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"Cognitive functionality and personality traits: impact of Val158Met polymorphism of Catechol-O-methytransferase (COMT)"

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First of all, I would like to thank Dr Panos Bitsios, Assistant Professor, who accepted to supervise this project, conducting me from the first to the final stage of the study.

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Contents

Abstract

The aim of the present study is on the effects of the Schizophrenia risk candidate polymorphism Val158Met of the Catechol-O-methyl trasnferase (COMT) and its implications in cognitive functionality and personality traits. The sample population was a large cohort of healthy males who underwent neuropsychological and personality assessment and genotyping of the COMT Val158Met polymorphism.

In the introduction, a brief report on Schizophrenia, its symptomatology, subtype division, heredity and general population frequency is presented followed by disordered cognitive functions and the implication of the prefrontal cortex (PFC). The functional specialization and the implications of PFC dysfunction are presented. Three personality models, *Eysenck's Personality model*, *Cloninger's Biosocial Theory* and *Gray's Reinforcement Sensitivity Theory* which are among the most empirically supported personality models, are then presented. The next chapter is on COMT, summarizing its biochemical properties and review its implications in cognition and personality traits, focusing on the rs4680 (or Val158Met) polymorphism.

In the Materials and Methods, we present information about the cohort that participated in the study, the personality scales (*[EPQ, TCI, BIS/BAS, Spielberger's State-Trait Anxiety Inventory-Trait Scale (STAI-T)* and *Schizotypal Traits Questionnaire (STQ)]* and the neuropsychological tasks [*Wisconsin Card Sorting Test (WCST), Iowa Gambling Task (IGT), Word List Task (WL), Stroop Interference Task, N-Back task* and a subset of *Cambridge Neuropsychological Test Automated Battery (CANTAB)* including *Spatial Working Memory task (SWM), Rapid Visual Information Processing (RVP)* and *Stocking of Cambridge (SoC)]*. The cohort was divided into two groups, val/val (N=217) and met carriers (N=548), and separate Principal Component Analysies (PCA) both for

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neupsychological and personality variables were conducted followed by and correlational analyses.

The categorical analyses did not reveal any significant differences between groups in any PCA personality or neuropsychological factor. However, when correlational analyses were conducted, a significant negative correlation between Novelty Seeking and declarative memory and a significant positive correlation between Novelty Seeking in the val/val homozygotes and between Novelty Seeking and Perseveration in the met-carriers' group was revealed.

Consistent with the present results, Novelty Seeking has been found to correlate with the Val allele and lower dopamine levels in the prefrontal cortex and reduced dopamine levels in the prefrontal cortex is associated with poorer memory retrieval. Also, consistent with the present findings, an effect of the val158met genotype on Wisconsin Card Sorting Test perseveration and an association between the Met allele and increased cognitive stability over cognitive flexibility has been reported.

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1. Introduction

The present study is on the effects of the Schizophrenia risk candidate COMT val158met polymorphism and its implications in aspects of cognition and personality traits in a large cohort of healthy males.

1.1 Schizophrenia

Schizophrenia (SZ) is a mental disorder, that belongs to the spectrum of Psychotic Disorders, along with Schizophreniform, Schizoaffective, Delusional, Shared Psychotic, Brief Psychotic, Psychotic Disorder due to General Medical Condition and Substance Induced Psychotic Disorder, according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV, APA, 1994). Schizophrenic symptoms can be categorized into positive or negative. Positive symptoms, in general, are characterized by excess or distortion of the normal functions, such as distortion of thought content (delusions), of perception (hallucinations), of language and thought (disorganized speech) and perception of self monitoring (disorganized or catatonic behavior). Positive symptoms can be further categorized into two dimensions: psychotic, including delusions and hallucinations, and disorganization symptoms, including impaired speech and behavior (Hirsch and Weinberger, 2003). The negative symptoms of SZ refer to a diminution or even a complete loss of the physiological functions, such as low emotional expression (affective flattening), reduced production of fluent speech (alogia) and the inability to initiate any kind of goal-directed behavior intended to accomplishing a personal need (Hirsch and Weinberger, 2003).

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SZ can be categorized into several subtypes, defined by the predominant symptomatology at the time of the evaluation. The SZ subtypes according to DSM IV (APA, 1994) are: ***Paranoid Subtype.*** The essential feature this subtype is the presence of prominent delusions or auditory hallucinations, in the context of a relative preservation of cognitive function and affect. ***Disorganised Subtype.*** The essential feature is the presence of disorganized speech, behavior and flat or inappropriate affect. The disorganized speech may be accompanied by silliness and laughter that are not closely related in the

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context of the speech. The behavioral disorganization may lead to severe disruption in the ability to perform every day living tasks. ***Catatonic Subtype.*** It is characterized by marked psychomotor disruption, that may involve motor immobility, excessive motor activity, extreme negativism, mutism, peculiarities of voluntary movement (inappropriate or bizarre postures or prominent grimacing), echolalia (pathological, parrotlike and apparently senseless repetition of a word or phrase just spoken by someone else) or echopraxia (repetitive imitation of a person's acts).

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Residual Subtype. The Residual subtype should be used where there has been at least one episode of SZ, but the current clinical picture is without prominent positive psychotic symptoms. There is continuing evidence of disturbance as indicated by the presence of negative symptoms or two or more positive symptoms. If delusions or hallucinations are present, they are not prominent and are not accompanied by strong affect.

Today the value of the SZ subtypes in clinical and research settings is questioned and alternative subtyping schemes are suggested. The alternative with the most empirical support to date, proposes that three dimensions of psychopathology (psychotic, disorganized and negative) may come together in different ways among individuals with SZ.

SZ morbidity risk in the general population is around 1% (Hirsch and Weinberger, 2003), Gottesman and Shields (1982) calculated it at 0,86% while Essen-Moller (1955) found a life time risk of 1,39%. Hirsch and Weinberger (2003) note that the risk of morbidity for siblings and offspring of a schizophrenic is 10% as well as in the case of a schizophrenic child and his parents.

Type of relative	Lifetime expectancy (%)
First-degree	
Parent	5.6
Siblings	10.1
Siblings with one schizophrenic parent	16.7
Children	12.9
Children with both parents schizophrenic	46.3
Second-degree	
Half siblings	4.2
Uncle/aunts	2.4
Nephews/nieces	3.0
Grandchildren	3.7
Third-degree	
Cousins	2.4

Table 1. Morbid risk in relatives of schizophrenics (Hirsch and Weinberger, 2003)

Morbidity risk increases among relatives of schizophrenics (Table 1). The risk is even higher among monozygotic twins (MZ), at about 46% and about 12% in dizygotic (DZ) twins (Hirsch and Weinberger, 2003) and shows that SZ has an important genetic component. Several loci have been implicated in the appearance of SZ (suggestively; Berretini, 2000; Vallada et al., 1995; Wright et al., 1998) among them 22p11, implicating in psychosis in Velocardiofacial Syndrome (VCFS) (Kelly et al., 2003) and also containing the Cathechol-O-methyl tranferase (COMT) gene, a possible SZ risk gene candidate (see below) (Dunham et al., 1992; Egan et al, 2001). Neurolegulin1 (NRG1) has also been heavily implicated in SZ (Mei and Xiong, 2008). NRG1 gene product has many functions, including radial neuron migration, axon guidance, myelination and synapse formation (Mei and Xiong, 2008). Oligodentrocyte transcription factor 2 (Olig2),

cyclic nucleotide phsphodiesterase (CNP) and transcription factor SOX-10 are also implicated in SZ (Craddock et al., 2006) and are connected with neurogenesis and myelination. However, apart from the genetic component, SZ has an environmental component. Suggestively, SZ is related with father's age, viral infections (Brown et al., 2002) and embryonic hypoxia (van Erp et al., 2002).

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2. Cognition and the Prefrontal cortex

Cognition includes the functions of memory, concept formation, language, attention, perception, action and problem solving. Many aspects of cognitive functions depend on the frontal lobe, and especially the prefrontal cortex (PFC), which seems to be the "ultimate coordinator" of cognitive functions. Impairments of the PFC produce changes in basic aspects of cognitive function, personality and social behavior. (Panagis, 2002).

The PFC is functionally specialized with dorsolateral regions mediating cognition and action (Fuster 1984, Goldman-Rakic et al., 1992) and ventromedial and orbitofrontal regions mediating emotion (Dias et al. 1996, Iversen and Mishkin 1970). The anterior medial regions are important in error (Lutcke and Frahm, 2008) and reality monitoring (Simons et al., 2008). The dorsolateral PFC (DLPFC) mediates working Memory (WM) (Goldman-Rakic, 1995), attention regulation (Gazzaley et al., 2007), action planning (Robbins, 1996), abstraction (Bunge et al., 2003), higher order decision making and insight (Wallis et al., 2001) as well as memory retrieval (Bunge et al., 2001) and suppression (Lepage et al., 2000). Thus, lesions in this region are the cause of a generalized cognitive impairment. On the other hand, lesions of the vendromedial PFC (VMPFC) can cause a disinhibited emotional state (Stuss et al., 1992) and altering responses to reward and punishment (Floden et al., 2008).

Several studies have reported reduced volume and interconnections of the PFC with other brain regions. Apart from SZ, impairments have been reported in Attention Deficit/Hyperactivity Disorder (ADHD) (Bremmer, 2002), Bipolar disorder (BD) (Murhy et al., 2001), chronic stress (Liston et al. 2006) and depression. Also, impairments in the PFC have been reported in 'antisocial' statuses like suicide victims,

incarcerated individuals, criminals and sociopaths (Rajkowska 1997) and in medical conditions like drug abuse and lead poisoning (Cecil et al. 2008).

2.1 PFC dysfunction in mental disorders

Disturbances of the PFC functions are the most common finding in mental disorders. Many common symptoms of mental illnesses, like distractibility, poor concentration, loss of insight, poor error monitoring and reality testing, weak emotional regulation, forgetfulness, disorganization, indicate PFC dysfunction (Arnsten 2009). Functional imaging studies of patients with mental illness commonly demonstrate hypo-frontality (Harisson, 1999), while structural imaging and post-mortem neuropathological studies often observe loss of PFC gray matter and reduction in spine density (Barch, 2005). These findings are consistent with the profound changes in PFC functions in these patient populations. The use of modern imaging methods has even allowed these approaches to be applied to symptoms such as delusions and hallucinations (Harrison 1999). Suggestively follows PFC dysfunction in Post Traumatic Stress Disorder (PTSD) (Bremmer, 2002), Bipolar Disorder (BD) (Murphy et al., 2001) and SZ (Barch, 2005; Simon et al., 2007).

PTSD is an anxiety disorder caused by the re-experiencing of a major stressor like war, natural disaster or sexual abuse. The experience is so vivid that the patient can not distinguish whether the event is re-occurring or is experiencing as a memory (Golier and Yehuda 2002). Symptoms also include hypervigilance and impaired executive operations of the PFC (Bremmer 2002; Golier and Yehuda 2002; Shin et al., 2006). PTSD is associated with amygdale cortex hyperactivity, hypoactivity of the PFC and increased norepinephrine (NE) signaling from Locus Coeruleus (LC) (Bremmer et al., 2008). The medial PFC is underactive during symptomatic states and that deficit is inversely proportional to PTSD severity (Shin et al., 2006). This PFC deficiency contributes to the inability of the patient to suppresses traumatic memories and amygdale complex and excessive NE signaling, resulting in hyper vigilance and anxiety (Arnsten 2009).

BD patients cycle between manic and depressive stages. Manic stage symptoms include increased risk taking, distractibility and reduced inhibition and when severe,

include hallucinations and delusions. Evidence of failure in cognitive control and executive functions also persist during the remission stage (euthymia) in patients (Phillips and Vieta, 2007). Due to the cyclic nature of the disorder, the stages of mania, depression and remission can be studied in the same brain. Such functional studies showed underactivity of the right PFC in mania (Altshuler et al., 2005; Blumberg et al., 2003). Transmagnetic activation of this region causes hallucinations and manic symptoms in depressed patients (Ella et al., 2002). In contrast, the left hemisphere is altered during the depression stage, consistent with imaging studies in patients with major depressive disorders (Blumberg et al., 2003). Imaging studies have also revealed impairments in orbitofrontal PFC patients with BD, a region implicated with emotion and the limbic circuitry (Blumberg et al., 2006).Important seems to be the hypothesis according to which the DA malfunction reported in SZ is secondary to PFC incapability of 'tuning' the subcortical DA levels (Andreasen *et al*. 1998; Grace 1993). According to a model introduced by Carlsson *et al*. (1999b), the PFC modulates activity of midbrain DA neurons via both an activating pathway and an inhibitory pathway, allowing tuning of dopaminergic activity by the PFC. The activating pathway is formed by direct and indirect glutamatergic projections onto the dopaminergic cells. The inhibitory pathway is formed by PFC glutamatergic efferents to midbrain GABAergic interneurones and striatomesencephalic γ-Aminobutiric-acid (GABA) neurons. This model predicts that a deficiency in N-methyl-D-aspartic acid (NMDA) transmission or GABA PFC function or DA PFC function would result in a failure of the PFC to inhibit subcortical DA activity under conditions of excessive stimulation such as stress or amphetamine challenge (Hirsch and Weinberger, 2003).

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Patients with SZ show both relative hypometabolism in DPFC and impaired performance in cognitive tests. Several Magnetic Resonance Imaging (MRI) studies have shown a reduction in dorsal PFC (DPFC) grey matter (McCarley *et al*. 1999). Postmortem studies have revealed a 3–12% decreased in cortical thickness in the DPFC in subjects with SZ (Pakkenberg 1993b, Daviss & Lewis 1995). However, it is suggested that the neuronal loss that is observed in DPFC is due to a 'simpler' organization of interconnectivity, as shown by the reduction of connection markers, such as

synaptophysin, and a more intense neuronal packing, with no alteration in the overall neuronal number.

A large variety of implications seems to exist in the connectivity between the DPFC and mediodorsal nucleus (MDN) of the Thalamus. Decreased number of the neurons in the MDN thalamic nucleus as well as decreased network integrity in the projections of the MDN to the PFC seems to disrupt the right network function. Decreased mRNA levels of Glutamate Decarboxylase (GAD) and GABA Transporter (GABAT) in GABAergic and Chandelier neurons in the PFC as well as decreased DA innervation of corticothalamic feedback have been implicated in the SZ neuropathology (Lewis 2000b).

2.2 Neuropathology of Schizophrenia

Since neurodegeneration is uncommon in SZ, as it is heavily supported by the absence of gliosis (Arnold et al. 1996; Casanova et al., 1990; Roberts et al.,1986), recent SZ neuropathology research is concentrated on the cytoarchitecture of the extended limbic system, hippocampus (HP), dorsolateral prefrontal cortex (DLPFC) and cingulated gyrus (CG) encouraged by the suggestion that psychotic symptoms originate in these regions (Stevens, 1973; Torrey and Peterson, 1974). Studies have reported several structural and functional neuronal lesions in SZ in microscopic and macroscopic level.

The first study to report cytoarchitectonic abnormalities in the entorhinal cortex (EC) was conducted by Jakob and Beckmann (1986), who reported shrunken and heterotopic cells in lamina II of the EC. Later Arnold et al., (1995, 1997a) provided further evidence of a disturbance in the location and clustering of the EC neurons. However, these data failed to be replicated. Notably, Akil and Lewis (1997) and Krimmer et al. (1997a) found no difference in the cytoarchitecture in the region.

In 1984, Kovelman and Scheibel, reported variable and even reversed aliment in pyramidal cells in the boundaries of CA1 region with CA2 and subiculum, in SZ. However, in this case too, results failed to be replicated by the same team and Altshuler et al., (1987) found no difference between cases and controls. HP neuron density and number seems to be unaltered in SZ. Heckers et al., (1991b), caring out a stereological study, found no difference between neuron number or density in SZ. However, have been

reported a smaller mean size of HP pyramidal neurons in SZ (Benes et al., 1991; Zaidel et al., 1997a).

As regards the DLPFC, Akbarian et al., (1993), reported subplate neurons to be distributed more deeply in the frontal and temporal cortex white matter in schizophrenics than in controls. The same team, using a larger sample confirmed the observation of fewer interstitial neurons in superficial white matter compartments of DLPFC. The total number of neurons in the frontal cortex was not found to be altered in SZ (Pekkenberg, 1993), and smaller neuronal size has also be reported in the DLPFC especially affecting lamina III neurons (Rajkowska et al., 1998).

Cytoarchitectonic findings have also been reported for the thalamus. Pekkenberg (1990) found markedly lower numbers of neurons in the dorsomedial nucleus (DMN), which projects mainly to the PFC. A similar effect has been observed in the anteroventral nucleus (AVN) which has primarily prefrontal connections too.

Qualitative studies identified a range of ultrastructural abnormalities of neuronal and synaptic elements in SZ (Miyakawa et al., 1972; Averback, 1981; Soustek 1989; Ong and Garey, 1993). In the hippocampal formation, presynaptic protein determinants were found to be reduced; synaptophysin, which is present in all synapses, shows only slight reductions (Browning et al., 1993; Eastwood and Harrison 1995), whereas SNAP-25 (Young et al., 1998) and complexin II (Harrison and Eastwood, 1998) which are both concentrated in subsets of synapses show greater decrements. Synaptophysin has also been found to be reduced in the DLPFC of SZ patients (Glantz and Lewis, 1997). The decrease of the presynaptic terminals is complemented by lower spine density on layer III pyramidal neurons. This pattern of alteration is not uniform throughout the cortex, since levels are unaltered in the visual cortex and increased in the CG (Gabriel et al., 1997).

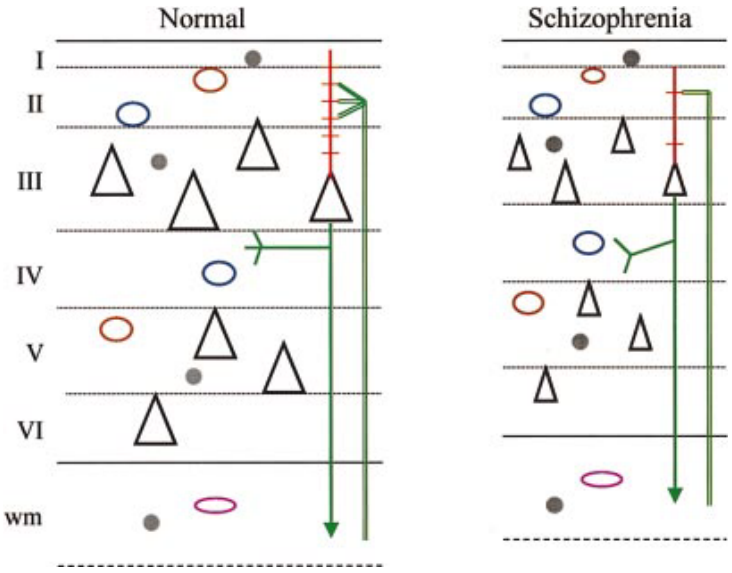

Figure 1. Schematic cartoon summarizing SZ cytoarchitecture (Harisson 1999)

A marked reduction of the synaptic protein rab3a from the thalamus was found in a large group of schizophrenics compared to the controls (Blennow et al., 1996). Several elements of synaptic pathology have also been reported in the striatum. However alterations in this region and especially altered size and proportions of synapses in caudate nucleus cannot be easily explained because of the impact of antipsychotic medication in basal ganglia (Harrison, 1999). As shown in Figure one, grey matter contains an unchanged number of cells but pyramidal neurons are smaller and densely packed (black triangles). The cortex is thinner, especially laminae II and III. Reduced neuronal size and densely packing leads to a reduced neuropil volume, which reflects abnormalities in affecting the axons and dendrites. Glial cells (dots and circles) are left unaffected. That pattern also applies in the PFC and the HP.

Concluding, it is broadly accepted that synaptic organization is altered in SZ. The above mentioned changes reflect a reduction in the number of synaptic contacts formed and received by PFC and HP. Evidence suggests that Glu synapses are impaired in PFC and HP and GABA synapses in CG. At the same time decreased neuronal size especially affecting DLPFC and HP is accompanied by increased neuronal density. Also

cytoarchitectonic data from the thalamus shows that dorsal portion is smaller with fewer neurons.

At a macroscopic level, regional lesions have been reported either by neuroimaging methods or post-mortem studies. The conclusion that the lateral and third ventricles are enlarged in SZ is robust enough: Daniel et al. (1991) and van Horn and McManus (1992) reported an increase of 20 – 70%. A median ~40% increase in ventricular size was reported by Lawrie and Abukmeil (1998) in a review of volumetric MRI studies. The ventricular enlargement is accompanied by a loss of brain tissue averaging 3% (Lawie and Abukmeil, 1998). Volumetric MRI studies indicated larger reductions in the temporal lobe overall, about 8% and in medial temporal structures (HP, parahippocampal gyrus and amygdale), varing 4-12% (Lawrie and Abukmeil, 1998).

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The brain size reduction is significantly greater in the axial than the sagittal plane (Ward et al., 1996) and grey matter appears to be reduced more than white matter (Zipursky et al., 1998). The thalamus is also reported to be smaller in SZ (Andreasen et al., 1994; Buchsbaum et al., 1996), unlike basal ganglia, reported by several studies to be enlarged due to antipsychotic medication (Chakos et al., 1994). Structural abnormalities have also been reported in the cerebellum (Katsetos et al., 1997).

Several conclusions have been drawn by twin and family imaging studies. The affected twin has the larger ventricles nearly in all pairs (Reveley et al., 1982; Suddath et al., 1990) and smaller cortical and hippocampal size (Noga et al., 1996). Family studies have shown that schizophrenics have larger ventricles and smaller brains than their unaffected relatives (Honer et al., 1994; Sharma et al., 1998). Interestingly, obligate carries in SZ families have larger ventricles than relatives who are not. However both groups have even larger ventricles from control individual without any SZ history in their family (Lawrie et al., 1999; Sharma et al., 1998).

Post-mortem studies have replicated the findings of neuroimaging studies. It has been reported a decrease in brain volume (Brown et al., 1986; Pakkenberg et al., 1987; Crow et al., 1989), brain length (Bruton et al., 1990) and cerebral hemisphere volume (Pakkenber, 1987). Concerning regional alterations, post-mortem studies reported enlargement of the lateral ventricles (Brown et al., 1986; Crow et al., 1990), reduced size of temporal lobe structures (Bogerts et al., 1985,1990; Brown et al., 1986; Vogeley et al.,

1998), decreased thalamic volume (Pakkenberg 1990, 1992; Danos et al., 1998) and enlarged basal ganglia (Heckers et al., 1991a)

Altered neurochemistry has also been implicated in the neuropathology of SZ, including altered DA, serotonine (5-HT) and Glutamate (Glu) activity. It has been proposed that the symptoms of SZ are caused by over-activity of the DAergic system. This conclusion was reached after two observations; amphetamine could cause paranoid psychosis and all the antipsychotic agents are DA receptor antagonists. The overactivity could be either due to the excess of DA itself or over expression of its receptors. There is a clear over-expression of D2 receptors in SZ (Zakzanis and Hansen 1998) but it is not known whether this is an effect of antipsychotic treatment. It has been reported that there is also altered number of D1 (Okubo et al., 1997) and D3 (Gurevich 1997) receptors in SZ but these studies are contradicted. In contrast, there is evidence of a presynaptic DAergic abnormality indicating elevated DA release, implying a dysregulation and hyperesponsiveness of DAergic neurons possibly by the circuit described above.

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5-HT was suggested to be involed in SZ neuropathology after the observation of the hallucinogen role of the LSD, a 5-HT agonist. The research is centered in 5-HT1A and 5-HT2A receptors. The number of the 5-HT1A receptors has been found to be elevated in post mortem cortical samples (Burnet et al., 1997). 5-HT2A gene polymorphisms are reported to be a minor risk factor for SZ (Williams et al., 1997) and it is shown that 5-HT2A receptors number is lowered in the frontal cortex in schizophrenics (Harrison 1999b).

The hypothesis that Glu was involved in SZ, was formulated after the observation that non-competive antagonists of NMDAgluR (N-methyl-D-aspartate Glutamatergic receptor), like phencyclidine (PCP, 'angel dust') (Javitt and Zukin, 1991) produce SZ-like psychosis. Harisson (1999), reported drecreased expression of hippocampal non-NMDA receptors, increased cortical expression of NMDAR subunits and increased Glu reuptake in frontal cortex, decrease cortical Glu release and altered concentrations of cortical Glu metabolites.

3. Personality

Several models have been proposed for the study of personality, with the most empirically supported being Eysenck's Personality Model and the Biosocial Model of Cloninger (Trull, 2000).

Eysenck's model introduced two major dimensions in personality, Neuroticism and Extraversion (Eysenck 1967), and later on a third dimension, Psychoticism (Eysenck 1975) was added. According to this model, Neuroticism is the tendency to experience negative emotions, like being angry, anxious, guilt-ridden, and depressed. Extraversion refers to the sociability levels of an individual. Finally, Psychoticism refers to an intrinsic inclination of an individual to develop psychotic disorders (Eysenck 1992). Eysenck's model is based upon the assumption that brain processes can be characterized by means of a 'conceptual nervous system' (c.n.s.) comprising the key circuits relevant to personality and behavior. The multitude of associations between personality and behavior may be derived from individual differences in quite simple parameters in brain function (Matthews and Gilliland, 1999). Eysenck identified two neuronal systems as key components of the c.n.s. (Eysenck 1967, Eysenck and Eysenck 1985), namely the reticulo-cortical and the reticulo-limbic circuits. The first one controls the cortical arousal generated by incoming stimuli while the latter, controls response to emotional stimuli (Matthews and Gilliland, 1999). Under strong emotional activity, the limbic arousal may spread to the cortex. Extraversion is related to the arousal of the reticulo-cortical circuit so that introverts are more aroused than extraverts. Two major problems have been reported. First, people actively seek a moderate level of arousal so that differences in behavior may be underlined by different individual strategies in seeking or avoiding arousal. Second, under high level of stimulation a protective transmarginal inhibition may lead to reduced arousal (Matthews and Gilliland, 1999). In the second case, Eysenck adopted the idea of an arousal threshold, beyond which inhibition is set in (Eysenck 1994). Neuroticism is related to the arousal of the reticulo-limbic circuit. Neurotics become more aroused under emotion inducing stimulation. Individual differences in Neuroticism can be reported only under stressful and emotional context. Eysenck suggested that the third dimension, Psychoticism could be related to serotonergic activity

(Eysenck, 1992) but reconsidering his theory he focused on the dopaminergic activity (Eysenck, 1997).

Cloninger (1994), developed a personality model based upon the division of personality in two dimensions, namely Temperament and Character. He reported that temperament traits are evident in early life and are strongly genetically determined. In contrast,the character traits develop later in life and are determined by experience during development with a lower genetic component (Cloninger, Svrakic and Svrakic, 1997). In the temperament dimension he included Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P) (Cloninger et al., 1993). Cloninger "connected" these four dimensions with different neurotransmitter systems: NS is linked with the DAergic system, HA is linked with the 5-HTergic system and RD with the noerpinephrine system. In the character dimensions he included Self-directedness, Cooperativeness and Self-transcendence. Two major problems regarding Cloninger's model have been reported: first, the character traits show the same level of heritability as the temperament traits (Ando et al., 2004), and second, evidence has accumulated to contradict the idea that a single temperament trait is only impaired by a single neurotransmitter (Paris, 2005).

Finally, based on Eysenck's Personality Model, Gray's Reinforcement Sensitivity Theory (Gray, 1970) was developed. Gray based his theory upon the assumption that personality and behavior are based upon three major dimensions: approach to rewarding stimuli (Behavioral Approach System, BAS), withdrawal from aversive stimuli/punishment (Behavioral Inhibition System, BIS) and a fight or flight decision making. Gray (1990) suggested that in the CNS three distinct but interacting systems exist, that mediate the above mentioned dimensions. Activation of the BAS leads to the initiation of a behavior toward a goal (Gray and McNeughton, 2000), while BIS regulates the defensive behaviors of avoidance and withdrawal. BIS is also associated with increased arousal and alertness in order to inhibit an already initiated behavior which is estimated as non-rewarding (Gray and McNeughton, 2000). As Gray and McNeughton note, (2000), BAS is based upon Impulsivity and its biological base is not clear although is believed to be mediated by DA pathways; BIS is based upon Anxiety

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and is mediated by a complex of pathways connecting septum, HP and amygdala (Gray and McNeughton, 2000).

Several psychometric inventories were developed, based upon these personality models. Based upon Eysenck's Model, the Eysenck's Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975) was developed, measuring Neuroticism, Extraversion and Psychoticism. The biosocial personality model of Cloninger lead to the development of the Temperament and Character Inventory (TCI) (Cloninger,1994). The BIS/BAS questionnaire (Carver and White, 1994) was finally developed for measuring the personality dimensions according to Gray's model.

In a fMRI study, Canli et al. (2003) showed that activation of the left amygdala complex a is correlated with high scores in Extraversion. Gray et al. (2005), in an other fMRI study, linked the Extraversion and Neuroticism traits with the activation of the dorsal anterior cingulated cortex (dACC), bilateral PFC and bilateral parietal cortex. Eisenberger et al. (2005) showed that the neural correlation for the Neuroticism can be the same with the Self-consciousness dimension, implicating activation of dACC and medial PFC.

Johnson et al. (1999), measuring cerebral blood flow, correlated introversion with lateral frontal robes, Broca's area, insular cortex, right temporal cortex and the anterior thalamic nucleus. In the same study, extraversion correlated with ACC, right insular cortex, bilateral temporal cortex and thalamic pulvinar nucleus. Interestingly, the brain areas that collated with introversion had a larger volume than extraversion, in accordance with the opinion that introverted individuals have a higher behavioral inhibition activity. Finally, anxiety traits have been correlated with low presynaptic DA synthesis in the caudate as assessed by [18F]fluorodopa (Laakso et al, 2003).

4. Catechol-O-methylotransferase

The Catechol-O-methylotransferase (COMT), catalyzes the transfer of a methyl group to catecholamines, including Dopamine, Norepinephrine and Epinephrine, using Mg2+ ions as a co-enzyme. This Oxygen methylation results in one of the major degradative pathways of the catecholamine transmitters. In addition to that major function, COMT is the degradative means of catecholic drugs, used in the hypertension (DA-R agonist), asthma and Parkinson's disease (Levodopa, L-Dopa). COMT is found in two forms in tissues, the soluble form (S-COMT) and the membrane bound form (MB-COMT), with a N-terminus sequence signaling membrane bounding (Harisson and Weinberger, 2005). MB-COMT has much greater affinity for dopamine than S-COMT, but a lower Vmax, suggesting that brain COMT has high efficiency but low capacity, suited for ending neurotransmission. COMT is expressed in neurons, and is much more abundant in prefrontal cortex and hippocampus than in striatum or in brainstem dopamine neurons, supporting conclusions from pharmacological studies that COMT inactivates catechols at postsynaptic sites (Harrison and Weinberger 2005). Also, COMT is the major component of ending DA signaling in brain regions with low DA transporter (DAT) expression such as the PFC (Mazei et al, 2002) so this enzyme could be an important determinant of PFC performance during executive cognition by enhancing prefrontal physiological efficiency. The COMT gene is presented in figure two**.** The *comt* gene is located in the 22q11, a region involved in SZ in linkage studies (Basset and Chow, 1999). It consists of six exons, enconding two transcripts, of 1,3 kb and 1,5 kb in human from two promoters (Tenhunen et al, 1994). The longer of the two transcripts encodes the two distinct types of COMT, with the MB-form differing in 50 hydrophobic, serving as the membrane anchor (Bertocci et al., 1991).

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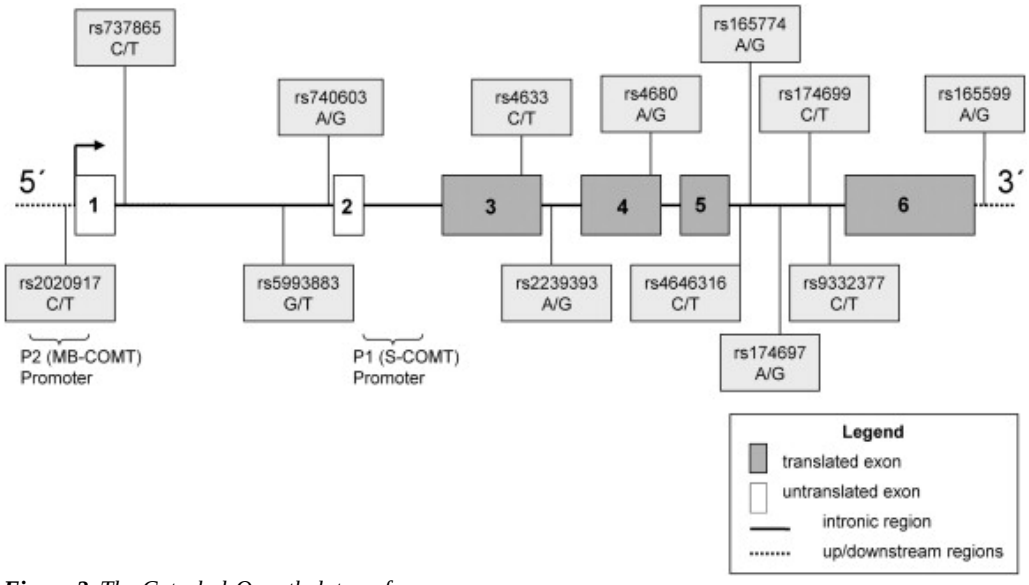

Figure 2. *The Catechol-O-methylotransferase gene.*

As mentioned above, COMT is the major determinant in normal PFC function, where it participates in catecholamine signaling and studies showed that neither too much nor too little cateholamine signaling is required for optimal function, known as the inverted-U model (Arnsten and Goldman-Rakic, 1990). According to this model, intermediate DA levels are mediated by D1 and D2 DA receptor activation on subsets of local PFC Glu and GABA neurons (Seamans and Yang, 2004). For example, WM is impaired by local infusion of D1 agonists and antagonists (Sawaguchi and Goldaman-Rakic, 1991; Zahrt, 1997). Normal PFC function is impaired in states of DA hypofunction such as aged subjects and Parkinsonic patients and is improved by D1 agonists and in states of DA hyperfunction such as stressed subjects and amphetamine-induced psychosis, improved by D1 antagonists (Tunbridge et al., 2006). Optimal DA signaling in the PFC is crucial for cognitive function, involved among other cases in attention shifting and WM on-line maintaining along with GABA interneurons (Arnsten 2009) and subcortical DA signaling tuning which is implicated both in SZ psychotic symptoms and antipsychotic drug effect (Grace 2000; Kinon and Lieberman, 1996). As mentioned before, the PFC is low in DAT, indicating that COMT is the main DA

degradation system, converting DA into 3-methxytyramine and the DA metabolite dihydroxyphenylacetic acid into homovanilic acid (Boulton and Eisenhofer, 1998).

Genetic variations in COMT have been associated with physiological functions (Egan et al., 2001; Winterer et al., 2006), and behavioral phenotypes related to PFC and hippocampal information processing, including cognition (Egan et al., 2001, Bertolino et al., 2004), anxiety (Drabant et al., 2006), Obsessive-compulsive disorder (Pooley et al.., 2007) and pain sensitivity (Nackley et al., 2006). In general increased COMT activity is a risk factor for cortically dependent cognitive dysfunction but a protective factor in stressful situations, whereas COMT reduction enhances WM processes but results in exaggerated stress reactivity (Papaleo, 2008).

The most studied functional polymorphism of the *comt* gene is the valine substitution for methionine in 158 codon of the MB-COMT and 108 codon in S-COMT, found as rs4680. The met allele results in a heat labile protein, with a fourfold reduction in the enzymatic activity (Mannisto and Kaakkola, 1999).

The rs4680 genotype is thought to exert a positive effect on the PFC function, by modulating the DA signaling. As regards WM , the met/met homozygotes performing better than the val/val, with the met/val individuals having an intermediate effect (Egan et al., 2001). In a study using the COMT inhibitor tolcapone (Da Prada, 2001), Giakoumaki et al. (2008) reported improved WM, as was reflected in the 'N-back' and 'Letter Number Sequencing' neuropsychological tasks only in the val/val homozygotes, a result consistent with inverted U model of optimal DA level signaling. In the same study the authors also reported increased Prepulse Inhibition (PPI) only in the val/val homozygotes. PPI is thought to reflect 'sensorimotor gating' a process which allows the CNS to filter the most important information (Giakoumaki et al., 2008). Schizophrenics are shown to have reduced PPI levels (Swerdlow et al., 2006). This decrease of PPI in SZ and the informational overload it produces, is suggested to underlie cognitive fragmentation, attentional deficits and some of the clinical symptoms of SZ (Geyer et al., 1990). Wisconsin Card Sorting Test (WCST), a task of cognitive flexibility) preservative errors are also reduced in met/met compared with val/val individuals indicating higher plasticity and behavioral shifting (Malhotra. et. al 2002). Nolan et al., (2004), using the computerized version of Competing Program Task (Bilder 1992), reported that the met

allele of rs4680 was associated with better cognitive stability but poorer cognitive flexibility, indicating that COMT genotype could be associated with cognitive performance and aggression. This effect could be mediated by the cortical overactivation of D1 receptors in met carriers due to low COMT reactivity. In contrast the val allele removes fastly the DA from the cleft in favor of the D2 receptors. The two receptor types effect pyramidal cells and interneurons in a different way, improving the signal-to-noise ratio and effecting positively stability over flexibility (Tunbridge et al., 2006). Also the striatum has been suggested to be involved in this effect. Bilder et al., (2004), suggested an alteration in the tonic and phasic ratio of DA receptor activation, similar to PFC. Stefanis et al., (2005), using the Continuous Performance Task, have also reported greater cognitive stability provided by the met allele, or 'enhanced tuning', possibly by stabilizing active neuronal representations in the PFC during tasks involving WM. The same team (Stefanis et al, 2007) in a study aimed to investigate whether the rs4680 polymorphism moderates the psychosis inducing effects of stress, showed that the carriers of the val allele where more susceptible to the effect of stress.

There is enough evidence to conclude that, in general, the met carriers have superior PFC cognitive abilities. However, Tunbridge (2006) reported a negative component of the met allele in affection. The met allele has been associated with high pain sensitivity (Zubieta et al., 2003), Obsessive-Compulsive Disorder (Karayiorgou et al., 1997), increased anxiety, especially in women, (Enoch et al., 2003) and panic disorder (Woo et al., 2004). A possible mechanism, underlying this effect could be the association of the met allele with greater reactivity of the limbic system, including the ventrolateral PFC (VLPFC), to unpleasant stimuli (Smolka et al., 2005; Drabant et al., 2006). The met carriers show exaggerated hippocampal and PFC activity in processing emotional stimuli, the opposite effect of cognitive process. Met carriers are more capable of dealing with cognitive than emotional involving tasks (Tunbridge et al., 2006). The same conclusion was reached by Roussos et al., (2008), when studying a different silent COMT polymorphism, rs4818, resulting in lower expressed COMT levels, thus more PFC DA signaling, using the Iowa Gambling Task (Bechara et al., 1998, 2005) which assesses emotional decision making, implicating VLPFC and Orbitofrontal cortex (OFC)

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and the Stocking of Cambridge (Soc), which assesses planning and problem solving (Baker et al,,1996; see 'Materials and Methods'), implicating the DLPCF.

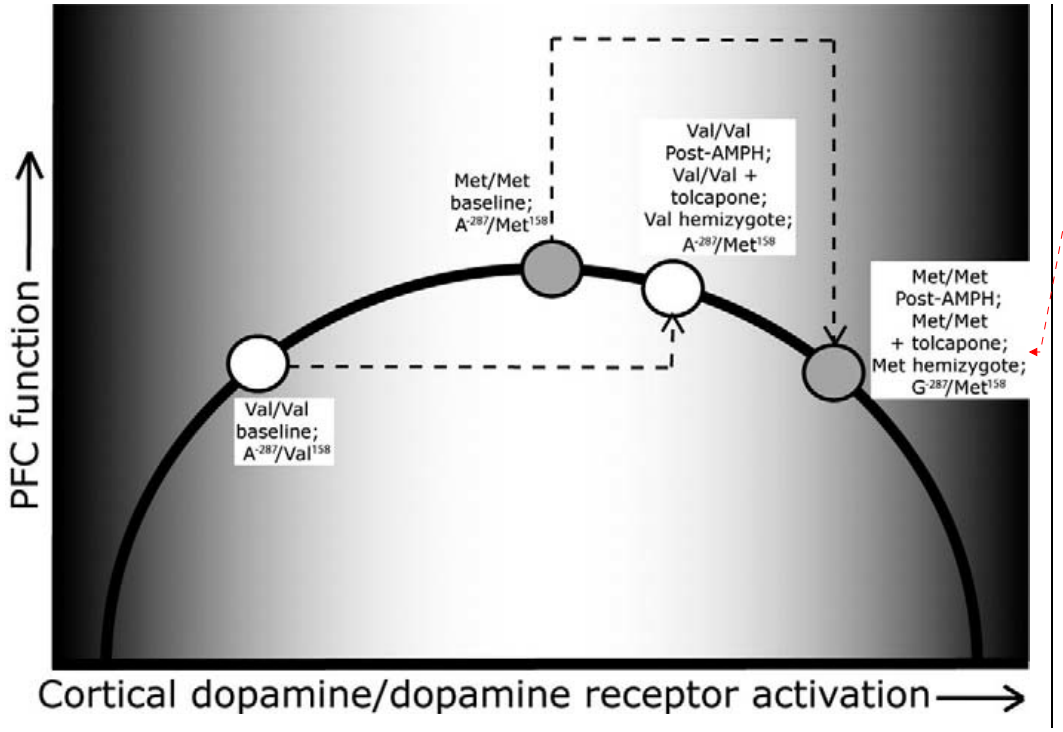

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Figure 3. Effect of COMT activity on PFC optimal function (Tunbridge et al., 2006)

Although the major part of the relevant research has focused upon the rs4680 polymorphism, there is evidence that other polymorphisms alter gene function and consequently impair the enzyme activity. These polymorphisms could affect the enzymatic activity of COMT either alone or in combination with rs4680 polymorphisms forming certain haplotypes. As shown in Figure 3, in val/val homozygotes, at baseline level DA signaling, COMT is associated with suboptimal PFC function and the same effect in observed in val158/A287 heterozygotes. PFC function moves near optimal after tolcapone administration, AMPH challenge or in met158 hemizygotic state. On the contrary met/met homozygotes are near optimal PFC function, which can be altered by tolcapone.

In personality studies, the rs4680 polymorphism has been associated with low extraversion, with more profound effect in the homozygotes than the carriers (Stein et al.

2005). High Neuroticism had been associated with the rs4680 polymorphism (Eley et al. 2003). Stein et al. (2005) reported that low extraversion and high neuroticism seem to be associated with COMT polymorphisms in the same way, with effects confined to women, in a study of 497 college students. The same team pointed out that extraversion is heritable (Jang et al., 1996) and has been associated with several anxiety disorders, such as agoraphobia and social phobia. However Henderson et al., (2000) failed to correlate COMT polymorphisms with Neuroticism. Hoth et al., (2006) reported that the met/met homozygotes had significantly lower extraversion and only a tendency toward higher Neuroticism, using the NEO-FFI, than the val/val homozygotes but failed to report any sex related effects, unlike previous studies (Stein et al., 2005). As mentioned before COMT polymorphisms resulting in alteration of PFC DA signaling levels can impair the decision making and planning when emotion is involving.

5. Materials and Methods

5.1. Subjects

Three hundred and forty three unrelated Greek healthy males aged 18-30 years entered the study. After presentation of the study, all participants gave written informed consent before screening. All underwent IQ testing with the Raven's progressive matrices, and medical history including mental illnesses, substance abuse and demographic data. Participants were assessed on a single occasion.

5.2 Personality assessment

Eysenck Personality Questionnaire (EPQ): EPQ (Eysenck and Eysenck, 1975) is a personality questionnaire consisting of four subscales to measure Extraversion, Neuroticism, Psychoticism and Lie. Each item is responded using a dichotomous response (yes/no) format. High scores on Extraversion reflect sociability, assertiveness and the tendency to experience positive emotions. High scores on Neuroticism reflect moodiness, worry and the tendency to experience negative emotions. High scores on Psychoticism reflect impulsiveness, tough mindedness and emotional detachment.

Temperament and Character Inventory (TCI): TCI (Cloninger, 1994) is a personality questionnaire designed to assess four temperament dimensions: Harm Avoidance (tendency to respond intensively to signals of aversive stimuli, thereby inhibiting or stopping a behavior), Novelty seeking (tendency to respond with intense excitement to novel stimuli), Reward Dependence (intensive response to reward signals, thereby maintaining a particular behavior) and persistence (preservation in behaviors associated with reward or relief from punishment). The questionnaire also assesses three character dimensions: Self-Directedness, Self-Transcendence and Cooperativeness.

Behavioural Inhibition/Activation System (BIS/BAS): BIS/BAS (Carver and White, 1994) is a 20-item scale that measures dispositional sensitivities of two motivational systems, a behavioral inhibition/withdrawal system and a behavioral activation/approach system. Each item is scored on a five point scale. Lower scores on BIS section reflect increased inhibition and lower scores on BAS scale reflect increased activation. The BAS scale is a composite of three subscales, drive, reward responsiveness and fun seeking.

Spielberger's State-Trait Anxiety Inventory—Trait Scale (STAI–T): Trait anxiety refers to relatively stable individual differences in proneness to anxiety. STAI–T (Spielberger, 1983) is a 20-item scale, with high internal consistency, high stability, and adequate test-retest reliability (Spielberger et al., 1970).

Schizotypal Traits Questionnaire (STQ): The STQ scale (Claridge and Broks, 1984) is a 37-item self-report questionnaire derived from the criteria for Schizotypal Personality Disorder in the DSM and is thought to provide the best measure of the underlying schizotypy dimension.

5.3. Neuropsychological assessment

Tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB): CANTAB includes several tasks, covering a wide range of cognitive domains, including visual memory, attention, working memory and planning. The use of a computer insures that testing is given in a standardized manner with standardized feedback, and both accuracy and speed can be evaluated. The set of the CANTAB tasks used in the present study included the following tasks:

- Spatial Working Memory (SWM). The SWM tests spatial working memory and spatial strategy (Owen et al., 1990). Subjects are required to search through an increasing number (two, three, four, six, and eight) of boxes shown randomly arranged on the screen, until they find a single token that, at any one time, is hidden in one of the boxes. The key instruction is that once a token has been found within a particular box, then that box should never be used again to hide a token. On each trial, every box is used once to hide a token such that the total number of tokens to be found corresponded to the number of boxes on the screen. Errors are scored according to the number of occasions on which a subject returns to open a box in which a token has already been found. An efficient strategy for completing this task is to follow a predetermined search sequence, beginning with a particular box and then returning to start each new sequence with that same box as soon as a token has been found. The extend to which this repetitive searching pattern is used as a strategy for approaching the problem is estimated from the

number of search sequences starting with the same box, within each of the more difficult 6- and 8-box problems. The total of these scores provides a single measure of strategy for each subject, with a high score (many sequences beginning with a different box) representing low use of the strategy and vice versa.

- Rapid Visual Information Processing (RVP). Subjects were asked to detect consecutive target sequences of digits presented at the rate of 100 digits per minute for 4 min and responses are registered by a button press. Main performance measures include: total hits (number of targets correctly detected), total misses (number of undetected targets), total false alarms (number of responses made in the absence of targets). From these, calculations of sensitivity (A: tendency to detect target sequences) and response bias (B: tendency to respond regardless of target sequence) are possible, derived from Signal Detection Theory (Sahgal, 1987; Sewts, 1996), which take both hit probability and false alarms into consideration.
- Stocking of Cambridge (SOC). The SoC is a modified, computerized version of the Tower of London (Owen, 1990; 1995). Subjects are asked to compare two different arrangements of "balls" in "socks" (one presented on the top half of the screen, the other on the bottom) and rearrange, in the minimum possible number of moves, the balls in the lower half of the screen such that their positions match the target arrangement in the upper half. The test presents the subject with easy 2- and 3-move and harder 4- and 5-move problems. Subjects are asked to plan the complete sequence of moves required to solve the problem prior to their first move. Initial thinking time (ITT) prior to execution of the firstmove, subsequent thinking time (STT) for the execution of all subsequent moves, and problems solved in minimum moves are recorded. Poor performance in this test is usually revealed for the difficult 3-, 4- and 5-move problems; it translates into shorter ITT (less time planning), and/or longer STT (more time executing the solution) with more mean moves and less perfect solutions
- **Wisconsin Card Sorting test (WCST)**: A computerized version was used. The task consisted of four stimulus cards that varied along three dimensions (color,

shape, and number). Participants were asked to match the cards in the deck with one stimulus card and feedback was provided after each selection. Once six consecutive cards were categorized correctly, the sorting principle changed. We used a modified version of the task, as suggested by Nelson (1976) so that the examiner tells the subject when the matching principle changes to reduce the potential distress in a vulnerable population. Outcome variables were the total number of categories achieved, perseverative errors, nonperseverative errors, and total number of errors

- **Iowa Gambling task (IGT)**: The Iowa Gambling Task (IGT) is a simulated gambling task administered on a computer. Participants are given D 2000 in computer money and are instructed to lose as little or make as much money as possible by selecting cards (one at a time) from four decks (A–D) displayed on their screen. They are advised that each card has a different monetary value but no other information is given. However, cards in decks A and B are associated with high monetary rewards but also high penalties (monetary loses) while those in decks C and D have lower rewards but also lower penalties. Participants learn of the monetary value of each card after they have selected it. Across 100 trials, more choices from the decks C and D lead to a net gain while choosing from the other two decks results in greater loss. Scores are (a) total money won and (b) the total numbers of cards selected from advantageous decks C and D minus the total numbers of cards selected from ("risky") decks A and B (CD−AB difference), with a higher score indicating superior performance.
- **Word Lists task:** We used the Word Lists subtest of the Weschler Memory Scale (WMS-III) from the WAIS-R (Weschler, 1997), to assess verbal learning and memory. A list of 12 words was read, and subjects were asked to recall the words in any order (immediate recall); this procedure was repeated four times. After Trial 4, an interference trial with a new list occurred, and subjects were subsequently asked to recall as many words as possible from the first list (short-delay recall). Thirty minutes later, subjects were asked to recall the words from the first list again (long-delay recall). The test finished with a recognition memory trial: a list of words was read, and subjects were asked to identify the words

included in the first list (recognition). Outcome variables were the number of correct responses per recall condition (immediate four trials, short delay, long delay) and intrusion errors (words identified that were not included in the list).

- **Stroop Interference test:** The standardized version of this test was used (Golden, 1975). Subjects were asked in three consecutive 45-s periods, first to read the names of colours written in black ink, then to name the color of patterns and, finally, to identify the colour of ink that is mismatched to a word (e.g. the word red printed in blue ink is identified as blue). These procedures result in a Word (W), a Color (C) and a Color–Word (CW) score. The increase in time taken to identify the color of the incongruent word list results in fewer correct responses in the 45-s period and is referred to as Stroop interference. Interference scores were calculated as the difference between the C–CW scores. The greater the C–CW difference, the greater the interference effect and the worse the performance in this test.
- **N-Back task:** The task consisted of four conditions (0-, 1-, 2-, and 3-back) where subjects were asked to respond by a button-press when they saw a target letter (letter 'X' for 0-back and any letter that was identical to the one presented in the preceding 1, 2, or 3 trials, respectively). The outcome variables were the number of correct responses and reaction time. The n-back task is a working memory test allowing 'online' manipulation of information, demonstrated to engage a wide network of brain regions with dorsal PFC activation being the most consistent finding (Fletcher and Henson, 2001).

5.4 Statistical analyses

Subjects were divided into two groups: Val/Val homozygotes (N=217) and Met-carriers (N=548). One-way ANOVAs with each demographic variable as the dependent variable and genotype as the grouping factor were conducted. All variables from the personality scales and the neuropsychological tasks were subjected to separate Principal Component Analyses (PCA) using the varimax rotation method; components with Eigenvalues >1 and factor loadings >0.5 were accepted. Categorical analyses were conducted with a series of one-way ANOVAs with each PCA factor as the dependent variable and genotype as the grouping factor. Separate Pearson correlations were run between the extracted PCA personality and neuropsychological factors for each genotype group (val/val and met-carriers). In order to reduce type I error from multiple testing (seven PCA neuropsychological factors), alpha was set at $\alpha=0.05/7=0.007$ and therefore, only results with $p<0.007$ were considered significant.

6. Results

6.1 Demographics

We performed Kruskal-Wallis one-way-analysis and Mann-Whitney U Test showing a normal distribution. There were no significant differences in any demographic variable (all p values > 0, Tables 2 and 3)

	Val/Val N=217	*Val/Met N=391*	*Met/Met N=157*	*P values*
Age	*22.62 +/- 3.901*	*22.53 +/- 3.731*	*22.04 +/- 3.796*	*> 0.1*
Years of Education	*14.88 +/- 2.624*	*14.82 +/- 2.497*	*14.50 +/- 2,729*	*> 0.1*
Cigars per day	*6.72 +/- 9.968*	*7.07 +/- 9.590*	*7.22 +/- 9.849*	*> 0.7*

Table 2. Kruskal-Wallis ANOVA. Age [$x^2 = 3.24$, $p > 0.1$]; Years of Education [$x^2 = 3.48$, $p > 0.1$]; Cigars per day [$x^2 = 0.7$, $p > 0.7$]

	Val/Val N=217	*Met carries N=548*	*P values*
Age	*22.62 +/- 3.901*	*22.38 +/- 3.739*	*> 0.5*
Years of Education	*14.88 +/- 2.624*	*14.73 +/- 2.566*	*> 0.3*
Cigars per day	*6.72 +/- 9.968*	*6.95 +/- 9.679*	*> 0.6*

Table 3. Mann-Whitney U-Test. Age [$U = 57945.50$, $p > 0.5$]; Years of Education [$U = 56755.00$, $p > 0.3$]; Cigars per day [$U = 58487.50$, $p > 0.6$]

6.2 Principal component analysis of personality variables

A total of 18 variables were included in the analysis, and five factors were extracted (Table 4). Namely, the factors were:

1) Anxiety (comprising STAI-T, BIS, EPQ extraversion and neuroticism, TCI harm avoidance and self-directedness; Eigenvalue: 4.568, variance explained: 28.55%)

2) Schizotypy (comprising TCI self-transcendence, STQ magical thinking, paranoid ideation and unusual experiences; Eigenvalue: 2.436, variance explained: 15.22%)

3) Behavioural Activation (comprising BAS reward responsiveness, drive and fun seeking; Eigenvalue: 1.727, variance explained 10.79%)

4) Novelty Seeking (comprising EPQ Lie and TCI Novelty seeking; Eigenvalue: 1.502, variance explained: 9.39%) and

5) Reward Dependence (comprising TCI reward dependence and Cooperativeness; Eigenvalue: 1.128, variance explained: 7.05%). For this model, the KMO=0.817, $p<0.001$ and the total variance explained was 71.012%)

		1. Anxiety	2.Schizotypy	3. Behavioural Activation	4. Novelty Seeking	5. Reward Dependence
STQ	Unusual experiences		0.786			
	Magical thinking		0.848			
	Paranoid ideation		0.675			
TCI	Self-transcendence		0.795			
	Harm avoidance	0.829				
	Self-directedness	-0.680				
	Persistence	Factor solution <0.5; variable excluded from analysis				
	Novelty seeking				0.814	
	Reward dependence					0.853
	Cooperativeness					0.742
EPQ	Psychoticism	Complex factor loading; variable excluded from analysis				
	Neuroticism	0.722				
	Extraversion	Complex factor loading; variable excluded from analysis				
	Lie				-0.784	
BIS/BAS	BIS	0.549				
	Reward responsiveness			0.896		
	Drive			0.858		
	Fun seeking			0.726		
STAI-T		0.825				

Table 4. PCA of personality variables

6.3 Categorical analysis of personality variables

There were no significant differences between the groups in any PCA personality factor (all p values >0.1).

6.4 Principal component analysis of neuropsychological variables

A total of 24 variables were included in the analysis, and seven factors were extracted (Table 5). Namely, the factors were:

1) Set-shifting (comprising WCST categories completed, unrelated cards, Milner and Nelson non-perseverative errors; Eigenvalue: 4.766, variance explained: 26.48%)

2) Declarative memory (comprising WL correct responses in immediate, short-delay and long-delay recall; Eigenvalue: 2.419, variance explained: 13.44%)

3) Problem solving (comprising SOC mean moves and problems solved; Eigenvalue: 2.102, variance explained 11.68%)

4) Spatial working memory (comprising SWM between, double and within errors; Eigenvalue: 1.829, variance explained: 10.16%)

5) Perseveration (comprising WCST Nelson and Milner-preservative errors; Eigenvalue: 1.475, variance explained: 8.19%)

6) Emotional decision making (comprising IGT total money and advantageous – disadvantageous card selection; Eigenvalue: 1.190, variance explained: 6.61%) and

7) Planning (comprising SOC mean initial and mean subsequent thinking times). For this model, the KMO=0.559, p<0.001 and the total variance explained was 82.719% (Table 8).

6.5 Categorical analysis of neuropsychological variables

There were no significant differences between the groups in any PCA neuropsychological factor (all p values >0.1).

		1. Set-shifting	2. Declarative memory	3. Problem solving	4. Spatial working memory	5. Perseveration	6. Emotional decision making	7. Planning
SWM	Between errors				0.592			
	Double errors				0.959			
	Within errors				0.946			
	Strategy	Factor solution <0.5; variable excluded from analysis						
SOC	Mean moves			0.916				
	Mean ITT							0.794
	Mean STT							0.752
	Problems solved			-0.928				
RVIP	A	Factor solution <0.5; variable excluded from analysis						
	B	Factor solution <0.5; variable excluded from analysis						
N-back	Correct 2-back	Factor solution <0.5; variable excluded from analysis						
	Correct 3-back	Factor solution <0.5; variable excluded from analysis						
WCST	Categories completed	-0.852						
	Unrelated cards	0.828						
	Nelson perseverative errors					0.898		
	Milner-perseverative errors					0.890		
	Nelson non-perseverative errors	0.818						
	Milner non-perseverative	0.795						

		1. Set-shifting	2. Declarative memory	3. Problem solving	4. Spatial working memory	5. Perseveration	6. Emotional decision making	7. Planning
	errors							
Stroop	Interference	Factor solution <0.5; variable excluded from analysis						
IGT	Money won						0.955	
	Advantageous-disadvantageous card selection						0.947	
WL	Correct immediate recall		0.804					
	Correct sort-delay recall		0.913					
	Correct long-delay recall		0.905					

Table 5. PCA of neuropsychological variables

6.6 Correlational analyses

In the val/val group, there was a significant negative correlation between Novelty Seeking and declarative memory (r=-0.208, p=0.004, figure 4) while in the met-carriers' group there was a significant positive correlation between Novelty Seeking and perseveration (r=0.118, p=0.007, figure 5) (all remaining p values >0.01).

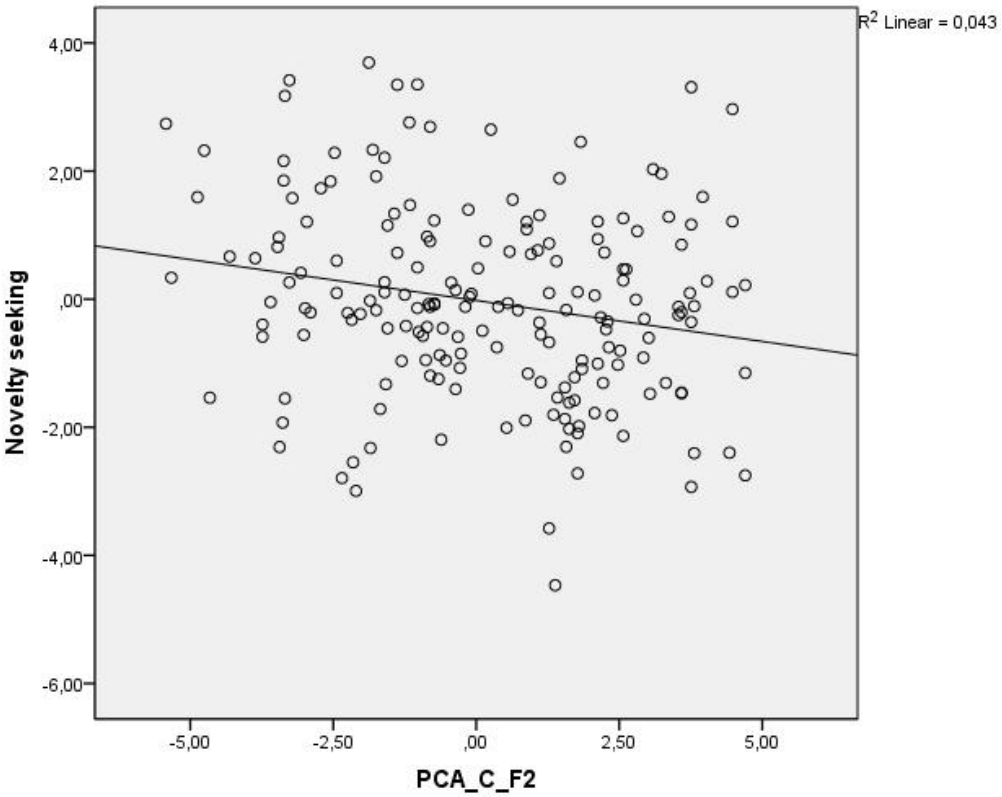

Figure 4. Negative correlation between Novelty Seeking and Declarative Memory in the val/val group.

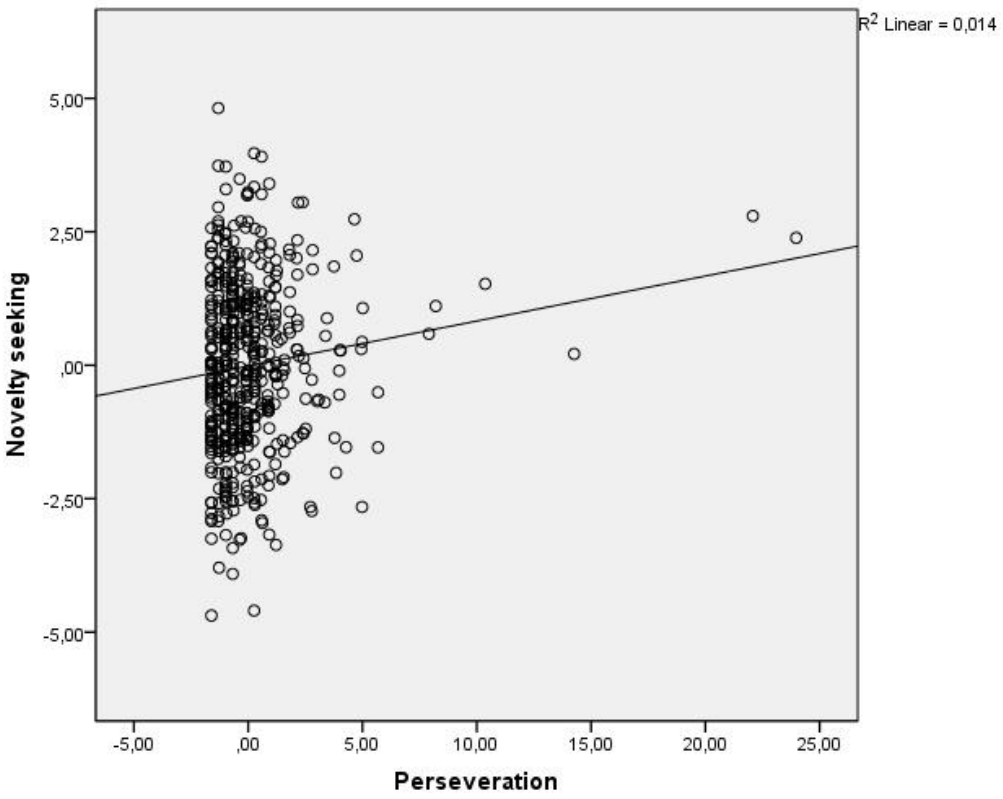

Figure 5. Positive correlation between Novelty Seeking and Perseveration in the met carriers group.

7. Discussion

In the present study, we found a negative correlation between the Novelty Seeking Factor (comprising EPQ Lie and TCI Novelty Seeking), and the Declarative Memory Factor (comprising WL immediate correct responses, short and long delay responses) in the val/val homozygotes. Novelty Seeking also correlated positively with the Preservation Factor (comprising WCST preservative errors) in the met carriers.

As suggested by Cloninger (1994) NS is mediated by the dopaminergic system and Reuter and Hennig (2005) found that val/val homozygotes present with higher NS compared with the met/met homozygotes. Interestingly, in an fMRI study, the COMT Val allele was associated with poorer performance at memory retrieval during a recognition memory task (Bertolino et al., 2006) along with reduced recruitment of neuronal resources in the hippocampus and increased recruitment in ventrolateral prefrontal cortex during both encoding and retrieval. The present findings are in accordance with these results, suggesting that the reduced levels of PFC dopamine in the val/val homozygotes are associated with poorer memory capacity.

The positive correlation of Novelty Seeking with Perseveration in the met-carriers is a very interesting. Barnett et al., (2007) conducted a meta-analysis of studies that reported WCST perseverative errors from healthy volunteers or patients with schizophrenia-spectrum disorders with respect to the val158met polymorphism. They found a modest effect of val158met genotype on WCST perseverative errors in the healthy volunteers, with a mean difference of 0.3 standard deviations between the two homozygous groups, while no evidence was found in patients with schizophrenia-spectrum disorders. However, other findings (Nolan et al., 2004) have suggested that the val158met genotype may differentially affect cognitive stability and flexibility such that the Met allele is associated with increased cognitive stability but decreased cognitive flexibility, suggesting an association between the met allele and increased persevering on the WCST.

Contrary to our hypotheses, no significant differences were revealed in the categorical analyses. This could be due to several reasons. First, we employed a quite lengthy testing session which might have lead to differential levels of subjective personal

feelings (e.g. discontentment and alertness) between the two groups. However, we did not check for such effects at the end of the session. Second, our sample consisted only of males, while in the majority of studies reporting significant effects, female participants are also included. Third, although 30-60% of the variation in personality characteristics may be inherited (Ebstein, 2006), a large part of this variation has been attributed to environmental factors (Guttman, 2002). The present study assessed personality but this additional effect of environmental influences was not taken into consideration. Finally, subjects were grouped into two groups: val/val homozygotes and met-carriers, including met/met homozygotes and val/met heterozygotes. However, when analyses only between the two homozygote groups also did not reveal any significant findings (data not shown); thus, the grouping into two groups was preserved to increase the sample size in the group carrying the met-allele.

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