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Brief Research Communication

Exploratory Association Study Between Catechol-O-Methyltransferase (COMT) High/Low Enzyme Activity Polymorphism and Hypnotizability

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Only recently have studies of electrocortical activity, event-related potentials, and regional cerebral blood flow begun to shed light on the anatomical and neurobiological underpinnings of hypnosis. Since twin studies show a significant heritable component for hypnotizability, we were prompted to examine the role of a common, functional polymorphism in contributing to individual differences in hypnotizability. A group of 109 subjects (51 male, 59 female) were administered three psychological instruments and tested for the high/low enzyme activity COMT val→met polymorphism. We observed a significant correlation between hypnotizability measured by the Stanford Hypnotic Susceptibility Scale (SHSS:C), ability to partition attention (Differential Attentional Processes Inventory or DAPI), and absorptive capacities (Tellegen Absorption Scale or TAS). The effect of COMT on the various dependent variables was initially examined by multivariate analysis that corrects for multiple testing. The dependent variables were SHSS:C hypnotizability scores, four attentional subscales of the DAPI, and TAS total score grouped by the COMT genotype (val/val, val/met, met/met) as the independent variable. Hotelling's Trace statistic was significant when scores were grouped by the COMT genotype (Hotelling's $T^2 = 1.88$, $P = 0.04$). Post-hoc testing using the Bonferroni correction shows that the only significant difference is between the val/met vs. the val/val COMT genotypes on hypnotizability. This association was significant for men but not for women. As for all case-control studies, these results need to be interpreted cautiously and require replication. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 96:771–774, 2000.

KEY WORDS: hypnosis; catechol O-methyltransferase; COMT; polymorphism; genetic; attention

Ever since mesmerism's eponymous discoverer attributed its beguiling effects to animal magnetism, the use of hypnosis for therapeutic ends [Larkin, 1999] has far outstripped an understanding of its mechanism. Recent decades of empirically based research have begun to provide some direction in unraveling hypnotism's underlying genetic [Hilgard, 1965; Morgan, 1973; Piccione et al., 1989], as well as physiological and anatomical substrates [Crawford, 1994]. Of special interest is the relationship between hypnotizability and attentional processes, subsumed under executive function, an umbrella term representing a variety of higher brain functions which are thought to be primarily mediated by dopaminergic brain pathways [Seamans et al., 1998].

A common biallelic polymorphism in the catechol O-methyltransferase (COMT) gene that determines high and low enzyme activity has been associated with neuropsychiatric disorders [Lachman et al., 1996] as well as disorders involving disturbances in attention [Karayiorgou et al., 1997, 1999; Eisenberg et al., 1999; Alsobrook et al., 2000]. We therefore hypothesized that the COMT polymorphism by modulating brain catecholamine levels would be a likely candidate for partially mediating individual differences in hypnotizability and attention.

The effect of the independent variable COMT genotype (val/val, val/met, met/met) on the various dependent variables including SHSS:C total hypnosis score, the Tellegen Absorption Scale (TAS) total score [Tellegen, 1982] and the four differential attentional processes inventory (DAPI) [Crawford et al., 1993] subscale scores (cognitive and physical, cognitive and cognitive, moderately focused, and extremely focused) was initially examined by multivariate analysis (sex,

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age, and ethnicity were entered as covariates). Only the multivariate Hotelling's Trace statistic for COMT was significant (the nonsignificant scores for the other dependent variables are not shown). The only significant univariate effect that was significant following Bonferroni post-hoc correction (significant at the 0.05 level) was for hypnotizability (val/met vs. the val/val genotypes: univariate ANOVA, $P = 0.004$, n = 77). As previously observed, hypnotizability in the current study is also significantly correlated (2nd column Table I) with the ability to partition attention [Crawford, 1994; Crawford et al., 1993] and with absorptive capacities [Dixon et al., 1996].

Since there were missing values for some of the subjects that resulted in a reduced sample size when all dependent variables and the three covariates were used in the multivariate model, we also examined the data by one-way ANOVA (COMT × each dependent variable). It appeared justified not to include demographic covariates in the analysis since none of them were significant by multivariate analysis. Again (data not shown), only total hypnotizability scores were significantly associated with the COMT genotype ($F = 6.06$, $P = 0.003$, n = 107). There are nonsignificant trends for an additive effect of the met allele on cognitive and physical ($P = 0.18$), cognitive and cognitive ($P = 0.15$), and moderately focused ($P = 0.18$). No difference was observed in the distribution of the COMT genotypes in the two principal ethnic groups (Ashkenazi vs. non-Ashkenazi Jews) examined in this study

TABLE I. Association of the COMT Polymorphism With Hypnotizability and Attention

Multivariate analysis			Hotellings trace (value)	F	Multivariate *P* value	Power
COMT			0.35	1.88	0.04	0.88
Univariate analysis test of between subject's effects		COMT val/val HIGH enzyme activity	COMT val/met Mean ± S.E.M.	COMT met/met LOW enzyme activity	Univariate *P* value	Power
SHSS:C total hypnosis	Correlation with SHSS:C	4.51 ± 2.88 (n = 19)	6.56 ± 2.52 (n = 41)	5.23 ± 3.03 (n = 77)	F = 5.89 *P* = 0.004	0.86
DAPI Cognitive & physical	r = 0.277 *P* = 0.008 n = 90	23.57 ± 5.72 (n = 19)	25.53 ± 4.74 (n = 41)	26.29 ± 4.46 (n = 77)	F = 1.77 *P* = 0.178	0.36
DAPI Cognitive & cognitive	r = 0.185 *P* = 0.078 n = 92	8.42 ± 3.81 (n = 19)	9.97 ± 11.76 (n = 41)	11.76 ± 9.98 (n = 77)	F =2.35 *P* = 0.102	0.46
DAPI Moderately focused	r = 0.313 *P* = 0.003 n = 91	30.78 ± 10.04 (n = 19)	32.00 ± 7.81 (n = 41)	34.70 ± 9.88 (n = 77)	F = 1.09 *P* = 0.339	0.27
DAPI Extreme focused	r = 0.109 *P* = 0.3, NS n = 90	41.05 ± 10.22 (n = 19)	40.78 ± 14.61 (n = 41)	39.94 ± 10.83 (n = 77)	F = 0.181 P = 0.834	0.08
TAS	r = 0.354 P = 0.001 n = 88	19.57 ± 7.89 (n = 19)	19.00 ± 8.03 (n = 41)	16.35 ± 9.49 (n = 77)	F = 0.917 P = 0.404	0.20
Age				F = 0.039	*P* = 0.845	0.05
Cognitive & phys				F = 0.756	*P* = 0.387	0.14
Cognitive & cog				F = 0.276	*P* = 0.601	0.08
Moderately				F = 7.102	*P* = 0.010	0.75
Extremely				F = 4.01	*P* = 0.049	0.51
Sex						
Total				F = 2.740	*P* = 0.102	0.37
Cognitive & phys				F = 0.021	*P* = 0.884	0.05
Cognitive & cog				F = 1.890	*P* = 0.173	0.27
Moderately				F = 0.113	*P* = 0.738	0.06
Extremely				F = 0.003	*P* = 0.954	0.05
Ethnicity						
Total				F = 0.079	*P* = 0.780	0.06
Cognitive & phys				F = 3.076	*P* = 0.084	0.41
Cognitive & cog				F = 1.164	*P* = 0.284	0.19
Moderately				F = 0.137	*P* = 0.713	0.07
Extremely				F = 5.331	*P* = 0.024	0.62

A semistructured interview by a trained researcher determined the absence of psychopathology according to DSM-IV axis 1, and that the subject was not currently taking psychotropic medication. 109 subjects participated (51 males and 58 females). Two withdrew consent, one for personal reasons and one on account of developing lightheadedness during the hypnotic induction. Average age was 33.5 (SD 11.7, range 19–71). Years of education: 15.6 ± 2.4. Hypnotizability was measured by the Stanford Hypnotic Susceptibility Scale, Form C (SHSS:C) [Hilgard, 1965]. All hypnotic testing was carried out by a single licensed hypnotist (PL). Two measures of attention were used: the Differential Attentional Processes Inventory (DAPI) [Crawford et al., 1993] and the Tellegen Absorption Scale (TAS) [Tellegen, 1982]. COMT was measured as previously described [Eisenberg et al., 1999]. All statistical tests were carried out using SPSS for Windows. We used a general linear model and tested the effects of factor variables including hypnotizability (SHSS:C score), demographic factors (ethnicity, sex, and age) and attentional measures (four DAPI subscales and TAS scores) on the means of the COMT genotype groupings of the subject group. Since we examined more than one dependent variable we first obtained a multivariate analysis of variance statistic. Since the overall multivariate Hotelling's F test was significant for COMT, we then felt justified in using univariate ANOVA and post-hoc test (Bonferroni) to evaluate differences among specific means. The Bonferroni post-hoc test was performed for each dependent variable separately.

(Pearson $\chi^2 = 0.054$, $P = 0.97$ NS) or in a larger control group we have genotyped (Pearson $\chi^2 = 1.334$, $P = 0.513$, n = 634 of whom 364 were Ashkenazi and 270 non-Ashkenazi Jews).

Since sex-selective association has been observed between COMT and obsessive compulsive disorder [Karayiorgou et al., 1997, 1999], particularly in males, we further examined the association between the COMT genotype and hypnotizability in both male and female subjects. In the 48 male subjects examined no significant association was observed ($F = 1.706$, $P = 0.193$), whereas in 57 female subjects a significant association with COMT was observed ($F = 4.873$, $P = 0.01$). We note, however, that there is a trend in the male subjects for the val/met and met/met genotypes to show higher hypnotizability scores, which reaches significance in female subjects.

Subjects with the met/val COMT heterozygote genotype show the highest mean values for hypnotizability scores, and post-hoc testing using the Bonferroni correction shows that the only significant difference is between the val/met vs. the val/val genotype. Such results are difficult to reconcile with the functional relationship between the met and val variants of this gene, which shows an additive relationship [Syvanen et al., 1997]. Conceivably, with a larger sample this inconsistency might be resolved. Alternatively, it may be that enzyme synthesis by the val/met genotype exceeds a threshold beyond which the additional activity of val/val is phenotypically irrelevant.

In order to clarify the underlying psychological processes that are likely mediating the effect of COMT on this phenomenon, we further employed two additional psychological instruments that are known to correlate with hypnotizability. Although both self-report tests are correlated with SHSS:C hypnotizability scores in the present study, they evidently tap into different facets of this complex behavior. Our finding that the moderately focused, but not extremely focused, subscale of the DAPI correlates significantly with the SHSS:C is the reverse of the finding of Crawford et al. [1993]. To resolve these differences a future strategy might rely not only on self-report questionnaires, but direct evaluation of attentional skills [Crawford et al., 1993].

There is a nonsignificant trend ($P < 0.2$) for subjects with the *met* allele to score higher on three of the four DAPI inventory subscales that correlate significantly with hypnotizability. No relationship was observed between the COMT polymorphism and the Tellegen Absorption Scale (TAS). Our results suggest that although both the TAS and the DAPI inventory subscales are correlated with hypnotizability, the underlying neurochemical pathways and genes mediating these processes are possibly different. Our results suggest that the role of COMT in hypnotizability may be mediated indirectly by this enzyme's modulation of attentional abilities, especially simultaneous dual attention.

Low COMT activity raises synaptic dopamine levels and individuals with the *met* allele would be expected to show elevated dopaminergic tone. Increased dopaminergic tone can arguably augment attentional processes such as measured by the DAPI inventory subscales since a number of studies suggest that dopaminergic pathways connecting basal ganglia and prefrontal cortex partially mediate this facet of executive function [Hayes et al., 1998; McDowell et al., 1998; Tamaru, 1997].

There are several reports describing sexually dimorphic COMT activity in normal individuals [Boudikova et al., 1990], apparently due to hormonally regulated gene expression. For example, hippocampal and hypothalamic COMT content show sexual dimorphism [Ladosky et al., 1984]. We are aware of three studies that demonstrate a gender effect between COMT and obsessive-compulsive disorder, albeit in opposite directions [Alsobrook et al., 2000; Karayiorgou et al., 1997, 1999]. In the current study, we also observe some evidence of sexual dimorphism regarding the effect of COMT polymorphism and its association with hypnotizability.

As for other complex traits in man, the role of any single gene such as the COMT polymorphism in contributing to individual differences in hypnotizability and attention processes should be considered neither necessary nor sufficient in explaining the genetic component of the variance. Other genes are surely involved in determining this complex trait and we are currently investigating additional candidates.

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