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Does the catechol-O-methyltransferase (COMT) Val158Met human polymorphism influence procrastination?

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Abstract

Genetic studies are enlightening how the expression of several genes influences neuronal activity and all facets of human normal and abnormal behaviour. Among these, a growing body of information shows that a few key genes regulating activity of central neurotransmitters have specific roles in cognitive and/or emotional processes, as 'procrastination'. We investigated the association of the 5-HTTLPR and COMT Val158Met polymorphisms with students' procrastination in an academic writing task. Results showed no relationship between procrastination and the 5-HTT polymorphism but they revealed an association with the COMT Val158Met one. Particularly, the presence of the Met158 allele was found to be significantly associated with the tendency to initiate and complete the assigned task. We hypothesize that the role of central monoamines and of dopamine already identified in impulsive behaviour, extends to procrastination. Since the 158Met allele provides neurons with significantly higher basal dopamine levels when compared to the 158Val allele, our observation suggests that under normal conditions the 158Met allele provides carriers with increased inhibitory control, resulting in an increased tendency to adhere to a planned schedule and therefore reducing procrastination. On the other hand, the Val158 allele may result more effective in increasing carriers' performances under stress conditions, namely when the schedule deadline is approaching, and dopamine release is increased. This would result in a higher tendency to procrastinate. This hypothesis can readily be tested by applying the experimental approach here employed to various samples of subjects belonging to different categories and extending the analysis to other putative neuron-expressed genes.

Keywords: procrastination; impulsivity; time management; COMT Val158Met SNP; COMT rs4680 SNP; 5-HTTLPR

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1. Introduction

The exchange of neuronal information between the prefrontal cortex and underlying limbic structures is fundamental in the regulation of human behavior, with reference to attention, cognition and emotions. Among neurotransmitters involved in this exchange are serotonin (5-HT) and dopamine (DA). The presynaptic serotonin transporter (5-HTT) is responsible for the reuptake of serotonin after its release from serotonergic neurons (Rudnick and Clark, 1993).

A genetic variation present in the transcriptional control region of this gene produces a biallelic polymorphism with the presence (long allele, *l)* or absence (short allele, *s)* of a 44 bp long fragment (5-HTTLPR) (Heils et al., 1996; Lesch et al., 1996; Nakamura et al., 2000), which has a functional effect: the *l* allele is associated with higher expression of the transporter compared to the *s* allele, in turn influencing levels of central serotonergic neurotransmission (Hu et al., 2006). Low serotonin levels have been associated with impulsive behavior and in line with this concept, *s* allele carriers, having

higher serotonin availability, appear to control their behavior, being less impulsive, better than *l* allele carriers in several cognitive tasks (Strobel et al., 2007; Borg et al., 2009; Nomura et al., 2015), or even perform better in a working memory task (Anderson et al., 2012). However, *s* allele carriers have been also found to exhibit less effective inhibitory control in other cognitive tasks (Paaver et al., 2007; Guilherme et al., 2010; Walderhaug et al., 2010; Landrøa et al., 2015). Furthermore, various studies have associated the *s* allele with impaired decision-making in patients with obsessive-compulsive disorder (OCD) (Da Rocha et al., 2008), and with the incidence of other mental disorders or drug dependence (Brown et al., 1982; Gerra et al., 2004; Brotman et al., 2006). In sum, the role of 5-HTTLPR in impulsive behavior in general and in the control of impulsivity in cognitive tasks in particular, is controversial and needs further analysis.

The membrane bound enzyme COMT regulates synaptic levels of catecholamines, namely dopamine (DA) and norepinephrine (NE), by catalysis of their conversion to 3-methoxytyramine and normetanephrine, respectively. The role of this enzyme appears to be unique in the regulation of synaptic DA levels in the prefrontal cortex, where this neurotransmitter has prominent activity and minimal levels of the DA transporter are observed. The human COMT gene contains an evolutionarily recent but common single nucleotide substitution (single nucleotide polymorphism, SNP) that produces an amino acid substitution at the protein level from Valine to Methionine, Val158Met (rs4680) (Mannisto and Kaakkola, 1999). The Met158 allele encodes a more thermolabile protein with three to fourfold lower activity (Lachman et al., 1996) that results in high levels of extrasynaptic DA (Mannisto and Kaakkola, 1999; Chen et al., 2004). Consistently with evidence that COMT is important in modulating prefrontal DA function, Egan et al. (2001) proposed that the COMT Val allele reduces prefrontal neuronal signal-to-noise ratio and makes processing less efficient, presumably by compromising the postsynaptic impact of the evoked DA response. Such a speculative role on prefrontal cognitive functioning has been corroborated by results obtained by other research groups (e.g. Joober et al., 2002; Malhotra et al., 2002; Bilder et al., 2004).

DA is considered to play an important role in the control of impulsive behavior and low extracellular levels of encephalic DA have been associated with attention deficit/hyperactivity disorder (ADHD) (Basay et al., 2016) and disrupting behavior disorder (Salatino-Oliveira et al., 2012), both belonging to the spectrum of impulsive behavior. In the mediation of impulsive behavior, COMT appears as a key enzyme: several studies have associated its Val158Met SNP with impulsivity in substance abuse and a variety of pathologies related to abnormalities of prefrontal cortical functions (Egan et al., 2001; Kinnear et al., 2001; Niehaus et al., 2001; Rotondo et al., 2002; Rujescu et al., 2003; Strous et al., 2003; Ira et al., 2013). As for its role in inhibitory control, the Val variant is thought to disrupt it (therefore priming impulsivity), while the Met variant to facilitate it (Congdon and Canli, 2008), but only a limited number of studies have assessed the effect of this SNP on impulsiveness in healthy subjects, with controversial results (see Soeiro-De Souza et al., 2013). The COMT Val158Met SNP is also associated with cognitive performance and the Met allele apparently provides better performances in cognitive tests and working memory (Egan et al., 2001; Bruder et al., 2005; Forber et al., 2009). On the contrary, the Val158 allele appears to provide protection against anxiety, with better performance in cognitive tasks requiring emotional processing (Mier et al., 2010).

Procrastination has been addressed from different perspectives, and different theoretical explanations of this phenomenon have been provided (see Steel, 2007, for a review). To our purposes, however, procrastination may be well defined as the outcome of a behavioral strategy involving deferral of a task and the function of which is -simply stated- to avoid unpleasant feelings associated with its completion. This strategy ceases to be functional and is therefore discarded as the deadline approaches. Many individuals, confusing causes and effects, often report to "work better under stress". Instead, they are stressed out because they mostly or solely work close to the deadline, when time is scarce and postponing ceases being a negative reinforcement.

This behavior may also be the result of a lack of immediate positive reinforcement for the activity to be carried out and the availability of other (immediately rewarding) activities. The temporary preference for a smaller-sooner reward over a larger-later reward is usually referred to as "impulsive choice". Recent studies on impulsive behavior apparently confirm the notion that a biological/genetic foundation links impulsivity and procrastination (see Gustavson et al., 2014, for a review), calling into account 5-HTT and the COMT as possible major candidate genes (Bevilacqua and Goldman, 2013).

To our knowledge, no attempt has been made yet to study 5-HTT and COMT polymorphisms in association with mild impulsivity-related forms of behavior like procrastination in normal population.

Procrastination is a serious concern in many fields, including education. As reported in a meta-analysis, 80 to

95 percent of college students procrastinate (Steel, 2007) and procrastination is one of the top reasons why doctoral students fail to complete their dissertations (Green, 1997). We have therefore investigated the association of 5-HTTLPR and COMT Val158Met SNP with students' procrastination in an academic writing task. There are two reasons for choosing the specific population and type of task. The first one is represented by the heuristic value of studying a phenomenon that is known to affect academic success (see Kim and Seo, 2015 for an extensive meta-analysis) and that has been almost exclusively investigated in correlational studies and in terms of students' time management abilities (Macan et al., 1990; Britton and Tesser, 1991; George et al., 2008; Perry et al., 2005; Wilson and Narayan, 2014). As for the second one, a difficult aspect of experimental studies on procrastination is that it occurs in contexts that are hard to control. To overcome this issue, we assigned a writing task to be performed using Google Documents and monitored students' performance exploiting the information provided by the Google Drive platform (namely, time on task). Therefore, the writing performance (longitudinally monitored) was more ecologically sound and free of any interference due to the laboratory setting.

2. Materials and methods

2.1 Participants

Twenty university students (13 females and 7 males; mean age = 23.7; st. dev. = 1.66) were involved in the study. All participants belonged to the same class. The study was preliminarily approved by the Department of Psychology Institutional Review Board. All students signed an informed consent prior to participation.

2.2. 5-HTTLPR and COMT Val158Met SNP genotyping

Participants were asked to pool 2 ml saliva into a polypropylene collection vial. Samples were mixed by vortexing and stored at -20°C until extraction and PCR analysis.

DNA was extracted by the "DNA-Presto Buccal Swab" kit (Geneaid Biotech LTD, Italy), from 200 μl of saliva and following the manufacturer's protocol. The purified DNA was stored at 4°C before PCR analysis.

For both polymorphisms, Polymerase chain reactions (PCR) were performed using 20ng genomic DNA, 1 μl (10 μmol) each of forward and reverse primers, with REDTaq ReadyMix PCR Reaction Mix 2X (Sigma-Aldrich) in a final volume of 25 μl. For the 5-HTTLPR polymorphism, primer sequences were as follows: forward - 5′-GGCCGTTGCCGCTCTGGAATGC-3′; reverse - 5′-GAGGGACTGAAGCTGGACAACCAC-3′. Thermal cycling consisted of an initial denaturation for 3 min at 95°C followed by 35 cycles of denaturation at 94°C for 30″, annealing at 68°C for 30″, elongation at 72°C for 35″, and a final extension at 72°C for 5 min. Allelic discrimination was performed by electrophoresis of the amplification products through 2.5% agarose gels to separate the 488 bp fragment relative to the *s* allele from the 528 bp fragment relative to the *l* allele.

For the COMT polymorphism, primer sequences were as follows: forward - 5′-GGGCCTACCTGTGGCTACTTC-3′; reverse - 5′-TTTTCCCCAGTCTGACAAACG-3′. Thermal cycling consisted of an initial denaturation for 3 min at 95°C followed by 35 cycles of denaturation at 94°C for 30″, annealing at 58°C for 30″, elongation at 72°C for 35″, and a final extension at 72°C for 5 min. Fifteen 15 μl of the amplified products were digested with 5U NlaIII (FastDigest® NlaIII enzyme, Fermentas®, Lithuania) at 37°C O.N. Allelic discrimination was performed using 3% agarose gel to separate uncut 114 bp fragments relative to the G (Val) allele, from the cut 96 bp and 13 bp fragments relative to the A (Met) allele. Analyses were performed twice for each sample and scored blindly.

2.3. Self-report measures

The Italian adaptation (Coletta et al., 2010) of the Time Management Behavior Scale (TMBS: Macan et al., 1990) was used to estimate personal productivity and time management abilities. The 34 items questionnaire explores four specific dimensions: goals and priorities; mechanics; preference for organization and perceived control of time.

2.4. Writing task

Students were asked to summarize an academic article ("Do Interruptions affect quality of work?" by Foroughi et al., 2014) with an 8-day deadline and gained additional grades for a final exam if they finished on time the assigned essay. Writing was allowed only in a Google Document that each subject shared with the experimenter. All participants were informed that copying and pasting from other document sources was an exclusion criterium.

2.5 Data analysis

Statistical analyses were conducted by use of *Statistica* software release 8.0 (Statsoft Inc., USA). $P < .05$ was considered statistically significant. A bootstrap

analysis was carried out using the "sample" function in R (https://stat.ethz.ch/R-manual/R-devel/library/base/html/sample.html).

3. Results

Genotypic and allelic frequencies for the two polymorphisms analyzed in this study are shown in table 1. They appear to match with frequencies already described in the European population for both 5-HTTLPR (Jacob et al., 2004) and COMT Val158Met SNP (Palmatier et al., 1999).

Writing time (in minutes) across the 8 days was visually inspected and a bimodal distribution was acknowledged (Figure 1). Accordingly, the amount of writing time was aggregated for the first half (days 1, 2, 3, 4) and second half (days 5, 6, 7, 8) of the 8-day writing period, and the difference between them was therefore used as an index of procrastination (negative values reflecting a delayed writing performance). The Procrastination Index (PIX) described above resulted to be distributed normally and was employed as dependent variable in two ANCOVA designs using genotypes of the 5-HTT (l/l vs. l/s vs. s/s) or COMT (Val/Val vs. Val/Met vs. Met/Met) polymorphisms as independent variables, and the four TMBS scales (setting goals and priorities; mechanics of time management; preference for organization, and perceived control of time) were used as covariates (to subtract their effect over the PIX).

No significant differences were found between genotypes for the 5-HTT polymorphism, apparently excluding that individual levels of synaptic serotonin contribute to procrastination, in agreement with the lack of association for this polymorphism with related traits such as perfectionism (Di Nocera et al., 2014) or other contrasting results concerning the involvement of the 5-HTT gene in the regulation of impulsive behavior and associated disorders.

On the contrary, results showed differences for the COMT polymorphism, since the Val/Val group displayed a significant writing delay (i.e. procrastination) when compared to the Met/Met group ($p < .01$) and the Val/Met group ($p < .05$), (Duncan post-hoc test) (Figure 2). Post-hoc analyses showed that the covariate "Goals and Priorities" resulted in a significant effect on this polymorphism ($p = .03$, $F = 5.88$, d.f. = 2.16 $p = .01$; $\eta^2 = .47$; observed power = .78).

Given the small sample size, the result obtained with the ANCOVA design was further subjected to bootstrap analysis to check its stability. The bootstrap (Efron & Tibshirani, 1993) is a computationally intensive statistical tool designed to assess statistical accuracy based on random sampling with replacement. One thousand bootstrap samples were randomly generated by assigning observed PIX values to the genotype. ANOVAs runs for each bootstrap sample provided a distribution of F values under the null hypothesis. Figure 3 shows the F distribution generated by this approach. The occurrence of F values that are by chance equal or larger than the observed F (the real one obtained from the original sample) is less than 50 out of 1,000 (corresponding to a probability of .05). This analysis further shows that the difference found is a stable result and does not depend on the composition of our sample.

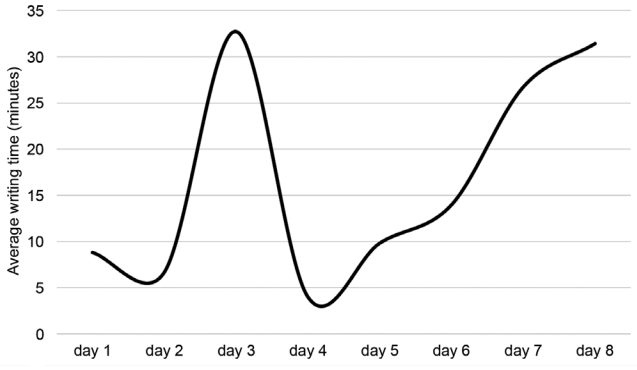

Figure 1. Average daily writing time (all subjects). Minutes of activity were computed from information (time on task) provided by the Google Drive platform, averaged for all subjects and plotted by day.

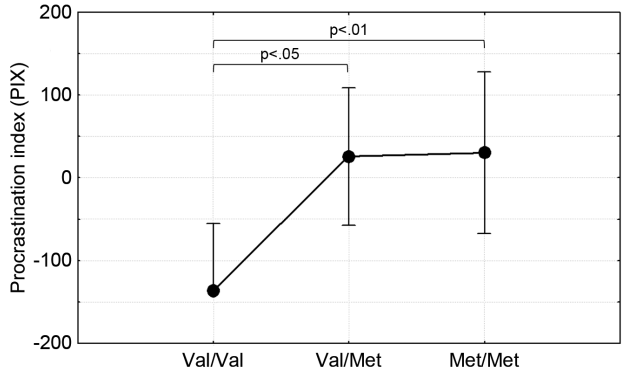

Figure 2. Procrastination Index relative to COMT genotypes. Black dots represent PIX values (± SEM). Global effect: F2,16=5.88, p=.01; η2=.47. Duncan post-hoc comparisons are reported over the brackets.

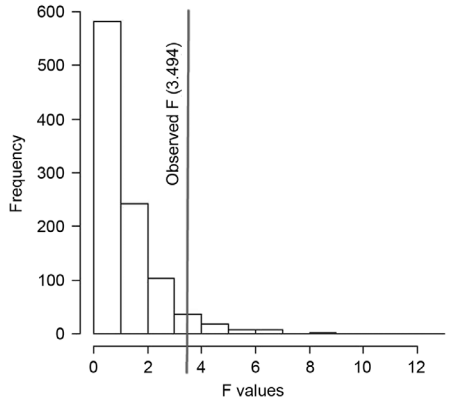

Figure 3. Empirical distribution of F under the null hypothesis. The vertical line indicates the observed F value (3.494).

4. Discussion

Recent research on time management in many fields of human activity, including education, has focused on procrastination, which is considered as a serious reason of failure in the approach to important academic/professional events (Green, 1997). Although procrastination appears to be linked to impulsivity under a biological/genetic perspective (Gustavson et al., 2014), to our knowledge no direct studies have so far addressed the role of genetic factors on procrastination. Since 5-HTT and COMT polymorphisms are associated with impulsivity and other disorders caused by impairment of prefrontal cortical functions, we have therefore assessed whether they are also associated with a tendency to procrastinate. To this purpose, we monitored twenty Italian University students for 8 days during their work activity in a writing task and evaluated their timed performance, expressed as a simple PIX, in relation with their 5-HTTLPR and COMT Val158Met genotypes.

We found no significant association between 5-HTT and procrastination, thus excluding that individual levels of synaptic serotonin contribute to procrastination. This finding agrees with another study from our research group that found no association for this polymorphism with a related trait such as perfectionism (Di Nocera et al., 2014). Investigating procrastination in association with the potential role of the functional A>G single nucleotide polymorphism (SNP) existing within the *l* 5-HTTLPR allele (see Gunthert et al., 2007) would be advisable to better characterize the involvement of such gene in the regulation of impulsiveness/perfectionism/procrastination and associated disorders (e.g. OCD).

Under an evolutionary point of view, existence of the 5-HTTLPR is object of discussion. In fact, prevalence of one allele or the other varies among different ethnic groups, being approximately equivalent in European samples (Jacob et al., 2004). One possible explanation of different frequencies observed in human populations is that they depend on neutral evolutionary processes, based on the assumption that the two alleles do not provide carriers with an obvious selective advantage (Eisenberg and Hayes, 2010).

On the contrary, we did observe an association for Val158Met polymorphism of the COMT gene. This polymorphism has a primary function in the control of DA degradation in the prefrontal cortex and has received much attention relatively to impulsivity. Individuals with Met158 alleles have reduced enzyme activity, increased prefrontal extracellular dopamine and neuronal activation. This has been associated with memory and attention tasks (Heinz and Smolka, 2006; Tunbridge et al., 2006) and with a protective function for impulsivity (e.g. Benedetti et al., 2010; Pivac et al., 2011), but also with increased limbic activation (Smolka et al., 2005; Lee and Prescott, 2014). On the contrary, individuals with the Val158 allele appear more impulsive but perform better in cognitive tasks requiring emotional processing (Mier et al., 2010).

Despite others' reports associating the Met158 allele with impulsive behavior (Han et al., 2006; Boettinger et al., 2007; Nedic et al., 2011), in our study the presence of this allele was found to be significantly associated with the tendency to complete the assigned task in the first half of the time, thus suggesting it may have a protective role in procrastination.

Based on the functional dynamics described above, this apparently fits into an intriguing hypothesis on how the COMT Val158Met polymorphism may influence procrastination. Under non-stressful conditions, normal prefrontal DA release allows Met158 carriers to perform better in cognitive tasks. By improving DA fluxes in the prefrontal cortex, the Met allele may thus allow carriers, via a parallel, increased inhibitory control, to reduce procrastination, i.e. conscientiously plan a scheduled performance over the assigned time.

On the contrary, under stressful conditions, increased prefrontal DA release improves Val158 carriers' cognitive performance. According to this view, Met158 carriers would have a natural tendency to complete cognitive tasks far from their deadline, under non-stressful and high performing conditions, while Val158 carriers would have a complementary tendency to complete

their tasks under stress conditions, when their performance is enhanced.

Similarly to the 5-HTTLPR, much discussion involves the origin and evolution of the COMT Val158Met polymorphism. TheMet158 allele has evolved relatively recently and its coexistence with the Val158 allele appears to depend on alternative but so far equally adaptive behavioral strategies of maximal performance on tasks of attention and memory (Met158) and maximal ability to respond in threatening conditions with proper decisions (Val158).

Depending on the circumstances, both strategies appear still potentially advantageous along with human evolution.

This study represents a first attempt in assessing the relationship between genetic polymorphisms and procrastination. Although carried out on a small student sample, it has various strengths: a) its empirical nature involving an assigned task. Correlational studies typically need larger samples to overcome the limitations of self-reported questionnaires; b) genotypic and allelic frequencies of our sample for both polymorphisms matched those typical of the European population (Palmatier et al., 1999; Jacob et al., 2004), thus indicating that our sample is aligned with the general population; c) the statistical power of our finding is satisfactory and corroborated by the bootstrap analysis.

Obvious limitations of this study are the needs of further analyses on larger samples to confirm the results and of the extension to other genetic polymorphisms. To this purpose, however, it is worth noting that the COMT SNP we analyzed is so far the only polymorphism of this gene with proven evidence of functional effects in other studies.

In conclusion, various psychological studies have linked procrastination and impulsivity in light of their shared phenotypic traits, and the idea that procrastination may represent only an evolutionary by-product of impulsivity has also been proposed (see Dingemanse and Réale, 2005 for an extensive account on "natural selection and animal personality"). We now present evidence supporting an association between procrastination and the Val158Met polymorphism of the COMT gene, which is already known to be associated with impulsivity. This finding supports the hypothesis that the phenotypic association of procrastination and impulsivity has a genetic foundation. Additional investigation on the possible role of other genes, their interaction, as well as gene × environment interactions are warranted to make this hypothesis stronger and better define procrastination in relation to the preference for a smaller-sooner reward over a larger-later reward (i.e. impulsivity) and in a more complete human biology framework.

Understanding how genetic variations within key central neurotransmitter systems contribute to the phenotypic expression of procrastination may also open new insight for future studies and treatment protocols.

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Conflict of interest

Authors declare no conflict of interest.

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