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Paranormal experience and the COMT dopaminergic gene: A preliminary attempt to associate phenotype with genotype using an underlying brain theory

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ABSTRACT

Paranormal belief and suggestibility seem related. Given our recent findings outlining a putative association between suggestibility and a specific dopaminergic genetic polymorphism, we hypothesized that similar exploratory genetic data may offer supplementary insights into a similar correlation with paranormal belief. With more affordable costs and better technology in the aftermath of the human genome project, genotyping is increasingly ubiquitous. Compelling brain theories guide specific research hypotheses as scientists begin to unravel tentative relationships between phenotype and genotype. In line with a dopaminergic brain theory, we tried to correlate a specific phenotype concerning paranormal belief with a dopaminergic gene (COMT) known for its involvement in prefrontal executive cognition and for a polymorphism that is positively correlated with suggestibility. Although our preliminary findings are inconclusive, the research approach we outline should pave the road to a more scientific account of elucidating paranormal belief.

1. Introduction

Attempts to characterize paranormal belief have been traditionally phenomenological. Several researchers have endeavored to characterize the differences among individuals who are skeptical about, believe in, or experience the paranormal. An emerging theme from these reports identifies variations in the tendency to perceive patterns in ambiguous or statistically random data. For example, one study showed that believers in Extrasensory Perception (ESP) were poorer at making probability judgments compared with skeptics (Blackmore, 1985). In addition, believers in ESP were more likely to attribute chance effects to non-chance causes, relative to non-believers. This notion has since been generalized, positing that believers in the paranormal are more likely to detect patterns in random noise where no such patterns exist (Brugger and Taylor, 2003).

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About three decades ago increased interest in the biological substrate of paranormal belief and religious experience identified the role of the temporal lobe and epileptic foci therein (Mandell, 1980). Support for this hypothesis came from several sources. One study reported that individuals diagnosed with temporal lobe epilepsy syndrome showed a tendency for multiple religious conversions (Geschwind, 1983). Electrophysiological accounts reported that electroencephalogram (EEG) of non-epileptic individuals revealed spontaneous paranormal experiences and proposed that the psychological components of complex partial (psychomotor) epilepsy may represent a continuum of temporal lobe sensitivity, suggesting that healthy people may display, albeit less strongly, experiences and non-convulsive behaviors similar to those of patients diagnosed with electrical foci within the temporal lobe (Persinger, 1984). Finally, EEG findings showed a positive correlation between higher numbers of major complex partial (temporal) epileptic signs and both paranormal experience and a specific personality profile, including stereotyped, ruminative and overly judgmental behavior (Persinger and Makarec, 1987).

Similar to other higher brain functions, paranormal belief probably involves both genes and specific experience. Although elucidating the role of genes in cognitive networks underlying human performance is still in its infancy (Fossella et al., 2002a, 2002b; Fan et al., 2003), recent investigations into the biological basis of paranormal belief and religious experience take the approach that human spirituality has an innate genetic component (Hamer, 2004). Rather than claiming that a specific gene is responsible for spirituality, humans may possess a predisposition for a well-characterized phenotype. For example, one gene that was at least correlated with a form of ''self-transcendence'' is vesicular monoamine transporter number 2 (VMAT2), a gene known to influence monoamines in the brain (Hamer, 2004). To avoid a ''fishing expedition,'' however, it is better to frame genotype–phenotype correlations within an overarching brain theory. As a case in point, multiple studies report that emotional sensitivity involves brain monoamines (Liu and Nakamura, 2006). Therefore, a positive correlation between VMAT2 and self-transcendence seems more meaningful than a correlation unsupported by such an underlying brain theory.

The gradual introduction of biological assays complements the phenomenological approach. In a yet-to-be-published study exploring the tendency to pick up meaningful information among scrambled words or faces, investigators administered the dopamine agonist levodopa (L-dopa) – a drug typically used to relieve the symptoms of Parkinson's disease by increasing levels of dopamine in the brain – to both skeptics and self-confessed believers in the paranormal (Krummenacher et al., 2002). In the no-drug condition, believers were more inclined than skeptics to assume the presence of meaningful information. Under L-dopa, however, the probability of seeing a meaningful pattern increased for the skeptics but remained unchanged for the believers, probably due to a ceiling effect.

Dopamine, which has been studied in the context of Magical ideation (MI) and suppressing negative schizotypal symptoms (Mohr et al., 2005a, 2005b, 2004), is also central to executive functions and selective attention (Raz, 2004; Raz and Buhle, 2006). We have recently outlined close links between mechanisms of attention and suggestion and provided preliminary data to support a candidate gene approach to suggestibility (Raz, 2005; Raz et al., 2005, 2006). Although suggestibility is a complex phenomenon likely associated with many genetic polymorphisms, we identified a positive correlation between a specific polymorphism of a dopaminergic gene and suggestibility (Raz et al., 2006) and have shown that neuroimaging assays and exploratory genetic associations from the domain of attention research may elucidate the underlying neural substrates (Fan et al., 2003).

Suggestibility, interchangeably termed hypnotizability (Raz, 2007), and paranormal belief likely share a common or largely overlapping phenotype (Braffman and Kirsch, 1999; Kirsch et al., 1999a, 1999b; Kirsch, 1997; Brugger, 2001; Brugger et al., 1994). For example, suggestibility shares at least some personality traits often seen in paranormal believers (Persinger and Makarec, 1987; Hines, 2003; Tellegen and Atkinson, 1974). The association between the genotype we previously identified – catechol-o-methyl transferase (COMT) high/low enzyme activity polymorphism – and suggestibility probably relates to COMT's role in the breakdown of dopamine in the central nervous system (Cooper et al., 2002).

The putative association between paranormal thoughts and high levels of dopamine in the brain (Krummenacher et al., 2002) contextualizes both the notion that differences in the COMT genotype correlate with multiple cognitive and psychiatric variables (Diamond et al., 2004; Zubieta et al., 2003; Craddock et al., 2006) and that individuals with a valine/methionine (VM) COMT polymorphism correlate positively with suggestibility (Raz, 2005; Raz et al., 2005, 2006). In addition, frontal brain regions, including the anterior cingulate cortex, are key nodes in executive functions and dopamine plays a pivotal role in such control networks (Raz, 2004; Raz and Buhle, 2006). The activity of COMT in the brain varies as a function of location therein and substantive evidence indicates that COMT has its greatest effect in the frontal areas (Craddock et al., 2006). Interpretation of functional magnetic resonance imaging data suggests that regions within human prefrontal cortex were involved in the perception of patterns in sequences of random stimuli (Huettel et al., 2002). Because individuals who believe in paranormal phenomena are typically more likely to construe non-existent patterns in random sequences, these individuals may well be endowed with a special ability to dissociate, get absorbed, and suspend belief – hallmarks of both suggestibility (Kirsch, 1999; Kirsch and Braffman, 2001) and paranormal belief (Brugger, 2001; Brugger et al., 1994; Hines, 2003). Thus, such individuals would be more likely to correlate with the heterozygous COMT genotype. Guided by this logic, in the present study we tested the hypothesis of whether a well-defined phenotype of believing in the paranormal will positively correlate with the dopaminergic VM COMT polymorphism.

2. Methods

2.1. *Participants*

One hundred and thirteen students from the Pleasantville campus of Pace University were recruited from various

undergraduate psychology classes to take part in this study. Unidentifiable genetic samples from six individuals precluded those data from the analysis. The final dataset comprised 107 individuals (20 male; 87 female) with a mean age of 20.7 years (SD = 2.5).

2.1.1. *Questionnaires*

In the classroom, participants filled out three questionnaires designed to measure paranormal belief/experience and handedness. For paranormal belief we used the magical ideation scale – MIS – (Eckblad and Chapman, 1983) and the anomalous experience inventory – AEI – (Gallagher et al., 1994). The MIS is a 30 item questionnaire that yields a single score; the AEI comprises 70 true or false items and yields five scores: experience (maximum score 29), belief (12), ability (16), fear (6) and use (7). In addition, we administered the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2. *Genetics*

Having read, understood and signed the appropriate consent form, participants were given small water bottles to rinse their mouths before inserting a sterile cheek swab into their oral cavity and gently swabbing the internal side of their cheeks for about 30 sec. COMT status was determined by genotyping of buccal swab DNA. Buccal swabs were then collected from consenting subjects and genomic DNA was prepared as previously described (Fossella et al., 2002b).

To describe this procedure in more detail, buccal swabs were obtained via buccal cell brush from consenting subjects and prepared as directed by the manufacturer. We used the MasterAMP Buccal Swab DNA Extraction Kit (Epicentre Technologies, Madison, WI). Yields range from 0.5 to 3 μg of DNA from each buccal sample. Yields were determined spectrophotometrically by absorbance at 260 nm. Taq polymerase, PCR buffer, and dNTPs were obtained from QIAGEN and used at recommended concentrations for a 20 μl PCR reaction. PCR reactions and restriction digests (PCR-RFLP) were optimized and performed on the PTC-100 Programmable Thermal Controller (MJ Research) outfitted with a heated lid for oil-free amplifications. A 'touchdown' PCR cycling regimen and the addition of DMSO (10% final v:v) was used in order to automatically optimize the hybridization stringency. Gel electrophoresis in either LE agarose followed by staining in ethidium bromide was used to resolve and visualize DNA fragments.

Turning in the swab to the experimenter, each subject thus provided a small DNA sample, which was later genotyped for the dopaminergic polymorphisms of interest as previously described (Fossella et al., 2002a, 2002b, 2003). The gene that codes for COMT comes in three allelic forms, valine/valine (VV), VM and methionine/methionine (MM) with substitutions taking place at codon 158 of the longer form, which is predominant in the brain. We focused on an abundant VM functional polymorphism of the COMT gene at codon 158. The alleles are codominant so that individuals with the VV genotype have the highest activity of COMT, those with the MM genotype have the lowest activity, and heterozygous individuals are intermediate. We compared variations in paranormal belief with differences in COMT polymorphisms in contributed DNA while assuring anonymity of all genetic samples throughout.

3. Results

Of the 107 participants who provided usable data, 26 (24%) were VV, 57 (53%) were VM and 24 (23%) were MM. The results from the gene analysis and self-report questionnaires can be found in Table 1. The table also displays the non-significant results of seven separate one-way analyses of variance. Of major interest to the present study, paranormal belief scores did not differ between the different COMT genotype groups.

4. Discussion

Based on the present results of this exploratory study we cannot reject the null hypothesis. Reporting negative results would not usually be grist for the scientific mill. However, this report is just a preliminary account in an ongoing research effort that we plan to extend, and we largely attribute the outcome of our findings so far to the limited range of responses on the survey measures. Perhaps because of the nature of the student body at Pace University's Pleasantville campus, very few participants in our sample had particularly high scores on any of the measures of paranormal belief and experience. For comparison, a description of normative data for the MI scale drawn from more than 1500 American college students reported that the mean scores were 8.56 (SD = 5.24) for men and 9.69 (SD = 5.93) for women (Garety and Wessely, 1994) – higher than the scores obtained from the present population. An experimental sample drawing on a higher proportion of participants who report paranormal beliefs will likely more adequately serve to test our hypothesis regarding the relationship between holding paranormal convictions and a dopaminergic genotype.

Table 1 – Mean scale scores (± standard deviations) for the three genotypes and statistical parameter of the seven separate one-way ANOVAs

Genotype	VV	VM	MM	F[a]
Magical ideation scale	7.9 (6.2)	6.7 (4.6)	7.0 (5.1)	.45
AEI: belief	5.5 (2.4)	5.4 (2.9)	6.0 (3.0)	.40
AEI: experience	6.9 (4.3)	5.5 (3.4)	6.2 (5.1)	1.23
AEI: ability	1.9 (1.8)	1.4 (1.7)	1.9 (2.6)	.83
AEI: fear	1.4 (1.4)	1.4 (1.8)	1.1 (1.4)	.19
AEI: use	2.3 (1.3)	2.1 (1.1)	2.1 (1.1)	.36
EHS	58.2 (33.4)	73.5 (34.0)	62.0 (40.5)	1.99

Note that all comparisons were non-significant.
AEI, anomalous experience inventory; EHS, Edinburgh handedness survey.
VV, valine/valine; VM, valine/methionine; MM, methionine/methionine.
a All *F*-values have 2 df with an *n* of 104 (except of an n of 103 for the comparison on the Edinburgh handedness survey; one participant failed to fill it in).

What is interesting about this study is its theoretical approach. Extending traditional twin studies (Fan et al., 2001), allelic association assays correlate specific genes with cognitive variation in unrelated individuals (Parasuraman and Greenwood, 2004). Although these effects tend to be small, by identifying brain networks and by tracing their underlying neurotransmitters, researchers have attempted to unravel links between single gene polymorphisms that influence chemical function and individual differences in cognitive function (Diamond et al., 2004; Egan et al., 2001; Fan et al., 2003, 2001; Greenwood and Parasuraman, 2003). Initial enthusiasm for this tactic has been dampened by limited progress and conflicting results – part of the difficulty may arise from the use of distal phenotypes, such as questionnaires in this case or reaction time and accuracy measures in other cognitive tasks. Toward this end, ''Imaging Genetics'' – a form of genetic association analysis where the phenotype is the physiological response of the brain that mediates a behavioral outcome – permits a more proximal, and perhaps more discernable, association (Hariri and Weinberger, 2003). Furthermore, given a likely polygenetic involvement and complex inter-gene interactions, it is unlikely that a single gene would be substantively revealing; ultimately, large-scale population studies will be needed to delineate these interactions.

Nonetheless, the more modest efforts pursued so far (e.g., in the field of attention) elucidate not only individual differences but also the way genes may build the physical basis of the neural networks that we study (Greenwood and Parasuraman, 2003; Parasuraman et al., 2005; Fan et al., 2003; Raz, 2006). Sometimes it is possible to come up with an animal model, such as knock-out mice that lack a specific gene of interest (Grandy and Kruzich, 2004). When trying to unravel paranormal belief, however, it is difficult to rely on animal models to describe how genes mediate the formation of both systems that are common among individuals and what alleles account for individual variability. And yet, a future time may find that individual differences in superstitious behavior can serve as candidate phenotypes whose genetic mediation scientists could explore (Brugger et al., 1994).

MI originated as an ''indicator of schizotypy'' and the gene for COMT is located in an area that has been implicated in the pathogenesis of schizophrenia on chromosome 22q11. Findings suggest a relationship between the COMT genotype for the functional VM polymorphism and self-reported schizotypy in healthy males (Avramopoulos et al., 2002). More recently, COMT genotype has been shown to modulate the relation between the negative schizotypal phenotype and cognitive performance (Smyrnis et al., 2007). COMT genotype may affect expression of negative schizotypy by direct or indirect effects on central dopaminergic alterations (Stefanis et al., 2004). For example, methionine genotype loading may confer enhanced flexibility or greater performance reliability, perhaps by stabilizing active neural representations in the prefrontal cortex during tasks involving attention and working memory (Stefanis et al., 2005). While schizotypal traits may be genetically related to schizophrenia and although several putative susceptibility genes for schizophrenia have been reported and replicated, only COMT has been tested in schizotypy (Fanous and Kendler, 2004). Nonetheless, schizophrenic symptom factors are etiologically distinct from each other and occur on an etiological continuum with their personality-based counterparts (Fanous et al., 2001). Phenotypic heterogeneity may be diluting the COMT effect (McClay et al., 2006) yet COMT is a promising therapeutic target for ameliorating the cognitive deficits associated with schizophrenia (Tunbridge et al., 2006, 2007). A recent notion promotes the idea that COMT genotype impacts the level of prefrontal physiologic ''noise'' (Winterer et al., 2006a) suggesting that dopamine stabilizes the dynamic of cortical networks by attending to the signal and dampening down the surrounding noise (Winterer et al., 2006b). These collective findings suggest that MI may be an index of schizotypy that is likely operationalized by COMT.

Unpublished findings suggest that administering the dopamine precursor L-dopa to skeptics decreased their perceptual sensitivity to a level comparable to that of paranormal believers (Krummenacher et al., 2002). The reduced perceptual sensitivity caused by L-dopa may result from an increase in top–down control that overrides the sensory input stream (Raz et al., 2007). The greater effect of L-dopa on the skeptical subjects may be due to a ceiling effect in the paranormal believers, perhaps related to a higher baseline level for dopamine. At least some evidence supports the notion of different baseline levels for highly suggestible individuals (Dixon et al., 1990a, 1990b, 1996; Dixon and Laurence, 1992). In the case of paranormal belief, increased dopamine may elicit disinhibited firing patterns in mesolimbic neurons and, perhaps via the introduction of neural noise, promote a system dynamic conducive to both increased susceptibility to paranormal belief and heightened suggestibility (Shaner, 1999).

We recently reported a relationship between a polymorphism in the COMT gene and suggestibility (Raz, 2005). Specifically, VM heterozygous subjects were more highly suggestible than either VV or MM homozygous subjects. The inverted U-shaped trend of VM COMT heterozygotes towards higher suggestibility is congruent with data collected by other researchers (Lichtenberg et al., 2000), but differs from our previous studies examining the role of COMT in executive attention as measured by the Attention Network Test (ANT) as well as by the Stroop (Sommer et al., 2003). Studies of the ANT (Fan et al., 2002) found that subjects with the VV genotype showed somewhat more efficient conflict resolution than subjects with the VM genotype (Fossella et al., 2002a, 2002b). This trend was also seen in subjects who performed the Stroop task (Sommer et al., 2003). The valine allele of COMT, which confers relatively higher levels of enzyme activity and thus lower relative amounts of extrasynaptic dopamine, has been examined in the context of neuroimaging studies where it correlated with lower activity of the dorsolateral prefrontal cortex (Egan et al., 2001), but other dopaminergic polymorphisms including the genes DRD3, DRD4, MAOA and DAT showed no significant associations with suggestibility.

For more than a decade, the Human Genome Project has made great progress in the identification of the protean 30,000 genes in the human genome as well as the approximately 1.7 million polymorphic sites scattered across the 6 billion base-pair length of the human genome (Wolfsberg et al., 2002). Normal allelic variations in single neurotransmitter genes influence individual differences in processing components of

cognitive functions in healthy individuals (Fossella et al., 2002a, 2002b). We now know how to detect genotype-cognition associations in healthy individuals with moderate-size samples, given that candidate genes are chosen on the basis of theories of brain function, and that appropriate cognitive task components are chosen as phenotypes (Parasuraman et al., 2005). Here we show an initial attempt to tap such an association, based on a dopaminergic theory and well-defined phenotypes for paranormal belief. While COMT should be confused with neither the ''suggestibility'' gene nor the potential ''paranormal belief'' gene, as data accumulate findings will likely increase our appreciation of genotyping as an important supplement to phenotyping paranormal belief. We speculate that by using a more diverse range of paranormal scores, correlations with COMT may become viable. We plan to report on these experiments before long.

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