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A genetic variant (COMT) coding dopaminergic activity predicts personality traits in healthy elderly

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ABSTRACT

Association studies between the NEO five factor personality inventory and COMT rs4680 have focused on young adults and the results have been inconsistent. However, personality and cortical changes with age may put older adults in a more sensitive range for detecting a relationship. The present study examined associations of COMT rs4680 and personality in older adults.

Genetic association analyses were carried out between the NEO and the targeted COMT rs4680 in a large, well-characterized sample of healthy, cognitively normal older adults ($N = 616$, mean age = 69.26 years).

Three significant associations were found: participants with GG genotype showed lower mean scores on Neuroticism ($p = 0.039$) and higher scores on Agreeableness ($p = 0.020$) and Conscientiousness ($p = 0.006$) than participants with AA or AG genotypes.

These results suggest that older adults with higher COMT enzymatic activity (GG), therefore lower dopamine level, have lower Neuroticism scores, and higher Agreeableness and Conscientiousness scores. This is consistent with a recent model of phasic and tonic dopamine release suggesting that even though GG genotype is associated with lower tonic dopamine release, the phasic release of dopamine might be optimal for a more adaptive personality profile.

1. Introduction

It is well-known that personality traits are highly heritable (e.g. Riemann, Angleitner, & Strelau, 1997), however despite the considerable progress in understanding the human genetic architecture of personality, genetic associations have been quite inconsistent in the literature. Furthermore, several studies have demonstrated the role of genetic factors in longevity (e.g. Grady et al., 2013) and it has also been proposed that these genetic effects might be mediated via personality traits (Eaton et al., 2012) indicating the importance of personality in predicting longevity. Also, personality traits, especially low Conscientiousness (Duchek, Balota, Storandt, & Larsen, 2007; Wilson, Schneider, Arnold, Bienias, & Bennett, 2007) or high neuroticism and low extraversion (Johansson et al., 2014) have been shown to be risk factors for Alzheimer Disease which makes this a particularly important topic for the growing older adult population.

Research on the neural systems underlying components of personality suggests there may be some linkage to more frontally mediated dopaminergic activity. For example, DeYoung et al. (2010) have reported that the volume in lateral prefrontal cortex, which is rich in dopaminergic pathways, covaried with Conscientiousness (i.e., larger volume was associated with higher Conscientiousness). Similarly, Jackson, Balota, and Head (2011) found that higher Neuroticism and lower Conscientiousness were associated with decreased volume in frontal areas in cognitively normal older adults.

COMT is one of several enzymes that degrade catecholamines in the brain such as dopamine, epinephrine, and norepinephrine (Grossman, Emanuel, & Budarf, 1992). The COMT gene plays an important role in coding an enzyme called Catechol-O-methyl-transferase (Chen et al., 2004). It has been proposed that people with Val alleles (G allele) of rs4680 have increased COMT activity and lower prefrontal extracellular dopamine compared with those with the Met (A allele) substitution (Chen et al., 2004). Since the COMT enzyme is one of the most important enzymes breaking down dopamine in the prefrontal cortex (Chen et al., 2004) and the prefrontal cortex has an important role in human personality

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(e.g. DeYoung et al., 2010), one would predict associations between COMT and personality traits. However, as noted above, such a link has been inconsistent in younger adults. Because there are prefrontal volumetric changes (e.g. prefrontal white matter decreased) in older adults compared to young adults (e.g. Raz et al., 2005; Salat et al., 2005), it is possible that an older adult population may be more sensitive to detect a COMT personality link (Martin, Long, & Poon, 2002).

A meta-analysis (Ebstein, 2006) of genetic association studies with personality indicated that the most frequently analyzed gene polymorphisms in association with personality traits are linked to the dopaminergic and the serotonergic systems. Although there are several studies on dopamine related polymorphisms and personality, the results from these studies have been inconsistent. Several association studies have focused on the possible association between the Catechol-O-methyltransferase (COMT) rs4680 dopamine related single-nucleotide polymorphism (SNP) and personality (Calati et al., 2011) measured by different personality questionnaires (e.g. Baeken, Claes, & De Raedt, 2014). For a summary of genetic association studies regarding COMT rs4680 and personality traits measured by the Neuroticism-Extraversion-Openness Five-Factor Inventory (NEO-FFI) see Table 1.

As shown in Table 1, there is a clear emphasis on younger adults in the past association studies. Hence, the aim of the present study was to analyze the possible association between COMT rs4680 SNP and personality traits as measured by the NEO Five-Factor Inventory (NEO-FFI; Costa & McCrae, 1992) in a large sample of well-characterized older adults.

2. Methods

2.1. Sample

A total of 616 unrelated cognitively normal older adults participated in this study (mean age = 69.26 years old, SD = 9.7; age range between 45 and 96 years; mean education = 15.50 years, SD = 2.8; gender = 273 males/343 females). Ethnicity of the participants was mainly Caucasian (91.2% of the sample), with fewer Afro-American (8.5%) and Asian 0.3%) participants. Participants were recruited from the Charles and Joanne F. Knight Alzheimer Disease Research Center (ADRC). This study was approved by the Institutional Review Board at WUSTL; all participants provided informed consent at the beginning of the study. All participants were originally screened for depression, untreated hypertension, reversible dementias, and other disorders that are potential causes of cognitive impairment. The inclusionary and exclusionary criteria for AD were consistent with the NINCDS-ADRDA criteria (McKhann et al., 1984). For screening depression, the Geriatric Depression Scale (Yesavage et al., 1982) was used, and highly trained neurologists and psychiatrists screened for other diseases that might produce cognitive decline. All participants were screened for dementia using the Clinical Dementia Rating (CDR) scale (Morris, 1993), and all were at the CDR 0 level, which indicates no clinical dementia. The CDR is based on a 90-min interview that assesses both the participant and also relies on information from a collateral source concerning the participant. Genotype distribution of COMT rs4680 among participants excluded and included into the final database was not significantly different (*Chi square* = 0.624, $p = 0.732$).

Table 2
Descriptive statistics of the NEO-FFI.

	N	Cronbach Alpha	Mean	SD	Min	Max
Neuroticism	616	0.866	15.318	7.43	0	39
Extraversion	616	0.808	29.763	6.37	10	45
Openness	616	0.703	28.615	5.73	10	46
Agreeableness	616	0.758	34.554	5.32	7	47
Conscientiousness	616	0.864	34.031	6.75	8	48

2.2. Phenotype measures

The NEO Five-Factor Inventory (Costa & McCrae, 1992) – a shortened version of the Revised NEO Personality Inventory – was administered to each participant. This questionnaire measures Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness with 60 items. Every item is rated on a 1–5 scale based on the answers from 'strongly agree' to 'strongly disagree'. The NEO-FFI is a commonly used personality trait questionnaire which is highly correlated with the NEI-PI-R and has strong internal consistency (Costa & McCrae, 1992).

The descriptive statistics for the NEO factors are presented in Table 2. To test the internal consistency of the self-report phenotypes, Cronbach Alpha values were calculated. In the present sample reliability coefficients were satisfactory for all factors (Table 2). It is noteworthy that the mean scores of the present sample are consistent with norms for another similar adult sample (McCrae & Costa, 2004).

2.3. Genetic data

Our sample was included in a previous genome wide association study of Alzheimer disease described elsewhere (Cruchaga et al., 2013) from which COMT rs4680 genotypes was apriori targeted for the present study. Details regarding the genotyping procedures are provided in Cruchaga et al. (2013).

Table 1
Summary of COMT rs4680 and NEO association studies.

Authors	Sample	Mean age in years	Results
Reuter & Hennig (2005)	363 healthy Caucasian students	24.4	GG higher Extraversion, Exploratory Excitability
Stein, Fallin, Schork, and Gelernter (2005)	497 undergraduate students	18.9	AA females lower Extraversion, higher on Neuroticism
Hoth et al. (2006)	486 controls	38.5	AA lower Extraversion, higher Neuroticism
Tochigi et al. (2006)	256 healthy Japanese	37.4	n.s.
Urata et al. (2007)	219 Japanese female students	20	n.s.
Sheldrick et al. (2008)	522 healthy controls	24.8	n.s.
Aoki et al. (2011)	143 healthy Japanese	19.9	GG lower Agreeableness, Conscientiousness
Pelka-Wysiecka et al. (2012)	406 healthy Polish subjects	38.5	AA males lower Neuroticism
Lehto, Akkermann, Parik, Veidebaum, and Harro (2013)	593 young Caucasians	Age 15, 18 and 25	GG females higher Neuroticism
Konishi et al. (2014)	470 panic disorder; 458 controls	37.9; 36.6	AA males with panic disorder lower Openness

Notes. Genetic association studies of COMT rs4680 and NEO-FFI and NEO PI-R.

The original dataset contained personality, age and gender data for 644 participants, from which 616 had COMT rs4680 data available. Thus, the call rate of the present sample was 94.92%. The inclusion criteria for the further analyses included available personality, COMT rs4680, age and gender data. Thus, genetic association analyses were carried out on a sample of 616 participants. COMT rs4680 was in Hardy–Weinberg equilibrium, there were no significant differences between the distributions of observed and calculated genotype frequencies (*Chi-square* = 0.045, $p = 0.978$). Observed genotype distribution of the studied COMT polymorphisms was: AA: 145 (23.5%), AG: 305 (49.5%), GG: 166 (26.9%).

2.4. Statistical analysis

To test the reliability of the genotype frequencies Hardy–Weinberg equilibrium test was carried out (Hardy, 1908). Independent-Samples *t*-tests were used to assess gender differences by the phenotypes, and Chi-square test was used for examining the gender differences by the genotypes. Relationship with age was tested by correlation analyses with the phenotypes and by ANOVA with the genotypes. One-way Analyses of Covariance (ANCOVA) were used to test genetic associations of single marker analyses where age and gender were used as covariates, coded as dummy variables. Post-hoc analyses with grouped genotypes were carried out to test the dominant model.

3. Results

3.1. Influence of age and gender

Because there is evidence that both age and gender modulate personality traits (e.g. Costa et al., 2001; Ebstein & Belmaker, 1997) we examined the relationship between age and gender on the NEO factor scores. Females showed significantly higher mean scores than males on Neuroticism (16.12 vs. 14.31), $t(614) = -3.020$, $p = 0.003$; Openness (29.10 vs. 28.01), $t(614) = -2.356$, $p = 0.019$; and Agreeableness (35.87 vs. 32.89), $t(614) = -7.192$; $p < 0.001$. There were no significant gender differences on Extraversion and Conscientiousness. There were significant correlations between age and Extraversion ($r = -0.116$, $p = 0.004$) and Openness ($r = -0.180$, $p < 0.001$). There were no significant correlations between age and Neuroticism, Agreeableness and Conscientiousness.

In addition, because there is evidence that genotype distributions change as a function of age (e.g. Gierman et al., 2014) and gender (e.g. Barnett et al., 2007), it is important to test the possible association between COMT rs4680 and age and gender. In the present sample there were no significant differences by gender in the distribution of the alleles. However, the ANOVA indicated that age varied as a function of COMT rs4680 with the A allele being associated with increased age, [$F(2,613) = 5.863$, $p = 0.003$, $\eta^2 = 0.019$, power = 0.874]. The mean age for the AA genotype group was 71.29 years, for the AG group 69.23 years and for the GG group 67.54 years.

Because there is evidence of relations among age and gender to either COMT and/or personality, both age and gender were used as covariates in all of the following association analyses.

3.2. Association between COMT rs4680 SNP and personality traits

ANCOVAs were carried out between NEO-FFI factors and COMT rs4680. Significant associations were observed between COMT and three factors of the NEO-FFI (Table 3): Neuroticism [$F(2,611) = 3.262$, $p = 0.039$, $\eta^2 = 0.011$, power = 0.620], Agreeableness [$F(2,611) = 3.922$, $p = 0.020$, $\eta^2 = 0.013$, power = 0.706] and Conscientiousness [$F(2,611) = 5.174$, $p = 0.006$, $\eta^2 = 0.017$, power = 0.827]. Participants with the GG genotype showed lower mean scores on Neuroticism and higher mean scores on Agreeableness and Conscientiousness than participants with AA or AG genotypes. Since the mean factor scores in the AA and AG genotype groups were similar, we assumed a dominance model (as also used in other studies, e.g. Reuter & Hennig, 2005) and therefore grouped together the AA and AG genotype groups for further post hoc analyses.

When analyzing the GG vs. AA + AG groups, the results indicated that the GG genotype group had significantly lower mean scores on Neuroticism (14.21) than the AA + AG group (15.73), [$F(1,612) = 5.461$, $p = 0.020$, $\eta^2 = 0.008$, power = 0.647]. Also, the GG group showed significantly higher mean scores on Agreeableness (35.27 vs. 34.29) and Conscientiousness (35.39 vs. 33.57), [$F(1,612) = 7.204$, $p = 0.008$, $\eta^2 = 0.012$, power = 0.764; $F(1,612) = 7.602$, $p = 0.006$, $\eta^2 = 0.012$, power = 0.786, respectively].

In order to more fully explore the possible modulating effects of age and gender on the COMT personality linkage, two-way ANOVAs examining the possible COMT × Gender interactions (COMT GG vs. AG/AA × Gender) and regression analyses examining the possible COMT × age interaction effects were conducted on

Table 3
Association analyses of COMT and NEO-FFI factors.

		COMT				Grouped COMT genotypes		
NEO-FFI factors		AA	AG	GG	*p*	AA + AG	GG	*p*
Neuroticism	Mean	15.08	16.04	14.21	**0.039**	15.73	14.21	**0.020**
	SD	7.252	7.387	7.560		7.349	7.560	
	N	145	305	166		450	166	
Extraversion	Mean	29.74	29.55	30.17	0.639	29.61	30.17	0.451
	SD	6.036	6.441	6.537		6.307	6.537	
	N	145	305	166		450	166	
Openness	Mean	27.92	28.81	28.87	0.501	28.52	28.87	0.759
	SD	5.335	5.836	5.862		5.689	5.862	
	N	145	305	166		450	166	
Agreeableness	Mean	34.52	34.18	35.27	**0.020**	34.29	35.27	**0.008**
	SD	5.371	5.471	4.927		5.435	4.927	
	N	145	305	166		450	166	
Conscientiousness	Mean	34.25	33.24	35.29	**0.006**	33.57	35.29	**0.006**
	SD	6.646	7.134	5.876		6.989	5.876	
	N	145	305	166		450	166	

Notes. Significant results are labeled in bold.

each of the 5 personality traits. These analyses did not yield any significant interactions. Finally, there were no significant associations between COMT rs4680 SNP and the Extraversion or the Openness factors (both p's > 0.05).

4. Discussion

The purpose of the present study was to examine the association between COMT rs4680 and personality in healthy older adults. Since the dopamine system is involved in anxiety related traits (e.g. Laakso et al., 2003), positive emotionality and incentive motivation which drive human behavior (e.g. Depue & Collins, 1999), previous literature has linked gene polymorphisms associated with the dopamine system to various personality traits (for review see Ebstein, 2006); for genome-wide association study see Kim et al., 2013). However, relatively few studies have specifically targeted the role of COMT in personality, as conceptualized by the Big Five model of personality traits (Table 1), and most of these studies have targeted younger adult samples. As can be seen in Table 1, the results of such studies have produced inconsistent results.

The present results produced reliable associations between COMT and three factors of the NEO-FFI in a large sample of well-screened cognitively healthy older adults. Participants with the GG genotype had lower mean scores on Neuroticism, and higher scores on Agreeableness and Conscientiousness than subjects with the AA or AG genotypes. On a molecular level, our results suggest that those with a higher COMT enzymatic activity (GG), therefore a lower dopamine level, have lower Neuroticism scores, and higher Agreeableness and Conscientiousness scores.

In this light, it is interesting to note that Lee et al. (2005) have reported that individuals who are high in neuroticism have higher central dopaminergic activity utilizing photon emission computed tomography measures. They proposed that higher central dopaminergic activity could cause more sensitive or excessive reactions to perceived stressors, which is one facet of high neuroticism. Thus, our results of higher neuroticism in individuals with lower COMT activity (i.e., higher dopamine levels) are consistent with the Lee et al. (2005) findings. Regarding Conscientiousness, structural magnetic resonance imaging results suggest that high Conscientiousness is associated with increased volume in lateral prefrontal cortex, a region involved in planning and the voluntary control of behavior (DeYoung et al., 2010). Since COMT has an important role in releasing enzymes breaking down dopamine in the frontal brain regions, the association between COMT and the personality trait of Conscientiousness is intriguing. The involvement of the dopamine system in reward mechanisms might be a key in the association between COMT and Conscientiousness. Furthermore, Jackson et al. (2011) have reported an association between decreased volume in frontal areas and high Neuroticism and low Conscientiousness in a sample of cognitively normal older adults. This is interesting in light of findings that high Neuroticism and low Conscientiousness may be risk factors for the onset of Alzheimer's disease (e.g. Duchek et al., 2007; Wilson et al., 2007). It is unclear based on the current literature, why high Agreeableness is associated with high COMT activity in the present sample.

4.1. Possible molecular mechanisms

Bilder, Volavka, Lachman, and Grace (2004) further proposed that the Met (AA) allele, linked with low COMT activity, increases the level of tonic dopamine release, which suppresses phasic release of dopamine, which may result in decreased sensitivity to novel stimuli. They proposed that an analogous mechanism may underlie behavior requiring reinforcement. In this case, carriers of the Met allele, in which the level of phasic dopamine is decreased, will tend to manifest behavior as seeking high levels of additional stimulation (e.g., drug abuse), with the consequence of an individual attempting to increase dopamine to an optimal level. This model suggests that even though the GG genotype is associated with lower tonic dopamine release, the phasic release of dopamine might be optimal decreasing reward seeking behavior and personality traits such as lower Neuroticism, higher Agreeableness and Conscientiousness (as we demonstrated here). Of course, further work will be needed to establish these specific relationships.

4.2. Other genetic association studies

As for other association studies of COMT and the Big Five personality traits (Table 1), our results are in line with the findings of Hoth et al. (2006) and Stein, Fallin, Schork, and Gelernter (2005) who carried out association analyses on large samples of healthy young adults. They both found that those with the AA genotype showed higher mean scores on Neuroticism.

However, our results are inconsistent with findings from other studies. For example, Pelka-Wysiecka et al. (2012) reported that AA males showed lower mean scores on Neuroticism in a healthy young adult Polish sample. In relation to Conscientiousness and Agreeableness, Aoki, Iwahashi, Ishigooka, and Ikeda (2011) reported lower scores on both traits for the COMT GG genotype in a smaller sample of young Japanese adults. Furthermore, some studies have reported no association between COMT genotypes and the Big Five personality traits as measured by the NEO-FFI (Sheldrick et al., 2008; Tochigi et al., 2006; Urata et al., 2007). Of course, it is important to note that all of these studies have focused on younger adult samples and in some studies the sample sizes were relatively small (Aoki et al., 2011, $N = 143$; Tochigi et al., 2006, $N = 256$; Urata et al., 2007, $N = 219$) which could contribute to the inconsistent results. It is also important to note, that different questionnaires measuring personality characteristics may be contributing to the inconsistency in findings. Clearly, further work is needed in this area to better understand the inconsistency in the studies in Table 1.

Our findings regarding age and personality characteristics are consistent with results from the literature suggesting some change in personality traits with increasing age. Meta-analyses indicate that Conscientiousness and Agreeableness are higher in older samples than in younger samples, while Neuroticism, Extraversion and Openness decrease in old age (McCrae et al., 1999; Roberts, Walton, & Viechtbauer, 2006). It has been argued that personality changes during aging are universal. McCrae et al. (1999) have shown similar patterns of personality change with age across different cultures (German, Italian, Portuguese, Croatian, and South Korean samples). However, the underlying mechanisms for these age-related personality changes are unclear. Based on twin studies, it appears that personality changes with age are primarily due to environmental factors, however there also appears to be some evidence of an epigenetic influence on age related changes in personality (e.g. Briley & Tucker-Drob, 2014).

Unfortunately, there are only a few developmental genetic association studies regarding personality and these tend to focus on the genetic influences of personality changes or development during late adolescence and early adulthood. For example, in a longitudinal study of young adults at age 15, 18 and 25, Lehto, Akkermann, Parik, Veidebaum, and Harro (2013) have reported developmental changes in the association between COMT rs4680 and personality from adolescence to early adulthood. They found that the association between the COMT genotype and Conscientiousness increased with age and the COMT association

with Neuroticism manifested in women by the time of young adulthood. One might speculate that these associations could be quite different in old age due to cortical changes across the life span (Sowell et al., 2003). For example, there is ample evidence that changes in the prefrontal cortex are differentially affected by aging (e.g. Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002; Raz & Rodrigue, 2006). Thus, the sensitivity of this brain region with age may in turn influence the association between COMT and personality in older adults.

In sum, several pieces of converging evidence provide motivation for examining the relationship between COMT and personality in older adults. Specifically, the relationship between COMT and dopaminergic activity in prefrontal cortex, the changes in prefrontal cortex with increasing age, the changes in personality with age (e.g., increased Conscientiousness) suggest that older adults may provide a more sensitive sample to examine the relationship between COMT and personality. To the best of our knowledge, the possible association between COMT and personality traits in older adults has not been examined yet. One of the important strengths of the present study is the well-characterized, large ($N = 616$) sample of cognitively normal older adults. In addition, we administered a widely used and reliable personality questionnaire (NEO-FFI). Further work exploring the genetic influences on personality and the modulating effects of different polymorphisms on personality in older adults is needed. Understanding the genetic and molecular influence of the characteristics of older adult's personality traits could contribute to a better understanding of successful aging since personality traits have a significant impact on subjective well-being (DeNeve & Cooper, 1998) and longevity (e.g. Friedman, Kern, & Reynolds, 2010) and both high Neuroticism and low Conscientiousness have been identified as potential risk factors for the onset of Alzheimer's disease (Duchek et al., 2007; Wilson et al., 2007).

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Declaration of interests

The authors have no competing interests to declare.

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