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Lack of Association Between *COMT* Polymorphisms and Apathy in Alzheimer's Disease

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Abstract. We tested the hypothesis that single nucleotide polymorphisms (SNPs) in *catechol-O-methyltransferase (COMT)* are associated with apathy in individuals with Alzheimer's disease (AD). We analyzed a cohort of 105 Caucasian individuals with AD (age = 79.3 ± 7.03 years; MMSE = 20.2 ± 4.4) according to the presence of apathy, as defined either by the Neuropsychiatric Inventory or the Apathy Inventory. Polymorphisms in seventeen SNPs in *COMT* were examined. A replication cohort consisting of 176 Caucasian AD subjects in the ADNI database was also analyzed. None of the candidate gene SNPs were significantly associated with the presence of apathy in either cohort. We did not find any SNPs in *COMT* that were consistently associated with apathy in individuals with AD.

Keywords: Alzheimer's disease, apathy, catechol-*O*-methyltransferase, dopamine, single nucleotide polymorphisms

INTRODUCTION

In addition to cognitive impairment, behavioral and psychological symptoms are now considered major components of the clinical expression of patients suffering from Alzheimer's disease (AD). Among these, apathy is one of the most common symptoms across all stages of AD [1, 2], having negative impact on the progress of the individual's disease that lead to earlier institutionalization [3], having a higher risk of conversion from mild cognitive impairment to AD [4], and having faster functional [5] and cognitive decline [6].

Apathy is a disorder of the initiation, direction, and intensity of goal-directed behavior. It was initially defined by Marin [7] as a lack of motivation in behavior, cognition, and affect. Several lines of evidence coming from animal and pharmacological studies suggest that the pathophysiology of apathy could be at least partially explained by a dysfunction of the dopamine system. Dopamine appears to

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf).

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contribute more to the neuromodulation of incentive salience ('wanting') rather than to hedonic 'liking' or to 'learning' [8]. Additionally, several studies have reported that dopamine agonists tend to promote reward-seeking behavior, while dopamine antagonists tend to have the opposite effect [9]. Further, from a behavioral point of view, lack of initiative and interest in human apathy are close to the concept of 'wanting' in animal studies. This relationship must be considered carefully, however, since in animal studies, the term 'wanting' is used for concrete and particular stimuli such as food, drugs and their cues while humans subjects are dealing with more abstract and cognitively loaded incentives. Studies using functional brain imaging in humans suggest relationships between apathy and abnormal perfusion in several specific areas such as anterior cingulate and orbitofrontal cortex, and the related fronto-subcortical structures [1, 10–16]. Considering the role of anterior cingulate and orbitofrontal regions in the reward system [17–21], apathy could be at least partially explained by a dysfunction of the dopaminergic system involving the mesolimbic and mesocortical dopaminergic neural pathways. The role of dopamine in the pathophysiology of apathy is underlined by a recent study by Starkstein et al. [22] that found an association between apathy and increased Parkinsonism during the follow-up of AD patients, suggesting a common neural pathway for these two clinical symptoms. Furthermore, the benefits of catechol-*O*-methyltransferase (COMT) inhibitors in controlling motor symptoms in Parkinson's disease are well established [23].

COMT is an enzyme involved in synaptic catecholamine inactivation that plays a role in the degradation of dopamine in the prefrontal cortex. Several studies have reported relationships between changes in expression of COMT and neuropsychiatric disturbances or personality traits [24–27]. More recently, Wang and colleagues found that a specific haplotype (rs4633–rs4680) of *COMT* was associated with several negative symptoms, including blunted affect and passive/apathetic social withdrawal, among subjects diagnosed with schizophrenia [28]. Because of the well-established pathophysiology of apathy involving the mesolimbic dopamine neural pathway and the role of COMT in the prefrontal cortex, we hypothesized that the presence of apathy could be associated with specific polymorphisms in *COMT*. The aim of the present study was to evaluate the relationship between apathy and the polymorphisms in *COMT* among Caucasian individuals diagnosed with AD.

MATERIALS AND METHODS

Sample

Nice/Stanford Cohort: 105 Caucasian individuals (age = 79.3 ± 7.03 years; ♂/♀ = 56/49; MMSE = 20.2 ± 4.4) with a diagnosis of probable AD were recruited. This diagnosis was determined using the NINCDS-ADRDA criteria [29]. The 105 participants in this cohort came from two sources: 63 were participants in an ongoing study at the Memory Disorders Clinic at the University of Nice School of Medicine and 42 were participants in an ongoing longitudinal study of AD at the Stanford/Veterans Affairs, National Institute on Aging Alzheimer's Disease Core Center.

An additional 176 Caucasian individuals (age = 79.4 ± 7.6 years; ♂/♀ = 96/80; MMSE = 23.3 ± 2.0) with a diagnosis of AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were also analyzed as a replication cohort. Data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI).

Behavioral assessment

Individuals in the Nice/Stanford Cohort were examined according to a standardized cognitive and behavioral protocol prior to collection of saliva used for DNA extraction. As part of the protocol, neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI) [30]. The NPI was administered in a structured interview of a caregiver familiar with the subject. Participants were considered to have apathy if their NPI apathy domain score (frequency × severity) was greater than three indicating clinically significant apathy [31]. Apathy was additionally assessed independently using a specific questionnaire for apathy, the Apathy Inventory (AI) [32], designed to provide a separate evaluation of three dimensions of apathy: emotional blunting, lack of initiative, and lack of interest. Using previously established guidelines, participants with an AI total score greater than three were considered to have apathy [33].

In the ADNI Cohort, apathy was assessed using the brief version of the NPI (NPI-Q) [34]. In this questionnaire completed by caregivers, each of the 12 domains of the full NPI is assessed by a single question (derived from the screening questions of the original NPI). Apathy was evaluated with the single question: "Does he/she seem less interested in his/her usual activities or in the activities of others?". Participants were con-

Table 1
SNPs in *COMT* that are found on the Illumina 610 Quad chip

	SNP #	Chromosome	Location	Nucleotides	Minor allele	MAF	HWE
1	rs1800706	22	5′ near gene	A/G	A	N/A	N/A
2	rs4646310	22	5′ near gene	A/G	A	0.16	0.050
3	rs2020917	22	5′ near gene	C/T	T	0.33	0.584
4	rs737866	22	intron	A/G	C	0.32	0.655
5	rs1544325	22	intron	A/G	A	0.38	0.752
6	rs174675	22	intron	C/T	T	0.30	0.150
7	rs5993883	22	intron	G/T	T	0.43	0.527
8	rs4646312	22	intron	C/T	C	0.42	0.584
9	rs165656	22	intron	C/G	C	0.48	0.439
10	rs165722	22	intron	C/T	N/A	N/A	N/A
11	rs2239393	22	intron	A/G	G	0.42	0.439
12	rs4646316	22	intron	C/T	T	0.22	0.752
13	rs165774	22	intron	A/G	A	0.31	0.439
14	rs174699	22	intron	C/T	C	0.07	0.479
15	rs165599	22	3′ UTR	A/G	N/A	N/A	N/A
16	rs165728	22	3′ UTR	C/T	C	0.06	0.294
17	rs4680	22	exon	G/A (Val/Met)	A	0.48	0.655

MAF: Minor Allele Frequency; HWE: Hardy-Weinberg Equilibrium (HapMap-CEU); N/A: not available.

sidered apathetic if the informant responded "yes" to this question.

Genotyping

DNA was extracted from saliva samples collected using Oragene DNA kits (DNA Genotek, Ontario Canada; DNA was extracted according to manufacturer's instructions). Genotypes of *COMT* SNPs were determined using the Human 610-Quad BeadChip (Illumina, San Diego CA) on an Illumina Beadstation according to manufacturer-provided procedures. Seventeen polymorphisms of *COMT* are available on the chip (Table 1), including the functional val/met polymorphism (rs4680) that leads to an up-regulation of dopamine activity [35, 36].

Statistical analysis

SPSS 14.0 was used to compute statistics. Group comparisons (apathy versus no apathy) for the demographic and neuropsychological and behavioral data were made using either a *t*-test (continuous variables) or a Chi-square test (categorical variables). Group comparisons (apathy versus no apathy) for the seventeen polymorphisms of *COMT* were made using a Chi-square test. A Bonferroni correction ($\alpha' = \alpha/n$) was applied such that overall $\alpha = 0.05$ and $n = 17$, so as to account for the 17 SNP comparisons tested in this study. Data are presented as mean ± SD.

RESULTS

The Nice/Stanford and ADNI cohorts were statistically indistinguishable for age and gender ratio, but there was greater general cognitive impairment in the Nice/Stanford cohort whose mean MMSE score was significantly lower ($t = 6.85$, df = 127.3, $p < 0.01$) than that of the ADNI Cohort. Percentage of apathy according to the NPI/NPI-Q apathy cut-offs was respectively 49% in the Nice/Stanford Cohort and 32.4% in the ADNI Cohort.

Genetic data for the 17 SNPs of interest were fairly robust, with call rates of 97.3% in the Nice/Stanford cohort and 99.1% in the ADNI Cohort. Comparison of genotypes distribution (Table 2) between the two cohorts, and with HapMap-CEU did not show major differences, indicating genetic comparability among the data sets. Examination of the association between presence of apathy and polymorphisms in *COMT* in the Nice/Stanford Cohort did not reveal any significant association when apathy was determined using either the NPI or the Apathy Inventory (Table 3). Similar results were found in the ADNI Cohort with the NPI-Q.

In order to investigate how representative the seventeen examined SNPs were of the *COMT* gene (more than four hundred SNPs are referenced in gene region in NCBI Entrez SNP database), we performed an additional linkage disequilibrium analysis between all available in *COMT* gene region-SNPs (SNAP Proxy, http://www.broadinstitute.org). Twenty-four

Table 2
Comparison of genotypes distribution for the 17 SNPs between the Nice/Stanford and ADNI cohorts, and HapMap-CEU (Pearson's Chi-square test with p's<0.05 in bold)

	SNP #	Nice/Stanford vs ADNI			Nice/Stanford vs HapMap-CEU			ADNI vs HapMap-CEU		
		Chi-square	*df*	*p-value*	*Chi-square*	*df*	*p-value*	*Chi-square*	*df*	*p-value*
1	rs1800706	11.6	3	**0.009**			N/A			
2	rs4646310	1.7	2	0.433	6.1	2	**0.047**	1.2	2	0.544
3	rs2020917	4.7	3	0.196	0.8	2	0.674	3.6	2	0.164
4	rs737866	3.1	2	0.211	1.5	2	0.470	0.6	2	0.730
5	rs1544325	6.7	3	0.082	0.0	2	0.987	3.4	2	0.177
6	rs174675	12.0	3	**0.008**	3.9	2	0.145	2.5	2	0.280
7	rs5993883	3.4	2	0.183	0.2	2	0.910	1.5	2	0.480
8	rs4646312	1.8	3	0.609	2.0	2	0.370	0.8	2	0.675
9	rs165656	0.2	3	0.983	0.3	2	0.850	0.3	2	0.850
10	rs165722	2.4	3	0.495			N/A			
11	rs2239393	2.9	3	0.408	1.9	2	0.380	1.2	2	0.550
12	rs4646316	10.6	3	**0.014**	0.7	2	0.690	0.2	2	0.910
13	rs165774	0.9	2	0.646	2.4	2	0.300	0.5	2	0.760
14	rs174699	3.2	2	0.198	1.0	2	0.590	0.7	2	0.700
15	rs165599	1.2	3	0.755			N/A			
16	rs165728	3.2	2	0.198	1.5	2	0.470	0.2	2	0.910
17	rs4680	0.7	3	0.881	0.6	2	0.750	0.0	2	0.980

Table 3
Association between *COMT* SNPs and apathy scores in the two cohorts

	SNP #	Nice/Stanford Cohort ($n = 105$)						ADNI Cohort ($n = 176$)
		NPI-apathy subscore >3			AI total score >3			NPI-Q apathy subscore = 1
		Chi-square	*df*	*p-values*	*Chi-square*	*df*	*p-values*	*p-values*
1	rs1800706	3.5	3	0.316	3.7	3	0.301	0.811
2	rs4646310	0.8	2	0.667	0.4	2	0.816	0.865
3	rs2020917	2.7	3	0.447	1.8	3	0.610	0.610
4	rs737866	1.0	2	0.605	0.4	2	0.824	0.639
5	rs1544325	1.8	3	0.625	2.5	3	0.473	0.545
6	rs174675	0.2	3	0.970	0.9	3	0.817	0.917
7	rs5993883	1.5	2	0.479	0.8	2	0.654	0.645
8	rs4646312	1.8	2	0.412	1.5	3	0.686	0.945
9	rs165656	3.8	3	0.288	0.5	3	0.919	0.310
10	rs165722	3.5	3	0.324	0.6	3	0.893	0.525
11	rs2239393	1.6	2	0.445	0.6	2	0.737	0.802
12	rs4646316	0.0	3	1.000	1.1	3	0.771	0.341
13	rs165774	1.0	2	0.614	3.0	2	0.221	0.532
14	rs174699	0.4	1	0.513	0.3	1	0.590	0.830
15	rs165599	1.8	2	0.399	2.1	2	0.353	0.636
16	rs165728	0.4	1	0.513	0.3	1	0.590	0.830
17	rs4680	4.6	3	0.201	1.8	3	0.609	0.497

Data are presented as p-values of Pearson's Chi-square test.

additional SNPs were in linkage disequilibrium at the $r^2 = 0.7$ threshold with the seventeen *COMT* SNPs available on Illumina chip.

The analysis conducted with 105 participants and 17 SNPs showed a 0.4 effect size (Chi-square Goodness-of-fit test with 80% power).

DISCUSSION

To our knowledge, this is the first study that has investigated the relationship between apathy and polymorphic variations in *COMT* among individuals diagnosed with AD. Our main result is the absence of association between the seventeen investigated SNPs in *COMT* and apathy among the 105 AD subjects from our cohort, as well as a replication of this result in the ADNI cohort. Several discrepancies, however, were observed between the cohorts. The ADNI cohort had a higher mean MMSE and fewer behavioral abnormalities than the Nice/Stanford Cohort. Assessment methods for apathy were not the same in the two cohorts: in the Nice/Stanford cohort, we used both the

NPI and the Apathy Inventory whereas only the single apathy item in the NPI-Q was used for the ADNI Cohort. Possibly because of a more vigorous ascertainment of apathy, the percentage of apathetic subjects was higher and closer to the commonly reported frequency of apathy in AD (around 55%) [37] in the Nice/Stanford cohort than in the ADNI cohort. Genotypes frequencies for the 17 examined SNPs were also slightly different between the two cohorts. Although all of the participants were Caucasian, variation in SNP frequencies have been observed in Caucasians of different ethnic backgrounds [38]. Nonetheless, there is little evidence for a single *COMT* polymorphism to explain the presence or absence of apathy in AD patients.

Several authors have investigated the associations between neuropsychiatric symptoms and polymorphic variations in dopamine genes. Borroni and colleagues [39] tested the association between neuropsychiatric symptoms and rs4680 (val/met, *COMT*) and observed a significant association with psychotic symptoms in AD. In the recent article of Wang et al. [28], a significant association between blunted affect and rs4680 was found in a sample of 290 Chinese patients diagnosed with schizophrenia. In our study, however, we did not observe a correlation between rs4680 and emotional blunting in individuals with AD. We did, however, observe an association between emotional blunting and rs1544325 (chi-square = 8.1, df = 2, $p = 0.018$) but only in the Nice subgroup. This discrepancy could be explained by differences in initial diagnosis (schizophrenia versus AD) or ethnicity (the A allele frequency in rs4680 is 51.7% in Caucasians and 25.6% in Han Chinese, HapMap). No significant association was found between the apathy item of the NPI-Q and rs1544325 in the ADNI Cohort and might be partially explained by the selectiveness of the apathy question of the NPI-Q (ADNI Cohort) that only captures one dimension of apathy (lack of interest).

As recently reported by Gershon et al. [40], the plausibility of cumulative effects of rare variants for explaining common disease risk is under current discussion. It is therefore possible, if not likely, that multiple rare SNPs may contribute to a phenotype such as apathy. We have a relatively small sample size, but did examine the association of select SNP pairs on apathy (rs4680/rs165656/rs1800706/rs1544325), which represent the best single SNP associations, as well as one SNP that we found to be associated with emotional blunting in the Nice group only (rs1544325). These SNP's were fairly independent as they had low linkage disequilibrium values (r^2's < 0.5). None of the combinations, however, were significantly associated with apathy (p's > 0.3, Pearson's Chi-square test).

The relatively small sample size of our cohort and the number of *COMT* SNPs we examined (seventeen SNPs with twenty-four in LD, out of more than four hundred known SNPs for *COMT*) are additional issues that do not allow for exclusion of *COMT* from consideration as being possibly involved in apathy in AD, but our results do indicate that either the effect size of such a polymorphism is small or the minor allele frequency is low.

CONCLUSIONS

The pathophysiology of apathy in those with AD was not explained by single SNPs in *COMT*. The complete brain dopamine pathway should be investigated relative to apathy and to its component dimensions.

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