative points’ was reset to 100. On each trial, subjects were

presented with a set of red and blue boxes, totaling ten. The ratio of red:blue boxes were varied over the course of the task pseudo-randomly (box-ratios: 9_1, 8_2, 7_3, 6_4). Subjects were informed that for each trial, the computer had hidden a 'token' inside one of the boxes, and that they had to decide whether they felt the token would be hidden behind a red or a blue box. After selecting 'red' or 'blue' using the touch-screen interface, subjects were required to gamble a proportion of their points as to whether this choice was correct or incorrect. The key outcome measures were: delay aversion (tendency towards wanting to make speedy responses rather than wait); quality of decision-making (i.e., the proportion of trials where the volunteer chose red when red boxes were in the majority and vice versa – i.e., made the logical color choice); the mean proportion of points gambled at each box-ratio; and risk adjustment (i.e., tendency to adjust how much one is betting depending on the degree of risk).

We assessed response inhibition using the Stop Signal Task, a paradigm in which the subject viewed a series of directional arrows appearing one per time on-screen, and made speeded motor responses depending on the direction of each arrow (Aron et al., 2004). On a subset of trials, an auditory stop-signal occurred ('beep') to indicate to volunteers that response suppression was needed for the given trial. This task estimated the time taken by each volunteer's brain to suppress an already triggered command.

Subjects underwent the Spatial Working Memory tasks (SWM) to examine aspects of strategy and working memory (Owen et al., 1990). Subjects attempt to locate tokens hidden underneath boxes on-screen and try to avoid returning to boxes that previously yielded such tokens. The key outcome measures include the "total number of errors" (inappropriately returning to boxes that previously yielded tokens), and "strategy score" (lower score equates to

superior strategy use), for each level of task difficulty. The spatial working memory paradigm is dependent on distributed circuitry including the prefrontal cortices (Owen et al., 1990).

COMT Status

Saliva was taken for analysis of COMT val158met (rs4680 G to A) genotyping. COMT val158met (rs4680) was the only gene examined in this study. TaqMan probes and primers were designed and synthesized by Applied Biosystems Inc. DNA samples were genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems Inc., Foster City, CA) using standard reagents and standard cycling protocols. Data were managed by The Applied Biosystems' ABI 7900 Real-Time Basic Software. Researchers involved in genotyping were blind to neuropsychological results, and researchers involved in neuropsychological assessments were blind to the genotyping results. COMT genotype was coded as a categorical variable (met/met, met/val and val/val) for further analysis.

Data Analysis

Subjects were compared based COMT status. Salient demographic, clinical, and cognitive variables were tabulated for the three groups. Differences between the groups were explored using independent sample t-tests (majority of measures that were single in nature) or chi-square tests (for binary variables). Where significant group differences were found, effect sizes were reported (Cohen's D). Statistical significance was defined as $p<0.05$, two-tailed, uncorrected. IBM SPSS Software, Version 21 was used for the analyses.

Results

The COMT genotype distribution was under Hardy-Weinberg equilibrium ($\chi 2=3.47$, $p=0.55$). The distribution of COMT genotype in our subjects were n=61 met/met, n=114 Val/Met, and n=85 Val/Val. The percentage of each level of gambling severity within each genotype group is presented in Figure 1. The Val/Val group had the most subjects with gambling disorder (31.8%), a rate significantly different from the Val/Met (13.2%) group ($p=0.001$). The Val/Val group was also associated with significantly more gambling disorder diagnostic criteria (reflected by the total number of SCI-GD criteria met) and greater frequency of gambling behavior compared to the met/met group (Table 1). In addition, comparison of the Val/Val group with the Val/Met group showed that they had significantly worse gambling symptoms (reflected by the subscales and total score of the PG-YBOCS) and met more SCI-GD criteria.

Table 2 shows the differences between COMT groups for the cognitive tasks. Although no differences were found on the stop signal task, the Val/Val group exhibited significantly worse cognitive performance on the CGT (risk adjustment and delay aversion) as well as on the SWM (total errors).

Discussion

This is the first study to explore clinical and cognitive associations between gambling behavior and COMT genotype in a large sample of young adults who gamble to varying degrees. Unlike many prior studies, we examined COMT genotypes in a representative non-treatment seeking community sample enriched for gambling behaviors. In this group of young adult gamblers, we found that a higher rate (31.8%) of the Val/Val group met criteria for gambling disorder compared to rates of 13.2% and 19.7% in the Val/Met and Met/Met groups, respectively. This finding was further reflected by the greater number of diagnostic criteria met

by the val/val subjects as well as greater weekly frequency of gambling behavior. The finding of worse gambling symptomatology in the Val/Val subjects appears to be consistent with what one would expect in gamblers based on the mechanism of the COMT enzyme. Continued gambling behavior may be related to less efficient prefrontal neural signaling and problems with executive cognitive functioning (van Holst et al., 2010; Ledgerwood et al., 2012). Our findings, however, conflict with a recent study of healthy controls which found that the met/met homozygotes were more likely to be at-risk gamblers Val/Val homozygotes (Guillot et al., 2014). The Guillot study, however, enrolled subjects based on alcohol use (and excluded heavier drinkers) and screened for gambling as a secondary aspect of the research. Our study specifically focused on gambling pathology and did not exclude subjects based on any issue other than ability to consent. The inconsistent findings, however, raise issues regarding how lower levels of gambling pathology are best measured and whether a range of impulsive behaviors (and which ones) may be associated with COMT genotype.

The key cognitive findings in this study were that the val/val genotype was associated with impaired risk adjustment and delay aversion on the Cambridge Gamble Task, and with spatial working memory problems, all with medium-large effect size, but intact performance on the task of response inhibition. The finding of decision making dysfunction in the val/val group was consistent with our hypothesis, but the fact that the differences were reflected by select measures (risk adjustment and delay aversion) rather than across all aspects of decision-making requires further examination. The val/val group exhibited significantly less risk adjustment than the met/met subjects on the task, indicating that, over the course of the task, they were insufficiently sensitive to changes in statistical risk and did not appropriately adjust the amount of points they gambled, depending on this changing risk. Gamblers tend to persist in their

behavior despite rising losses and this cognitive impairment in the val/val group may explain, in part, their difficulties with gambling.

The val/val group also exhibited greater problems in SWM than the met/met group, in terms of the number of errors made. These data are consistent with those found in mice using a spontaneous alternation task as well as data from human studies which have shown better performance by Met carriers compared with Val carriers on certain tasks of working memory (Barnett et al, 2007; Diaz-Asper et al, 2008). Working memory influences self-regulation as those with low working memory capacity show more automatic behavior than individuals with high working memory capacity. Deficits in working memory may result in impaired self-regulation and by extension worse gambling behavior.

Both of these cognitive deficits may suggest that cognitive therapy and pharmacotherapy for gambling behavior may ultimately wish to consider genotyping as a means of better targeting treatment approaches. If core cognitive deficits are shown consistently in certain subgroups of gamblers based on genotype, then a simple saliva test may be a useful means of directing patients to more successful treatment. Similarly, because tolcapone has demonstrated evidence of reversing certain cognitive deficits such as working memory in subjects with the val/val genotype (Giakoumaki et al, 2008; Farrell et al, 2012) this might be a particularly attractive medication option for gamblers with a combination of genotype and cognitive dysfunction (Grant et al., 2013). Future research may need to consider the relationship between genotyping and cognitive assessment when targeting pharmacotherapies for gambling problems.

Despite this being one of the first studies to explore the clinical and neurocognitive correlates of COMT genotype in young adult gamblers, several limitations should be noted. We selected cognitive tests based on a review of the existing literature (30) coupled with the need not

to expose subjects to excessively long testing batteries; as such we did not quantify all domains of cognition and future work could examine other functions such as temporal discounting, Iowa Gambling Task performance, or executive planning. We did not track medication use in the subjects, and so these findings may benefit from replication in subjects who are known not to be taking medications. We did not exclude substance dependent individuals as we wished this to be an ecologically representative sample; however, our results showed that in any event the groups did not differ significantly on this measure. The issue of potential racial/ethnic differences in genotype and how this relates to gambling is clinically important, but our study was not powered or designed to address this issue, which merits attention in its own right in a future study.

In summary, this study adds to the growing literature on the role of COMT in impulsive behaviors by showing that the val/val genotype was associated with specific clinical and cognitive elements among young adults who gamble, in the absence of differences on demographic measures and other cognitive domains. Future work should consider using COMT genotyping to track whether certain genotypes predict which young people will develop gambling disorder or other impulsive behaviors over time.

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Table 1. Demographic and Clinical Characteristics of Gamblers based on COMT Status

				p-values			Effect Size		
	Met/Met (N=61)	**Val/Met (N=114)**	**Val/Val (N=85)**	**Val/Val Vs. Val/Met**	**Met/Met Vs. Val/Met**	**Val/Val Vs. Met/Met**	**Val/Val Vs. Val/Met**	**Met/Met Vs. Val/Met**	**Val/Val Vs. Met/Met**
Age, years	26.1 (10.7)	23.8 (6.9)	27.0 (10.2)	**.011t**	.088t	.638t	.367	-	-
Sex female, n (%)	20 (32.8)	42 (36.8)	39 (45.9)	.199c	.593c	.112c	-	-	-
Ethnicity Caucasian, n (%)	41 (75.9)	75 (69.4)	42 (57.5)	.153c	.444c	.097c	-	-	-
Education, n (%) Some college +	55 (90.2)	103 (90.4)	77 (90.6)	.955c	.968c	.932c	-	-	-
Gambling Level, n (%)									
Disordered	12 (19.7)	15 (13.2)	27 (31.8)	**.001c**	.256c	.103c	.226	-	-
At-Risk	17 (27.9)	33 (28.9)	28 (32.9)	.546c	.880c	.513c	-	-	-
Low-Risk	32 (52.5)	66 (57.9)	30 (35.3)	**.002c**	.490c	**.039c**	-.224	-	-.171
SCI-GD Criteria	1.5 (2.1)	1.3 (2.0)	2.3 (2.5)	**.001t**	.447t	**.044t**	.442	-	.347
PG-YBOCS, urges	3.1 (3.8)	2.5 (3.0)	4.0 (4.8)	**.009t**	.327t	.201t	.375	-	-
PG-YBOCS, behaviors	3.3 (4.5)	2.9 (3.5)	4.0 (4.5)	**.047t**	.452t	.380t	.273	-	-
PG-YBOCS, total score	6.4 (8.1)	5.4 (6.2)	8.0 (9.0)	**.017t**	.374t	.266t	.336	-	-
Frequency of gambling behavior, per week	1.5 (2.1)	1.8 (2.2)	2.4 (2.2)	.158t	.423t	**.044t**	-	-	.418

Data refer to mean (standard deviation) unless otherwise specified.
SCI-GD=Structured Clinical Interview for Gambling Disorder;
PG-YBOCS=Yale-Brown Obsessive Compulsive Scale for Pathological Gambling; c=Chi Squared; t=t-test

Table 2. Current Comorbid Psychiatric Disorders in Gamblers based on COMT Status

				p-values			Effect Size		
	Met/Met (N=61)	Val/Met (N=114)	Val/Val (N=85)	Val/Val Vs. Val/Met	Met/Met Vs. Val/Met	Val/Val Vs. Met/Met	Val/Val Vs. Val/Met	Met/Met Vs. Val/Met	Val/Val Vs. Met/Met
Major depressive disorder									
Bipolar disorder									
Obsessive compulsive disorder									
Generalized anxiety disorder									
Panic disorder									
Any phobia									
Post- traumatic stress disorder									
Alcohol use disorder									
Substance use disorder									
Any eating disorder									
Any psychotic disorder									

Table 3. Cognitive Measures in Gamblers based on COMT Status

	Means			p-values			Effect Size		
	Met/Met (N=61)	**Val/Met (N=114)**	**Val/Val (N=85)**	**Val/Val Vs. Val/Met**	**Met/Met Vs. Val/Met**	**Val/Val Vs. Met/Met**	**Val/Val Vs. Val/Met**	**Met/Met Vs. Val/Met**	**Val/Val Vs. Met/Met**
SST SSRT	177.21 (63.44)	181.17 (67.53)	186.46 (63.24)	.578	.709	.390	-	-	-
SST median go reaction time	497.02 (180.12)	485.81 (183.17)	494.41 (165.93)	.736	.700	.929	-	-	-
CGT Delay aversion	.24 (.25)	.31 (.28)	.33 (.25)	.502	.123	.034	-	-	.360
CGT Overall proportion bet	.53 (.13)	.54 (.14)	.55 (.13)	.608	.682	.405	-	-	-
CGT Quality of decision making	.95 (.09)	.95 (.08)	.95 (.08)	.784	.879	.940	-	-	-
CGT Risk adjustment	1.88 (1.25)	1.47 (1.22)	1.28 (1.20)	.284	.052	.007	-	-	-.490
SWM Strategy	29.11 (6.49)	30.43 (6.18)	30.89 (6.19)	.625	.211	.119	-	-	-
SWM Total Errors	15.72 (15.81)	19.13 (17.14)	22.67 (21.37)	.220	.224	.046	-	-	.370

All values are mean (± SD)
SST=Stop Signal Task; SSRT=Stop Signal Reaction Time; CGT=Cambridge Gamble Task; SWM=Spatial Working Memory task