COMT as a Drug Target for Cognitive Functions and Dysfunctions

Diego Scheggia[1], Sara Sannino[1], Maria Luisa Scattoni[2] and Francesco Papaleo[*,1,3]

[1]*Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, via Morego, 30 16163 Genova, Italy*

[2]*Neurotoxicology and Neuroendocrinology Section, Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Viale Regina Elena, 299, 00161 Rome, Italy*

[3]*Dipartimento di Farmacologia ed Anestesiologia, Università degli Studi di Padova, Largo Meneghetti, 2, 35131 Padova, Italy*

Abstract: Catechol-O-methyltransferase (COMT) is a promising target for modulation of cognitive functions and dysfunctions. COMT dominates the regulation of dopamine metabolism in the prefrontal cortex. Thus, COMT effects are particularly evident in prefrontal cortex-dependent cognitive functions including executive control, working memory, attentional control and long-term memory. This has been determined by both genetic and pharmacological studies that we will highlight in the present review. In particular, we will discuss how common functional variants of the COMT gene may predict individual variation in selective cognitive abilities and vulnerability to cognitive deficits that characterize several neuropsychiatric disorders. Moreover, COMT genetic variants represent one source of individual differences in the cognitive responses to medications such as those used in psychiatric illnesses. COMT genetic testing may then predict some cognitive dysfunctions often seen in certain psychiatric illnesses even from presymptomatic stages and the efficacy/dosage of drugs used to treat them. The consideration of COMT-dependent differences may be important for the development of more efficient personalized healthcare.

Keywords: Executive function, working memory, attention, development, prefrontal cortex, psychiatric disorders, pharmacological treatment.

INTRODUCTION

Cognitive functions and intelligence are strongly dependent on genes [1-5]. An evolving and exciting field of research is focusing on how genetic variations and their correlated neural mechanisms might modulate cognitive functions. Understanding the connection between genetic variation and cognitive function is crucial for the development of more effective treatments for several neuropsychiatric disorders characterized by cognitive dysfunction. One of the most promising candidate genes affecting cognition is catechol-O-methyltransferase (COMT) [6]. The COMT gene is mapped at the q11.2 band of human chromosome 22 and encodes distinct soluble-COMT and membrane-bound (MB-COMT) isoforms [7]. MB-COMT is the dominant form in brain, primarily expressed in cortical neurons, and has a 10-fold higher affinity for dopamine than does soluble-COMT [8-10]. In principle, MB-COMT could constitute a more critical target for modulating cognitive functions.

COMT is one of the major enzymes involved in the catabolism of dopamine in the brain, especially in the prefrontal cortex (PFC) [11-14]. Dopamine in the PFC plays a central role in modulating higher-order cognitive functions, impacting many domains of human behavior such as thought and emotion [15]. In particular, in humans as well as in monkeys and rodents, cortical dopamine levels finely control cognitive functions following an inverted U-shaped dose-response curve, with too much and too little dopamine having detrimental effects [16-20]. Thus, COMT, working as a regulator of this important balance, constitutes a key factor and therefore an excellent target to modulate higher order cognitive functions.

In agreement, we will focus our attention on cognitive functions primarily dependent on the PFC and on how COMT could be used as a key target to modulate them in healthy humans and in psychiatric patients based on functional variations in its gene. Endogenous COMT enzymatic activity is genetically determined by proven functional common single nucleotide polymorphisms and/or haplotypes [21-24]. Human studies have primarily focused on a 158/108Val/Met (rs4680) functional single nucleotide polymorphism [25, 26] hereafter referred to as Val/Met. This single mutation results in a substantial change in stability and enzymatic activity of COMT: the Val form leads to higher COMT protein levels and ~40% greater enzymatic activity compared to the Met allelic variant [8]. Because the two alleles are codominant, heterozygotes show intermediate COMT activity, leading to a trimodal distribution of COMT activity across the human population [27]. However, most studies have so far overlooked the effects of other COMT functional haplotypes which might better account for variability in COMT enzymatic activity and protein levels compared to the single Val/Met polymorphism. This might explain some current inconsistencies in COMT genetic effects in cognitive functions. We will discuss how genetic variants of COMT may predict individual variations in selective cognitive abilities. We will address how these

*Address correspondence to this author at the Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, Via Morego 30, 16163 Genova, Italy; E-mail: francesco.papaleo@iit.it

1871-5273/12 $58.00+.00

genetic variants may alter the vulnerability to cognitive abnormalities present in some neuropsychiatric disorders. Moreover, we will highlight how COMT genetic variants may represent the basis for individual variation in drug responses on brain functions. Finally, a separate section will focus on how COMT could be used already from early developmental stages for diagnosis and therapeutic purposes. We will explore these ideas by looking at a) evidence from healthy human conditions, b) from pathological states, c) existing support from experimental animals, then d) possible interactions of COMT with pharmacological interventions.

COMT MODULATION OF PFC-DEPENDENT COGNITIVE FUNCTIONS

Executive Control

The control of processing of goal-directed responses is governed by the PFC and is usually referred to as executive control [28]. Executive control allows for more efficient actions within: decision-making, working memory, and behavioral adaptation to novel situations and environments [29]. The most commonly used task for evaluation of executive control in humans is the Wisconsin Card Sorting Test (WCST) [30, 31], or its more recent computerized analogue: the intra- and extra-dimensional attentional set shifting (ID/ED) of the Cambridge Neuropsychological Test Automated Battery [32, 33]. These human tasks have been successfully adapted to rodents in the attentional set-shifting test [34-37]. These tests measure the ability to form a cognitive set and to apply a strategy that involves maintenance and shifting of this cognitive set. These are established measures of PFC-mediated functions in humans, monkeys and rodents, as confirmed by behavioral [34, 38-40], pharmacological [41, 42], neuroimaging [43, 44], neurochemical [28] and lesions studies [34, 36, 45, 46]. In particular, a double dissociation or functional specialization effect has been shown between the lateral (in monkeys and humans), medial (in rodents) and orbital regions of the PFC in the attentional set-shifting test [28, 36, 45, 47]. While the orbitofrontal cortex is selectively involved in the reversal phases of these tasks, the lateral/medial PFC region governs the extra-dimensional shift stages [28, 36, 43, 44, 48].

COMT genetic variations have been associated with differential WCST performance both in healthy individuals [49, 50] and patients with psychiatric disorders [51-53]. COMT Val-carrier subjects have shown impaired performance and higher number of perseverative errors during the extra-dimensional shift phase compared to individuals with two copies of the Met-allele, without affecting general intelligence [50, 51, 54]. Similarly, patients with schizophrenia carrying two Val alleles show a higher frequency of perseverative errors during the WCST and a higher number of errors in the ID/ED task compared to Met-carriers [52, 55]. Nevertheless, in contrast with these findings other studies have reported no association between COMT Val/Met and performance on the WCST [56, 57]. These discrepant results might be explained by differences between the samples. In particular, we point out that attention should be paid to sex-dependent differences as the studies showing negative results had higher percentages of female subjects. This might be supported by the numerous evidences of COMT-dependent sex differences [58] and by our own data in genetically modified mice showing negative effects in executive functions following relative reduced COMT activity in females but not males (Papaleo *et al*., unpublished data). Furthermore, experimental animal findings demonstrate that male subjects with increased COMT activity are impaired in their ability to shift an attentional set. Indeed, transgenic mice overexpressing the human COMT-Val polymorphism (COMT Val-tg), simulating human genetic conditions leading to increased COMT activity, have shown a selective impairment in their extra-dimensional shifting ability [37]. These effects might be due to the lower availability of synaptic dopamine in the PFC of subjects with increased COMT enzyme activity. Similar deficits are produced by dopamine depletion in monkeys during the ID/ED task [59].

In contrast, the same Val/Met COMT polymorphism seems to have opposite executive control effects in patients in the early stages of Parkinson's disease. In fact, compared to Val-, Met-carriers patients at early stage of Parkinson's disease were not able to form an 'attentional set' and showed prolonged response times during all the stages of the ID/ED task [60]. Further, subjects at early stage of Parkinson's disease and COMT Met homozygotes were significantly slower to respond than Val/Val subjects in the Tower of London planning task, another test for the assessment of executive control [61-63]. These findings can be explained by the fact that in the early stages of Parkinson's disease the patients present a hyperdopaminergic state in the PFC and decreased striatal dopamine [64, 65]. Thus, in early stages, the low activity COMT-Met allele would increase PFC dopamine levels, leading to excessively high levels of dopamine that become detrimental to executive functions (Fig. **1**). Conversely, in later disease stages, when PFC dopamine levels fall, the COMT Met effect in executive functions disappears and may even reverse [63]. This demonstrates that the same genetic variants of COMT may have different outcomes on executive processing, depending on the background dopamine level in the PFC. Thus, it is imperative to consider the "dopaminergic state" in the PFC to have a better prediction of COMT effects in executive functions. Moreover, analysis of all possible COMT haplotypes and not only the Val/Met polymorphism may provide more compelling conclusions on the effects of COMT in executive control. So far this has been scarcely investigated and will require more attention in future studies.

It is interesting to note that COMT genetic variations do not irreversibly alter executive functions but might be involved in the dynamic regulation of these cognitive functions. In fact, pharmacological manipulations that alter dopaminergic transmission can interact acutely with COMT genetic variations in modulating executive performance. Acute pharmacological inhibition of COMT in adult rats produced by tolcapone, a selective, brain-penetrant COMT inhibitor, can improve executive control. This is demonstrated by a decrease in the number of trials needed to finish the extra-dimensional shift stage of the attentional set shifting task [66]. This has not been replicated in a human study, as tolcapone failed to enhance the extra-dimensional shift performance [67]. However, this might be due to a strong order effect from the crossover design which might alter the performance. Amphetamine increases synaptic dopamine levels, improves cognitive performance during the

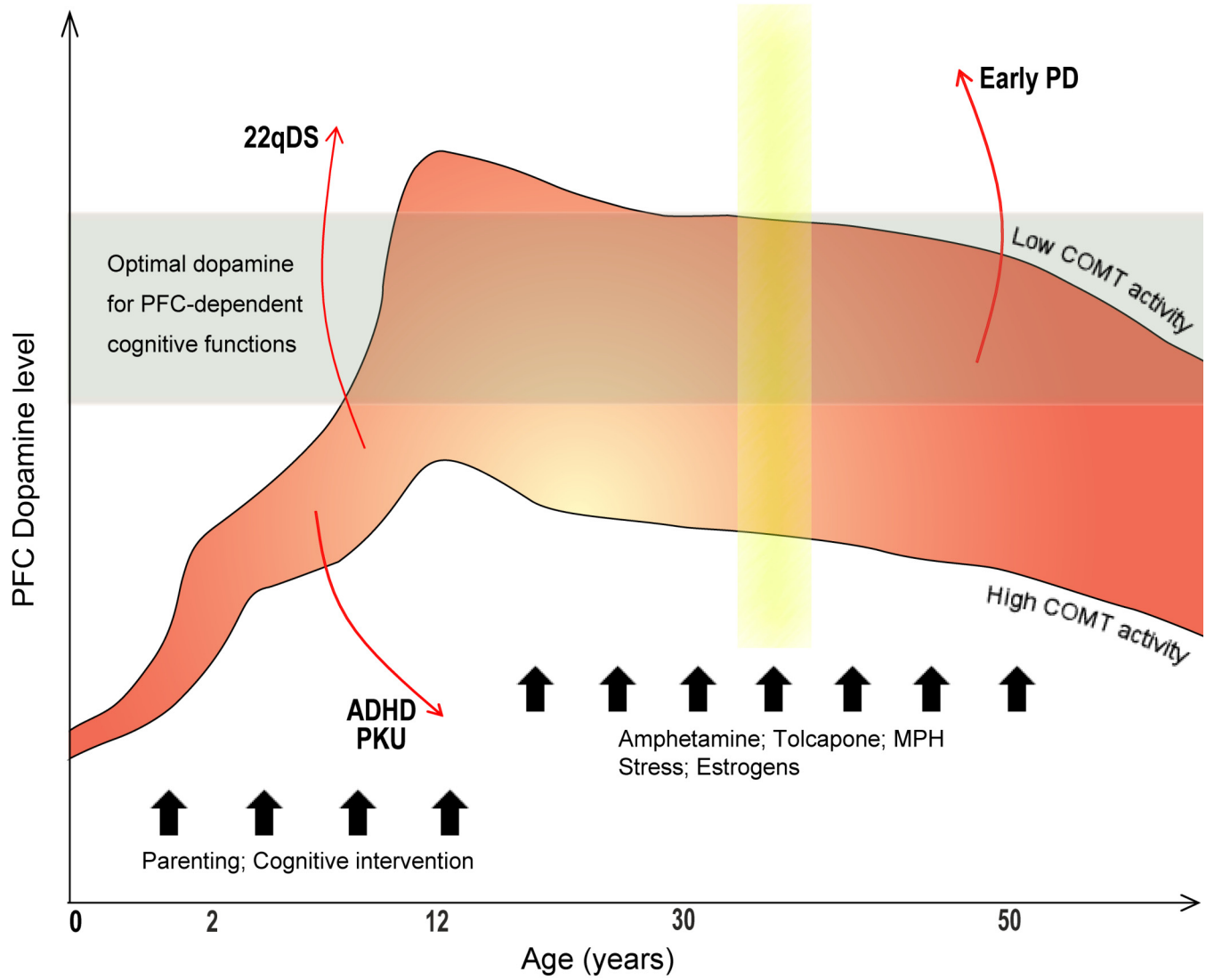

Fig. (1). Dopamine level in the PFC during development of PFC-dependent cognitive abilities (red area). Note that COMT enzymatic activity peaks during adulthood (yellow translucid area). The grey area represents optimal levels of dopamine for performance in PFC-mediated tasks. It appears that, in general, low COMT enzyme activity (e.g. COMT Met/Met) is associated with that optimal level, whereas high COMT enzyme activity (e.g. COMT Val/Val) is associated with less than optimal levels of dopamine in the PFC, therefore showing poorer executive functions. Other factors that increase dopamine in PFC would be more beneficial for subjects having higher rather than lower COMT enzyme activity. It follows that, for example, COMT Met/Met homozygotes have less protection against the detrimental effects of excessive PFC dopamine levels than COMT Va/Val homozygotes. Factors that can increase dopamine in the PFC are stress, estrogens or drugs like tolcapone, amphetamine and MPH. Other environmental factors such as parenting and cognitive intervention might enhance PFC-dependent cognitive abilities. Thus, since COMT Val/Val homozygotes generally have worse executive control than Met/Met homozygotes, it follows that interventions or environmental factors that are likely to improve executive control would be likely to benefit Val/Val homozygotes more than Met/Met subjects, since it is a general principle that those with poorer executive control tend to gain most from interventions or environmental benefits (the Met/Met being closer to ceiling) [142]. Red arrows show pathological conditions that push a subject towards too much (e.g. early stage Parkinson's disease or 22qDS) or too little (e.g. ADHD or PKU) dopamine in the PFC. In these conditions, carriers of lower or higher COMT enzyme activity might have heavier PFC-dependent cognitive disadvantages, respectively.

WCST in homozygous Val-carriers but impairs it in Met carriers as demonstrated by decreased and increased totals of perseverative errors, respectively [53]. These compelling results from both human and animal studies emphasize the importance of accounting for COMT functional genetic variants when using pharmacological treatments impacting the dopaminergic system. This will improve their effectiveness and avoid deleterious side effects such as dysfunction in executive control. Due to their proven similarities to human conditions, COMT genetically-modified mice may constitute an effective tool in the screening and prediction of the effects of pharmacological compounds in executive functions.

COMT genetic variants can also interact with potentially executive function enhancing environmental interventions. Cognitive exercise for potentiating specific executive functions can be useful to improve executive disadvantages that are often critical in a social community [68]. In patients

with schizophrenia, function-specific cognitive exercise protracted for 3 months efficiently decreased the number of perseverative errors in the WCST compared to the baseline but only in patients with the COMT Met allele [69]. This new strategy for cognitive remediation further points to COMT as a putative genetic clinical biomarker able to predict the effectiveness in cognitive improvement after therapy.

In conclusion, COMT is a compelling modulating factor for executive functions and COMT genetic variants represent a heritable mechanism for variable clinical responses to drugs and environmental factors. Thus, COMT might be used as a potential biomarker and target for cognitive enhancers and therapies aiming to ameliorate executive dysfunctions as those present in many psychiatric illnesses.

Working Memory

Working memory is a system meant to keep information in mind while performing complex tasks and is coordinated by related executive processing (e.g. attention, inhibition and planning behavior) [70]. The executive control occurring during working memory performances is different from the one discussed in the previous paragraph. This does not involve abstract reasoning and problem solving, but rather facilitates the temporary storage of small amounts of information over brief periods and for subsequent retrieval during complex tasks such as reasoning and learning. Dopamine in the PFC has a critical role in working memory performances [71, 72]. Thus, genetic modifications of COMT may play an important role in working memory as well. Indeed, a number of studies reported the effect of COMT polymorphisms on working memory using the N-back test, one of the most commonly used tasks activating the cortical working memory network [73-75]. Healthy COMT Val/Val individuals showed poorer working memory performance compared to COMT Met-carriers as demonstrated by lower accuracy and slower reaction time in the N-back test [52, 76, 77]. In agreement, prefrontal physiological response, assayed with functional magnetic resonance imaging (fMRI) during the task, showed that, at the same level of cognitive performance, the COMT Val allele is associated with the greatest activation of the dorsolateral-PFC, indicating a less efficient activation [52]. Closely mimicking these findings, a relative increase in COMT enzymatic activity in COMT Val-tg mice produced working memory impairments in a PFC-dependent T-maze task that recapitulated important elements of working memory functions in humans [37]. Conversely, COMT knockout mutant mice demonstrated better performance on the same working memory task [37]. Nevertheless, results from other human studies have not been uniformly positive regarding the robustness of the Val/Met polymorphism effect on N-Back performance. For example, Stefanis *et al*. [78] did not find a relationship between COMT Val/Met and working memory functions tested with the N-Back task in healthy young men. However, in this study it is not clear which N-back memory load was used and if the consideration of only the COMT Val/Met genotype might have masked the real effect of the resulting COMT enzyme activity. In agreement, fMRI during the N-Back task in normal subjects revealed that the haplotype derived from the combination of the COMT Val/Met variant and a cis functional variant in the P2 promoter region of COMT which drives MB-COMT form transcription (rs2097603) had stronger effects on prefrontal activation than the single Val/Met single nucleotide polymorphism (SNP) [23]. Thus, it is suggested for future studies to control not only for the Met/Val genotype but also for other potential functional polymorphisms. In conclusion, even if some inconsistencies still exist, human and experimental animal findings seem to be convergent indicating that in healthy conditions subjects with genetic variants resulting in relative decreased COMT activity have working memory advantages.

It is important to consider that this conclusion might be only valid in "baseline" conditions. In fact, COMT activity is associated with stress responsivity [37] and this might interact with working memory functions. Furthermore, conditions of stress might differently modulate DNA methylation silencing of the COMT gene in Val/Val subjects compared to Met-carriers and this can eventually alter the working memory performance [79].

Pharmacologic COMT inhibition with tolcapone decreases reaction time during the N-back test in normal human subjects [67]. Interestingly, on the N-Back test tolcapone was able to improve the accuracy [80] and the reaction time of responses [81] in COMT Val/Val individuals but impaired the performance in Met-carriers [80]. Similarly, amphetamine treatment significantly improved the reaction time on the N-back test and enhanced the efficiency of PFC identified by fMRI only in COMT Val/Val healthy individuals, while impairing the same parameters in Met carriers [53]. Instead, in patients with schizophrenia, treatment with the atypical antipsychotic olanzapine for 8 weeks increased the correct responses on the N-back task and cortical efficiency activation more in Met homozygous compared to Val-carriers [82]. This indicates that specific COMT genetic/pharmacologic interactions should be taken into account to employ more efficient and *ad personam* strategies aiming to improve working memory. This is crucial for schizophrenia [75, 83], bipolar disorders [84], major depressive disorders [85] and attention deficit hyperactivity disorder (ADHD) [86] in which working memory dysfunctions are one of the main symptoms.

Control of Attention

The main features of attentional control such as selection, choice impulsivity, perseveration and speed of processing are all dependent on PFC functions [87], and are intimately related to fundamental aspects of executive control [71]. Healthy subjects with COMT Val/Val and Val/Met genotypes have shown higher inattention compared to Met/Met individuals on Deviation from Mode test, a variant of Reaction-Time tasks for assessing speed of processing abilities [88]. However, two different studies have found no effect of the COMT Val/Met genotype on measures of attention using the continuous performance test (CPT) [89, 90]. Discrete elements of attentional control functions such as attention, impulse control, perseverative and reactivity-related functions can be effectively studied in experimental rodents using the five choice serial reaction time task which is modeled after its human analogue CPT [91]. Using this task, we

are now accumulating evidence in mice that genetic-driven reductions in COMT activity might have marginal effects on general attentional processes but might have greater selective effects in impulsive and compulsive control (Papaleo *et al*., unpublished observations).

Pharmacological studies have shown that attentional performance on the Deviation from Mode test can be improved with amphetamine administration only in individuals with one or two COMT Val alleles, but not in Met homozygous [88]. This is consistent with previous findings that amphetamine administration failed to improve executive function and working memory in Met/Met subjects [53]. Again, this is presumably due to the inability of COMT Met/Met subjects to compensate robust increases of dopamine in the PFC.

Similar findings have been reported also in pathological states. Individuals with chronic schizophrenia that carry the COMT Met/Met genotype show better attention and speed of processing performances on Trails-A, Trails-B and Digit-Symbol tasks from the Wechsler Adult Intelligence Scale - Revised [92]. Moreover, schizophrenia patients with at least one copy of the Met variant show faster reaction time responses during the Stroop task, another neuropsychological assessment of attentional skills [93]. In contrast, children with 22q11.2 Deletion Syndrome (22qDS) and hemizygous for the COMT Met allele show greater attentional deficits compared to subjects with the Val allele as measured with the Attention Network Task (ANT) [94]. This might be due to the extreme situation in 22qDS, in which COMT is always hemideleted, and then the COMT Met condition might have opposite cognitive effects due to the consequent exaggerated dopamine overload. A similar explanation might be given in children with ADHD, in which methylphenidate treatment had beneficial effects only in COMT Val carriers but not Met/Met subjects in measures of inattention and impulsivity [95]. As ADHD is a neurodevelopmental disorder and COMT-ADHD associations have been studied prevalently in children, we will discuss this in more detail in the "early intervention" paragraphs below.

In conclusion, COMT should be considered a target for medical intervention in conditions characterized by altered attentional and impulsive behaviors. Moreover, patients with the COMT Val/Val genotype might have a larger margin of therapeutic improvement compared to Met-allele carriers.

Long-Term Memory

Recent theories of memory consolidation point to a functional role of hippocampal interaction with the PFC in the storage of permanent memories [96-98]. Even if much less investigated, we hypothesize that COMT might then affect also long-term memory consolidation because of its modulation of cortical networks.

Classical fear conditioning tests are very suitable to test this hypothesis, as fear-associated memories are long-lasting [98]. Moreover, these tasks imply strong stress- and emotional-related components that can trigger increased dopamine levels in the PFC [99, 100] and are modulated by COMT genetic variants [37]. Healthy subjects with the COMT Met/Met genotype show a greater fear-potentiated startle reaction during recall of fear learning compared to Val/Val individuals [101]. This might suggests a stronger fear associated memory and inability to extinguish the conditioned fear in COMT Met homozygous subjects. Similarly, other studies have reported that healthy individuals with the COMT Met allele have higher scores on long-term memory test [102] and recall of episodic memory [103]. Conversely, COMT Val-carriers show poorer performance during retrieval of a recognition memory task concomitant with increased activation of ventro-lateral PFC and decreased hippocampal formation activation [104]. More fMRI studies further demonstrated differences in activation during long-term memory encoding and retrieval with the Val/Val subjects showing greater, therefore less efficient, activation of the PFC [105].

Particularly interesting is the extinction process of long-term memories that is thought to be dependent on PFC [106]. This might be an important memory component in pathologies such as post-traumatic stress disorders (PTSD). Moreover, PTSD is an anxiety disorder reflecting deficits in emotional regulation, a key feature also regulated by COMT [37]. Indeed, COMT Met homozygous subjects have been shown to present higher risk of developing PTSD [107].

In conclusion, these findings suggest that COMT genetic differences might modulate long-term memory formation and recall even if the mediating mechanisms and the exact COMT role are still poorly explored. In particular, additional investigations considering the diversity of the tasks employed and the presence of other confounding factors such as age, ethnicity, and psychiatric diagnosis are required to better disentangle the involvement of COMT in long-term memory formation. Experimental animal models are a suitable tool for these kinds of memory studies and might be useful to improve the treatment of psychiatric disorders such as PTSD or other anxiety-related disorders.

COMT AS A TARGET AND BIOMARKER FOR EARLY INTERVENTION

COMT in the Neurodevelopment of PFC-Dependent Cognitive Functions

The PFC dopamine system is refined until young adulthood in humans [108, 109], as well as in primates [110, 111] and in rodents [112]. This process is directly correlated to a gradual improving performance from infancy to adulthood in behavioral tasks mediated by the PFC [113-115]. Abnormal development of these circuits might thus provoke a serious impact on adult social and working daily life. Clinically, this might be evident in the PFC-dependent cognitive impairments that characterize a number of neurodevelopmental diseases such as schizophrenia [116], 22qDS [117], ADHD [118, 119], obsessive-compulsive disorder [120-122] and phenylketonuria (PKU) [123, 124]. Importantly, the first cognitive symptoms in these disorders often arise in childhood [120, 123, 125-127], constituting a crucial phenotype for early diagnosis and intervention.

COMT may critically modulate cognitive development because of its: a) unique role in the catabolism of dopamine in the PFC [12]; b) expression from early embryonic stages [128]; c) increase in expression and enzymatic activity during postnatal maturation which follow the refinement of the dopamine system and the maturation of PFC-dependent

cognitive functions [113, 114] (for more details see Fig. **1**). The increased COMT activity in the PFC from neonates to adulthood has been hypothesized to reflect an increasing need for dopamine catabolism, accompanying the expansion in dopaminergic innervations that occurs during adolescence [129]. Furthermore, the COMT Val/Met polymorphism impacts prefrontal connectivity in young adults [130] and frontal cortical thickness already in children and adolescents [131], indicating that COMT modulates brain morphology and connectivity from infancy. However, despite the contribution of COMT variation to individual differences in cognitive performance and vulnerability to PFC-related dysfunctions, its exact role in neurodevelopment during childhood is still poorly understood.

COMT and Early Intervention

We hypothesize that COMT might constitute a useful target in the modulation of cognitive functions/dysfunctions during ontogeny. Diamond *et al*. [132] found that healthy children from 6 to 14 years with COMT Met/Met genotype perform better on the Dots-Mixed tasks than Val carriers. This task requires working memory and behavioral inhibition; both are sensitive to dopamine levels in the PFC [133]. Moreover, no COMT-dependent differences were observed (in these same children) on PFC-independent tasks requiring recall memory [132]. Barnett's workgroup tested the hypothesis that a combination of five COMT SNPs (rs 4680: Val^{158}Met SNP, SNP rs 6269 in the P1 promoter, SNP rs 2075507 in the P2 promoter, rs 165599: a SNP in the 3'UTR, rs 4633 in exon 3 and rs 4818 in exon 4) predicts working memory performance in 10-year-old children. Interestingly, they found that the 3-SNPs haplotype leading to the greater increase in COMT enzymatic activity exerts the major working memory disadvantages [134]. However, a different pattern of behavioral response was reported by Wahlstrom's group in adolescents: COMT Met/Met and Val/Val adolescents performed worse than COMT Val/Met in tasks requiring attention and working memory [135]. These apparently contrasting results might depend on the shifting profiles in dopamine transmission and COMT enzymatic activity across postnatal development. In fact, dopamine turnover is highest during infancy [136], basal PFC dopamine reaches a peak in adolescence [110, 112, 113], and COMT activity undergoes elevation from infancy to adulthood [129]. Moreover, during adolescence further changes in the dopamine system might be sex-dependent [137] and COMT activity is also regulated by estrogens [138]. Thus, in these evolving conditions, slight differences in COMT activity (e.g. between Val/Val, Val/Met and Met/Met) might act differently on the inverted U-shaped curve to give optimal or non-optimal dopamine levels depending on the developmental stage. In agreement, a longitudinal and cross-sectional investigation of subjects from 6 to 20 years old demonstrated that COMT Met/Met subjects gradually switched from being underperformers (at 6 years) to exhibiting the best performance in working memory task during adolescence (around 16-18 years) [139]. Taken together, these findings suggest that COMT genetic variations have a crucial neurobehavioral impact in childhood but that their effects are strongly dependent on developmental stage.

These COMT-related effects might also critically interact with environmental factors during development. For instance, Voelker and colleagues [140] provided evidence that the COMT Val/Met variant interacts with parenting quality and influences the executive attention network in healthy toddlers between 18 and 21 months. Parental quality was assessed observing parents' behavior while playing with their children. This study found that higher COMT activity in toddlers enhanced the beneficial effects of parental care and improved the development of executive attention.

Disturbances in executive function abilities during early learning periods may lead to severe impairments and potential detrimental disparities later in life [141, 142]. In this context, preschool and kindergarten children may benefit from activities aimed at improving executive abilities [142, 143]. COMT might play an important role in these processes. For example, we already mentioned that cognitive rehabilitation using function-specific computer-aided exercise improves cognitive outcome in patients with schizophrenia, with COMT Met carriers being more likely to acquire enhanced benefits from these cognitive exercises [69]. These findings emphasize the importance of early intervention in neurodevelopmental diseases and the value of pre-intervention on cognitive and social interaction to ameliorate disease progression. Despite the recognized importance of early intervention, neither specific drugs nor behavioral therapies are currently available to ameliorate and/or prevent PFC-dependent cognitive disabilities. Further studies focused on the role of COMT in the development of executive functions in infancy, childhood and adolescence are needed and could provide new important insights.

The 22qDS syndrome provides a good example of a complex neurodevelopmental disease in which COMT might have prominent effects in the development of cognitive dysfunctions [94, 145-148]. Indeed, significant associations have been found between COMT genetic variations and cognitive impairments in 22qDS, even if results are often inconsistent [94, 149]. Bearden and colleagues [150] found that children with 22qDS and hemizygous for the COMT-Met allele show enhanced performance on the digit span working memory task compared to children with 22qDS but COMT Val hemizygous. In contrast, other studies demonstrated that 22qDS young individuals carrying the low-activity COMT-Met allele show a more robust age-dependent cognitive decline from 13 to 18 years and gray matter volume reduction in PFC as compared with 22qDS Val carriers [145, 149]. The reason for this discrepancy is still unknown, but may be related to the different age of subjects (13-18 years old in Gothelf *vs* 11 years old in Bearden). Moreover, in 22qDS several genes other than COMT are present in hemizygosity. Thus, more complex genetic mechanisms that might interact and/or compensate for COMT deficiency should be considered, too. Longitudinal studies specifically considering the impact of COMT alone and/or epistatic interactions with contiguous genes in the 22q11.2 band and other additional loci in the genome should be performed in the future. Mouse models of 22qDS genetic deletion and other relevant mutant mice may help to address these questions faster than more complex clinical studies.

Another interesting example of a neurodevelopmental disorder in which COMT might have great potential as a drug target is PKU. Children with PKU lack phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine, and suffer severe brain damage and mental retardation [151]. The primary cause of these cognitive deficits is the high levels of phenylalanine that produce a selective reduction in dopamine and dopamine metabolites in the PFC [152]. Early treatment for PKU consists in reducing dietary intake of phenylalanine, restoring IQ to a normal range and preventing signs of gross brain dysfunction [151]. However, if not strictly monitored to keep phenylalanine levels very low [151], this treatment is still not able to ameliorate specific cognitive deficits dependent on the PFC, as shown by impairments in the WCST and in the Tower of London tasks [123, 153, 154]. Compliance with the dietary restrictions in PKU is a very difficult issue, because it is rigid, not palatable and hard to follow [155]. Moreover children and adolescents following the phenylalanine-restricted diet might show growth retardation, bone pathologies and deficient intake of various nutrients [153]. We then speculate that COMT might be potentially useful as a drug target for a joint therapy to improve the prognosis and the quality of life in PKU patients.

COMT has also been implicated in ADHD [156-158]. This disorder appears during childhood and is characterized by age-inappropriate inattention, hyperactivity and impulsivity believed to depend on dopaminergic hyperfunctioning [159]. Children with ADHD that carry the COMT Val/Val genotype show higher inattention in the Task-Orientated Behavior, a task used to discriminate subjects with ADHD and that highlights disturbances in problem-focused activity [156]. Furthermore, ADHD subjects with the COMT Val allele have a higher number of false alarm responses on the CPT test [157]. In contrast, ADHD children with the Val/Val genotype showed significantly better performance on a sustained attention task compared to subjects with at least one copy of the Met allele [158]. This discrepancy might be due to the high percentage of children under methylphenidate (MPH) medication in the latter study that could exacerbate dopamine signaling and interact with the COMT genotype. In fact, COMT genetic modifications can also differently modulate the response to MPH pharmacological treatments in children with ADHD. MPH is the main drug for children affected by ADHD [160] and is effective in 75% of children diagnosed with ADHD improving attention, self control, school performance and reducing impulsiveness [161]. MPH exerts its therapeutic effects through an increase in dopamine signaling [162]. Over a period of 3-6 months of MPH treatment, children (mean age 10 years) diagnosed with ADHD and carrying the COMT Val allele were more likely to benefit from MPH treatment than children with the Met/Met polymorphism [163]. However, this COMT-MPH interaction might be visible only in the long run as acute MPH treatment in ADHD children (mean age 9 years) seems to give benefits in measures of sustained attention in both COMT Val and Met subjects [156]. These findings suggest that COMT might modulate MPH therapeutic effects in ADHD. However, further studies considering different developmental ages, interaction with sex, and other COMT functional haplotypes are needed to effectively predict COMT-dependent treatment response modulations in ADHD.

In conclusion, a full understanding and dissection of all the genetic factors (such as COMT) involved in the development of PFC-driven behaviors may help to design more effective and less risky preventive interventions in children based on personalized healthcare. In this context, COMT represents both a possible genetic biomarker and a promising target in the early treatment of PFC-dependent cognitive impairments during development.

CONCLUSIONS AND FUTURE DIRECTIONS

The literature discussed in this review indicates a subtle (though important) effect of COMT, on specific aspects of frontal cognition. COMT genetic polymorphisms might prove to be useful biomarkers in presymptomatic genetic testing for estimating individual differences and the vulnerability/risk to conditions characterized by executive dysfunctions. Moreover, COMT polymorphisms can modulate PFC-dependent cognitive responses to drugs, especially those that impact the dopaminergic system (e.g. antipsychotics, MPH etc.). Moreover, despite the fact that COMT genetic background produces individual cognitive differences; these can be modulated by pharmacological treatment later on in life. Thus COMT might constitute a promising drug target, and COMT genetic background might be used in the future as an important factor in determining the best treatment and/or drug dosage aiming to ameliorate cognitive dysfunctions. Much less is known about the putative impact of COMT on cognitive abilities regulated by other brain areas other than PFC or regions that may interact with the PFC itself. Thus, future studies will need to explore this facet using parallel effective human and mouse paradigms. In particular, genetically modified mouse models provide unique advantages for unraveling molecular mechanisms and effectiveness of new therapeutic strategies based on neural circuits regulated by COMT activity.

COMT modulates PFC-dependent cognitive functions which are altered in many debilitating psychiatric disorders such as schizophrenia, ADHD, obsessive-compulsive disorder, and 22qDS. To better unravel the modulation of COMT as potential risk factor in these mental disorders, future studies should consider all validated functional COMT genetic variations and not only the Val/Met single nucleotide polymorphism. This might also allow preventing the overt outcome of mental illnesses and to better ameliorate the associated cognitive impairments (or at least a subgroup of them) on a person-by-person basis, with safer and more effective results.

Identification of suspected genetic variations might indicate, already in early development, conditions that are more likely to develop into cognitive disadvantages or even psychiatric illnesses. Due to the vulnerability of brain maturation during infancy and adolescence, peculiar attention has to be paid to the precocious development of cognitive deficits that are implicated in so many disorders [116-118, 120, 124]. New pharmacological and cognitive interventions must take into account their impact on brain maturation and their interaction with genetic modifications

that might modulate the effectiveness of the interventions (e.g. COMT).

Individual polymorphisms do not act by themselves but interact with environmental and other genetic factors. This means that we should not overlook a number of interacting factors such as the additive or compensatory effect of multiple genes, social context and the effect of sex. For example, estrogens affect COMT [164] and the same COMT Val/Met variant might result in different PFC dopamine levels in adult males compared to females [12]. Moreover, there is evidence for sexually dimorphic associations between COMT polymorphisms and cognitive or psychiatric phenotypes, such as in schizophrenia [165, 166], obsessive-compulsive disorder [167, 168] and ADHD [169]. For complex brain functions, it is likely necessary to examine interactions with multiple polymorphisms within a gene, between genes, and with environmental factors. This complexity can be addressed in future investigations. Studies using genetically modified mice, closely paired with human genetic/behavioral studies addressing multiple gene alterations, may contribute to understanding the interactions between genes that impact the PFC networks and that are critical for the development of cognitive alterations. The findings from research of this kind will facilitate progress towards the development of new and more efficient *ad personam* therapeutic strategies in psychiatric disorders and their cognitive components.

ACKNOWLEDGEMENTS

We thank Dr. G. Carr and A. Bebensee for critical reading of the manuscript. Authors were supported by the Istituto Italiano di Tecnologia (DS, SS and FP), the Marie Curie FP7-Reintegration-Grant N° 268247 (FP and SS) and the Italian Ministry of Health-Young Researcher Project 2008-GR3 (MLS). The authors declare that they have no financial conflicts of interest.

ABBREVIATIONS

ADHD	=	Attention deficit hyperactive disorder
COMT	=	Catechol-O-metyltransferase
CPT	=	Continuous performance test
22qDS	=	22q11.2 deletion syndrome
fMRI	=	Functional magnetic resonance imaging
ID/ED	=	Intradimensional/extradimensional
MB-COMT	=	Membrane bound COMT
MPH	=	Methylphenidate
PFC	=	Prefrontal cortex
PKU	=	Phenylketonuria
PTSD	=	Post-traumatic stress disorders
SNP	=	Single nucleotide polymorphism
WCST	=	Wisconsin card sorting test

REFERENCES

[1] Davies, W. Using mouse models to investigate sex-linked genetic effects on brain, behaviour and vulnerability to neuropsychiatric disorders, *Brain Res Bull,* **2011**.

[2] Savitz, J.; Solms, M.; Ramesar, R. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav.,* **2006**, *5*, 311-328.

[3] Barnett, J.H.; Xu, K.; Heron, J.; Goldman, D.; Jones, P.B. Cognitive effects of genetic variation in monoamine neurotransmitter systems: A population-based study of COMT, MAOA, and 5HTTLPR. *Am. J. Med. Genet. Part B Neuropsych. Genet.,* **2011**, *156*, 158-167.

[4] Papaleo, F.; Lipska, B.K.; Weinberger, D.R. Mouse models of genetic effects on cognition: Relevance to schizophrenia. *Neuropharmacology,* **2012**, *62*(3), 1204-1220.

[5] Davies, G.; Tenesa, A.; Payton, A.; Yang, J.; Harris, S.E.; Liewald, D.; Ke, X.; Le Hellard, S.; Christoforou, A.; Luciano, M.; McGhee, K.; Lopez, L.; Gow, A.J.; Corley, J.; Redmond, P.; Fox, H.C.; Haggarty, P.; Whalley, L.J.; McNeill, G.; Goddard, M.E.; Espeseth, T.; Lundervold, A.J.; Reinvang, I.; Pickles, A.; Steen, V.M.; Ollier, W.; Porteous, D.J.; Horan, M.; Starr, J.M.; Pendleton, N.; Visscher, P.M.; Deary, I.J. Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Mol. Psychiatry,* **2011**, *16*, 996-1005.

[6] Axelrod, J.; Tomchick, R. Enzymatic O-Methylation of epinephrine and other catechols. *J. Biol. Chem.,* **1958**, *233*, 702-705.

[7] Männistö, P.T.; Kaakkola, S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacol. Rev.,* **1999**, *51*, 593-628.

[8] Chen, J.; Lipska, B.K.; Halim, N.; Ma, Q.D.; Matsumoto, M.; Melhem, S.; Kolachana, B.S.; Hyde, T.M.; Herman, M.M.; Apud, J.; Egan, M.F.; Kleinman, J.E.; Weinberger, D.R. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am. J. Hum. Genet.,* **2004**, *75*, 807-821.

[9] Chen, J.; Song, J.; Yuan, P.; Tian, Q.; Ji, Y.; Ren-Patterson, R.; Liu, G.; Sei, Y.; Weinberger, D.R. Orientation and cellular distribution of membrane-bound Catechol-O-methyltransferase in cortical neurons. *J. Biol. Chem.,* **2011**, *286*, 34752-34760.

[10] Roth, J.A. Membrane-bound catechol-O-methyltransferase: a reevaluation of its role in the O-methylation of the catecholamine neurotransmitters. *Rev. Physiol. Biochem. Pharmacol.,* **1992**, *120*, 1-29.

[11] Yavich, L.; Forsberg, M.M.; Karayiorgou, M.; Gogos, J.A.; Mannisto, P.T. Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J. Neurosci.,* **2007**, *27*, 10196-10209.

[12] Gogos, J.A.; Morgan, M.; Luine, V.; Santha, M.; Ogawa, S.; Pfaff, D.; Karayiorgou, M. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc. Natl. Acad. Sci.,* **1998**, *95*, 9991-9996.

[13] Matsumoto, M.; Weickert, C.S.; Akil, M.; Lipska, B.K.; Hyde, T.M.; Herman, M.M.; Kleinman, J.E.; Weinberger, D.R. Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. *Neuroscience,* **2003**, *116*, 127-137.

[14] Karoum, F.; Chrapusta, S.J.; Egan, M.F. 3-methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. *J. Neurochem.,* **1994**, *63*, 972-979.

[15] Goldman-Rakic, P.S. The cortical dopamine system: role in memory and cognition. *Adv. Pharmacol.,* **1998**, *42*, 707-711.

[16] Verma, A.; Moghaddam, B. NMDA receptor antagonists impair prefrontal cortex function as assessed *via* spatial delayed alternation performance in rats: modulation by dopamine. *J. Neurosci.,* **1996**, *16*, 373-379.

[17] Seamans, J.K.; Gorelova, N.; Durstewitz, D.; Yang, C.R. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. *J. Neurosci.,* **2001**, *21*, 3628-3638.

[18] Williams, G.V.; Goldman-Rakic, P.S. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature,* **1995**, *376*, 572-575.

[19] Arnsten, A.F.; Cai, J.X.; Murphy, B.L.; Goldman-Rakic, P.S. Dopamine D1 receptor mechanisms in the cognitive performance

of young adult and aged monkeys. *Psychopharmacology,* **1994**, *116*, 143-151.

[20] Vijayraghavan, S.; Wang, M.; Birnbaum, S.G.; Williams, G.V.; Arnsten, A.F. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat. Neurosci.,* **2007**, *10*, 376-384.

[21] Lachman, H.M.; Papolos, D.F.; Saito, T.; Yu, Y.M.; Szumlanski, C.L.; Weinshilboum, R.M. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics,* **1996**, *6*, 243-250.

[22] Nackley, A.G.; Shabalina, S.A.; Tchivileva, I.E.; Satterfield, K.; Korchynskyi, O.; Makarov, S.S.; Maixner, W.; Diatchenko, L. Human catechol-o-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science,* **2006**, *314*, 1930-1933.

[23] Meyer-Lindenberg, A.; Nichols, T.; Callicott, J.H.; Ding, J.; Kolachana, B.; Buckholtz, J.; Mattay, V.S.; Egan, M.; Weinberger, D.R. Impact of complex genetic variation in COMT on human brain function. *Mol. Psychiatry,* **2006**, *11*, 867-877.

[24] Bray, N.J.; Buckland, P.R.; Williams, N.M.; Williams, H.J.; Norton, N.; Owen, M.J.; O Donovan, M.C. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. *Am. J Hum. Genet.,* **2003**, *73*, 152-161.

[25] Bertocci, B.; Miggiano, V.; Da Prada, M.; Dembic, Z.; Lahm, H.W.; Malherbe, P. Human catechol-O-methyltransferase: cloning and expression of the membrane-associated form. *Proc. Natl. Acad. Sci.,* **1991**, *88*, 1416-1420.

[26] Lundstrom, K.; Salminen, M.; Jalanko, A.; Savolainen, R.; Ulmanen, I. Cloning and characterization of human placental catechol-O-methyltransferase cDNA. *DNA Cell Biol.,* **1991**, *10*, 181-189.

[27] Floderus, Y.; Ross, S.B.; Wetterberg, L. Erythrocyte catechol-O-methyltransferase activity in a Swedish population. *Clin. Genet.,* **1981**, *19*, 389-392.

[28] Robbins, T.W. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Phil. Trans. R. Soc. B. Biol. Sci.,* **2007**, *362*, 917-932.

[29] Robbins, T.W. Chemical neuromodulation of frontal-executive function in humans and other animals. *Exp. Brain Res.,* **2000**, *133*, 130-138.

[30] Eling, P.; Derckx, K.; Maes, R. On the historical and conceptual background of the Wisconsin Card Sorting Test. *Brain Cogn.,* **2008**, *67*, 247-253.

[31] Milner, B. Effects of different brain lesions on card-sorting: the role of the frontal lobes. *Arch. Neurol.,* **1963**, *9*, 100-110.

[32] Roberts, A.C.; Robbins, T.W.; Everitt, B.J. The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. *Q. J. Exp. Psychol. B.,* **1988**, *40*, 321-341.

[33] Barnett, J.H.; Robbins, T.W.; Leeson, V.C.; Sahakian, B.J.; Joyce, E.M.; Blackwell, A.D. Assessing cognitive function in clinical trials of schizophrenia. *Neurosci Amp. Biobehav. Rev.,* **2010**, *34*, 1161-1177.

[34] Birrell, J.M.; Brown, V.J. Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J. Neurosci.,* **2000**, *20*, 4320-4324.

[35] Garner, J.P.; Thogerson, C.M.; Würbel, H.; Murray, J.D.; Mench, J.A. Animal neuropsychology: Validation of the Intra-Dimensional Extra-Dimensional set shifting task for mice. *Behav. Brain Res.,* **2006**, *173*, 53-61.

[36] Bissonette, G.B.; Martins, G.J.; Franz, T.M.; Harper, E.S.; Schoenbaum, G.; Powell, E.M. Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. *J Neurosci,* **2008**, *28*, 11124-11130.

[37] Papaleo, F.; Crawley, J.N.; Song, J.; Lipska, B.K.; Pickel, J.; Weinberger, D.R.; Chen, J. Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. *J. Neurosci.,* **2008**, *28*, 8709-8723.

[38] Owen, A.M.; Roberts, A.C.; Polkey, C.E.; Sahakian, B.J.; Robbins, T.W. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia,* **1991**, *29*, 993-1006.

[39] Rahman, S.; Sahakian, B.J.; Hodges, J.R.; Rogers, R.D.; Robbins, T.W. Specific cognitive deficits in mild frontal variant frontotemporal dementia. *Brain,* **1999**, *122*, 1469-1493.

[40] Barch, D.M.; Braver, T.S.; Carter, C.S.; Poldrack, R.A.; Robbins, T.W. CNTRICS final task selection: executive control. *Schizophr. Bull.,* **2009**, *35*, 115-135.

[41] Egerton, A.; Reid, L.; McKerchar, C.E.; Morris, B.J.; Pratt, J.A. Impairment in perceptual attentional set-shifting following PCP administration: a rodent model of set-shifting deficits in schizophrenia. *Psychopharmacology,* **2005**, *179*, 77-84.

[42] Goetghebeur, P.; Dias, R. Comparison of haloperidol, risperidone, sertindole, and modafinil to reverse an attentional set-shifting impairment following subchronic PCP administration in the rat—a back translational study. *Psychopharmacology,* **2009**, *202*, 287-293.

[43] Weinberger, D.R.; Berman, K.F.; Zec, R.F. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. *Arch. Gen. Psychiatry,* **1986**, *43*, 114-124.

[44] Hampshire, A.; Owen, A.M. Fractionating attentional control using event-related fMRI. *Cereb. Cortex,* **2006**, *16*, 1679-1689.

[45] Dias, R.; Robbins, T.W.; Roberts, A.C. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature,* **1996**, *380*, 69-72.

[46] Roberts, A.; De Salvia, M.; Wilkinson, L.; Collins, P.; Muir, J.; Everitt, B.; Robbins, T. 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: possible interactions with subcortical dopamine. *J. Neurosci,* **1994**, *14*, 2531-2544.

[47] Brown, V.J.; Bowman, E.M. Rodent models of prefrontal cortical function. *Trends Neurosci.,* **2002**, *25*, 340-343.

[48] Berman, K.F.; Ostrem, J.L.; Randolph, C.; Gold, J.; Goldberg, T.E.; Coppola, R.; Carson, R.E.; Herscovitch, P.; Weinberger, D.R. Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: A positron emission tomography study. *Neuropsychologia,* **1995**, *33*, 1027-1046.

[49] Barnett, J.H.; Jones, P.B.; Robbins, T.W.; Muller, U. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Mol. Psychiatry,* **2007**, *12*, 502-509.

[50] Malhotra, A.K.; Kestler, L.J.; Mazzanti, C.; Bates, J.A.; Goldberg, T.; Goldman, D.A. Functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am. J. Psychiatry,* **2002**, *159*, 652-654.

[51] Joober, R.; Gauthier, J.; Lal, S.; Bloom, D.; Lalonde, P.; Rouleau, G.; Benkelfat, C.; Labelle, A. Catechol-O-Methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Arch. Gen. Psychiatry,* **2002**, *59*, 662-663.

[52] Egan, M.F.; Goldberg, T.E.; Kolachana, B.S.; Callicott, J.H.; Mazzanti, C.M.; Straub, R.E.; Goldman, D.; Weinberger, D.R. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc. Natl. Acad. Sci USA,* **2001**, *98*, 6917-6922.

[53] Mattay, V.S.; Goldberg, T.E.; Fera, F.; Hariri, A.R.; Tessitore, A.; Egan, M.F.; Kolachana, B.; Callicott, J.H.; Weinberger, D.R. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc. Natl. Acad. Sci.,* **2003**, *100*, 6186-6191.

[54] Rosa, A.; Peralta, V.; Cuesta, M.J.; Zarzuela, A.; Serrano, F.; Martinez-Larrea, A.; Fananas, L. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *Am. J. Psychiatry,* **2004**, *161*, 1110-1112.

[55] Diaz-Asper, C.M.; Weinberger, D.R.; Goldberg, T.E. Catechol-O-methyltransferase polymorphisms and some implications for cognitive therapeutics. *NeuroRx,* **2006**, *3*, 97-105.

[56] Tsai, S.-J.; Yu, Y.W.Y.; Chen, T.-J.; Chen, J.-Y.; Liou, Y.-J.; Chen, M.-C.; Hong, C.-J. Association study of a functional catechol-O-methyltransferase-gene polymorphism and cognitive function in healthy females. *Neurosci. Lett.,* **2003**, *338*, 123-126.

[57] Ho, B.C.; Wassink, T.H.; O'Leary, D.S.; Sheffield, V.C.; Andreasen, N.C. Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Mol. Psychiatry,* **2005**, *10*, 287-298.

[58] Harrison, P.J.; Tunbridge, E.M. Catechol-O-Methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology,* **2007**, *33*, 3037-3045.

[59] Robbins, T.; Roberts, A. Differential regulation of fronto-executive function by the monoamines and acetylcholine. *Cereb. Cortex,* **2007**, *17*, i151-i160.

[60] Williams-Gray, C.H.; Hampshire, A.; Barker, R.A.; Owen, A.M. Attentional control in Parkinson's disease is dependent on COMT val158met genotype. *Brain,* **2008**, *131*, 397-408.

[61] Williams-Gray, C.H.; Hampshire, A.; Robbins, T.W.; Owen, A.M.; Barker, R.A. Catechol O-Methyltransferase val158met genotype influences frontoparietal activity during planning in patients with parkinson's disease. *J. Neurosci.,* **2007**, *27*, 4832-4838.

[62] Foltynie, T.; Goldberg, T.E.; Lewis, S.G.J.; Blackwell, A.D.; Kolachana, B.S.; Weinberger, D.R.; Robbins, T.W.; Barker, R.A. Planning ability in Parkinson's disease is influenced by the COMT val158met polymorphism. *Movem. Disord.,* **2004**, *19*, 885-891.

[63] Williams-Gray, C.H.; Evans, J.R.; Goris, A.; Foltynie, T.; Ban, M.; Robbins, T.W.; Brayne, C.; Kolachana, B.S.; Weinberger, D.R.; Sawcer, S.J.; Barker, R.A. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort, *Brain,* **2009**, *132*, 2958-2969.

[64] Rakshi, J.S.; Uema, T.; Ito, K.; Bailey, D.L.; Morrish, P.K.; Ashburner, J.; Dagher, A.; Jenkins, I.H.; Friston, K.J.; Brooks, D.J. Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [18F]dopa-PET study. *Brain,* **1999**, *122*, 1637-1650.

[65] Kaasinen, V.; Nurmi, E.; Brück, A.; Eskola, O.; Bergman, J.; Solin, O.; Rinne, J.O. Increased frontal [18F] fluorodopa uptake in early Parkinson's disease: sex differences in the prefrontal cortex. *Brain,* **2001**, *124*, 1125-1130.

[66] Tunbridge, E.M.; Bannerman, D.M.; Sharp, T.; Harrison, P.J. Catechol-O-Methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. *J. Neurosci,* **2004**, *24*, 5331-5335.

[67] Apud, J.A.; Mattay, V.; Chen, J.; Kolachana, B.S.; Callicott, J.H.; Rasetti, R.; Alce, G.; Iudicello, J.E.; Akbar, N.; Egan, M.F.; Goldberg, T.E.; Weinberger, D.R. Tolcapone improves cognition and cortical information processing in normal human subjects. *Neuropsychopharmacology,* **2006**, *32*, 1011-1020.

[68] Green, M.F.; Nuechterlein, K.H. Should schizophrenia be treated as a neurocognitive disorder? *Schizophr. Bull.,* **1999**, *25*, 309-319.

[69] Bosia, M.; Bechi, M.; Marino, E.; Anselmetti, S.; Poletti, S.; Cocchi, F.; Smeraldi, E.; Cavallaro, R. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neurosci. Lett.,* **2007**, *417*, 271-274.

[70] Baddeley, A.Working memory. *Curr. Biol.,* **2010**, *20*, R136-R140.

[71] Chudasama, Y.; Robbins, T.W. Functions of frontostriatal systems in cognition: Comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biol. Psychology,* **2006**, *73*, 19-38.

[72] Brozoski, T.; Brown, R.; Rosvold, H.; Goldman, P. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science,* **1979**, *205*, 929-932.

[73] Weickert, T.W.; Goldberg, T.E.; Mishara, A.; Apud, J.A.; Kolachana, B.S.; Egan, M.F.; Weinberger, D.R. Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications, *Biol. Psychiatry,* **2004**, *56*, 677-682.

[74] Pomarol-Clotet, E.; Fatjó-Vilas, M.; McKenna, P.J.; Monté, G.C.; Sarró, S.; Ortiz-Gil, J.; Aguirre, C.; Gomar, J.J.; Guerrero, A.; Landin, R.; Capdevila, A.; Fañanás, L.; Salvador, R. COMT Val158Met polymorphism in relation to activation and de-activation in the prefrontal cortex: A study in patients with schizophrenia and healthy subjects. *NeuroImage,* **2010**, *53*, 899-907.

[75] Callicott, J.H.; Bertolino, A.; Mattay, V.S.; Langheim, F.J.P.; Duyn, J.; Coppola, R.; Goldberg, T.E.; Weinberger, D.R. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb. Cortex,* **2000**, *10*, 1078-1092.

[76] Goldberg, T.E.; Egan, M.F.; Gscheidle, T.; Coppola, R.; Weickert, T.; Kolachana, B.S.; Goldman, D.; Weinberger, D.R. Executive Subprocesses in Working Memory: Relationship to Catechol-O-methyltransferase Val158Met Genotype and Schizophrenia. *Arch. Gen. Psychiatry,* **2003**, *60*, 889-896.

[77] Tunbridge, E.M.; Harrison, P.J.; Weinberger, D.R. Catechol-o-Methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biol. Psychiatry,* **2006**, *60*, 141-151.

[78] Stefanis, N.C.; Os, J.V.; Avramopoulos, D.; Smyrnis, N.; Evdokimidis, I.; Hantoumi, I.; Stefanis, C.N. Variation in catechol-o-methyltransferase val158met genotype associated with schizotypy but not cognition: A population study in 543 young men. *Biol. Psychiatry,* **2004**, *56*, 510-515.

[79] Ursini, G.; Bollati, V.; Fazio, L.; Porcelli, A.; Iacovelli, L.; Catalani, A.; Sinibaldi, L.; Gelao, B.; Romano, R.; Rampino, A.; Taurisano, P.; Mancini, M.; Di Giorgio, A.; Popolizio, T.; Baccarelli, A.; De Blasi, A.; Blasi, G.; Bertolino, A. Stress-related methylation of the catechol-O-methyltransferase Val 158 allele predicts human prefrontal cognition and activity. *J. Neurosci.,* **2011**, *31*, 6692-6698.

[80] Farrell, S.M.; Tunbridge, E.M.; Braeutigam, S.; Harrison, P.J. COMT Val158Met genotype determines the direction of cognitive effects produced by catechol-o-methyltransferase inhibition. *Biol. Psychiatry,* **2012**, *71*(6), 538-544.

[81] Giakoumaki, S.G.; Roussos, P.; Bitsios, P. Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism. *Neuropsychopharmacology,* **2008**, *33*, 3058-3068.

[82] Bertolino, A.; Caforio, G.; Blasi, G.; De Candia, M.; Latorre, V.; Petruzzella, V.; Altamura, M.; Nappi, G.; Papa, S.; Callicott, J.H.; Mattay, V.S.; Bellomo, A.; Scarabino, T.; Weinberger, D.R.; Nardini, M. Interaction of COMT Val108/158 Met genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. *Am. J. Psychiatry,* **2004**, *161*, 1798-1805.

[83] Manoach, D.S. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr. Res.,* **2003**, *60*, 285-298.

[84] Jogia, J.; Dima, D.; Kumari, V.; Frangou, S. Frontopolar cortical inefficiency may underpin reward and working memory dysfunction in bipolar disorder. *World J. Biol. Psychiatry,* **2011**, in press.

[85] Murrough, J.W.; Iacoviello, B.; Neumeister, A.; Charney, D.S.; Iosifescu, D.V. Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. *Neurobiol. Learn. Mem.,* **2011**, *96*(4), 553-563.

[86] Martinussen, R.; Hayden, J.; Hogg-Johnson, S.; Tannock, R.A. Meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adoles. Psychiatry,* **2005**, *44*, 377-384.

[87] Chudasama, Y.; Passetti, F.; Rhodes, S.E.; Lopian, D.; Desai, A.; Robbins, T.W. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. *Behav. Brain Res.,* **2003**, *146*, 105-119.

[88] Hamidovic, A.; Dlugos, A.; Palmer, A.A.; de Wit, H. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. *Psychiatric Genet.,* **2010**, *20*, 85-92.

[89] Goldberg, T.E.; Egan, M.F.; Gscheidle, T.; Coppola, R.; Weickert, T.; Kolachana, B.S.; Goldman, D.; Weinberger, D.R. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch. Gen. Psychiatry,* **2003**, *60*, 889-896.

[90] Stefanis, N.C.; Van Os, J.; Avramopoulos, D.; Smyrnis, N.; Evdokimidis, I.; Hantoumi, I.; Stefanis, C.N. Variation in catechol-o-methyltransferase val158met genotype associated with schizotypy but not cognition: a population study in 543 young men. *Biol. Psychiatry,* **2004**, *56*, 510-515.

[91] Muir, J.L.; Everitt, B.J.; Robbins, T.W. The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. *Cereb. Cortex,* **1996**, *6*, 470-481.

[92] Bilder, R.M.; Volavka, J.; Czobor, P.á.; Malhotra, A.K.; Kennedy, J.L.; Ni, X.; Goldman, R.S.; Hoptman, M.J.; Sheitman, B.; Lindenmayer, J.-P.; Citrome, L.; McEvoy, J.P.; Kunz, M.; Chakos, M.; Cooper, T.B.; Lieberman, J.A. Neurocognitive correlates of the

COMT Val158Met polymorphism in chronic schizophrenia. *Biol. Psychiatry,* **2002**, *52*, 701-707.

[93] Rosa, E.; Dickinson, D.; Apud, J.; Weinberger, D.; Elvevag, B.COMT Val158Met polymorphism, cognitive stability and cognitive flexibility: an experimental examination. *Behav. Brain Func.,* **2010**, *6*, 53.

[94] Takarae, Y.; Schmidt, L.; Tassone, F.; Simon, T.J. Catechol-O-methyltransferase polymorphism modulates cognitive control in children with chromosome 22q11.2 deletion syndrome. *Cogn. Affect. Behav. Neurosci.,* **2009**, *9*, 83-90.

[95] Kereszturi, E.; Tarnok, Z.; Bognar, E.; Lakatos, K.; Farkas, L.; Gadoros, J.; Sasvari-Szekely, M.; Nemoda, Z. Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. *Am. J. Med. Genet. Part B. Neuropsychiatric Genet.,* **2008**, *147B*, 1431-1435.

[96] Quinn, J.J.; Ma, Q.D.; Tinsley, M.R.; Koch, C.; Fanselow, M.S. Inverse temporal contributions of the dorsal hippocampus and medial prefrontal cortex to the expression of long-term fear memories. *Learn. Mem.,* **2008**, *15*, 368-372.

[97] Restivo, L.; Vetere, G.; Bontempi, B.; Ammassari-Teule, M. The formation of recent and remote memory is associated with time-dependent formation of dendritic spines in the hippocampus and anterior cingulate cortex. *J. Neurosci.,* **2009**, *29*, 8206-8214.

[98] Fanselow, M.S.; Gale, G.D. The amygdala, fear, and memory. *Ann. NY Acad. Sci.,* **2003**, *985*, 125-134.

[99] Feenstra, M.G.P.; Botterblom, M.H. A. Rapid sampling of extracellular dopamine in the rat prefrontal cortex during food consumption, handling and exposure to novelty. *Brain Res.,* **1996**, *742*, 17-24.

[100] Arnsten, A.F. Stress impairs prefrontal cortical function in rats and monkeys: role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. *Prog. Brain Res.,* **2000**, *126*, 183-192.

[101] Lonsdorf, T.B.; Weike, A.I.; Nikamo, P.; Schalling, M.; Hamm, A.O.; Öhman, A. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. *Psychol. Sci.,* **2009**, *20*, 198-206.

[102] Enoch, M.A.; Waheed, J.F.; Harris, C.R.; Albaugh, B.; Goldman, D. COMT Val158Met and cognition: main effects and interaction with educational attainment. *Genes Brain Behav.,* **2009**, *8*, 36-42.

[103] de Frias, C.M.; Annerbrink, K.; Westberg, L.; Eriksson, E.; Adolfsson, R.; Nilsson, L.G. COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behav. Genet.,* **2004**, *34*, 533-539.

[104] Bertolino, A.; Rubino, V.; Sambataro, F.; Blasi, G.; Latorre, V.; Fazio, L.; Caforio, G.; Petruzzella, V.; Kolachana, B.; Hariri, A.; Meyer-Lindenberg, A.; Nardini, M.; Weinberger, D.R.; Scarabino, T. Prefrontal-hippocampal coupling during memory processing is modulated by COMT Val158Met genotype. *Biol. Psychiatry,* **2006**, *60*, 1250-1258.

[105] Schott, B.H.; Seidenbecher, C.I.; Fenker, D.B.; Lauer, C.J.; Bunzeck, N.; Bernstein, H.G.; Tischmeyer, W.; Gundelfinger, E.D.; Heinze, H.J.; Duzel, E. The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. *J. Neurosci.,* **2006**, *26*, 1407-1417.

[106] Quirk, G.J.; Garcia, R.; González-Lima, F. Prefrontal Mechanisms in Extinction of Conditioned Fear. *Biol. Psychiatry,* **2006**, *60*, 337-343.

[107] Kolassa, I.-T.; Kolassa, S.; Ertl, V.; Papassotiropoulos, A.; De Quervain, D.J.F. The risk of posttraumatic stress disorder after trauma depends on traumatic load and the Catechol-O-Methyltransferase Val158Met polymorphism. *Biol. Psychiatry,* **2010**, *67*, 304-308.

[108] Tau, G.Z.; Peterson, B.S. Normal development of brain circuits. *Neuropsychopharmacology,* **2010**, *35*, 147-168.

[109] Wahlstrom, D.; White, T.; Luciana, M. Neurobehavioral evidence for changes in dopamine system activity during adolescence. *Neurosci. Biobehav. Rev.,* **2010**, *34*, 631-648.

[110] Rosenberg, D.R.; Lewis, D.A. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. *J. Comp. Neurol.,* **1995**, *358*, 383-400.

[111] Lambe, E.K.; Krimer, L.S.; Goldman-Rakic, P.S. Differential postnatal development of catecholamine and serotonin inputs to identified neurons in prefrontal cortex of rhesus monkey. *J. Neurosci.,* **2000**, *20*, 8780-8787.

[112] Kalsbeek, A.; Voorn, P.; Buijs, R.M.; Pool, C.W.; Uylings, H.B. Development of the dopaminergic innervation in the prefrontal cortex of the rat. *J. Comp. Neurol.,* **1988**, *269*, 58-72.

[113] Lewis, D.A. Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology,* **1997**, *16*, 385-398.

[114] Luna, B.; Garver, K.E.; Urban, T.A.; Lazar, N.A.; Sweeney, J.A. Maturation of cognitive processes from late childhood to adulthood. *Child Dev.,* **2004**, *75*, 1357-1372.

[115] Casey, B.J.; Galvan, A.; Hare, T.A. Changes in cerebral functional organization during cognitive development. *Curr. Opin. Neurobiol.,* **2005**, *15*, 239-244.

[116] Cannon, T.D.; van Erp, T.G.; Bearden, C.E.; Loewy, R.; Thompson, P.; Toga, A.W.; Huttunen, M.O.; Keshavan, M.S.; Seidman, L.J.; Tsuang, M.T. Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. *Schizophr. Bull.,* **2003**, *29*, 653-669.

[117] Woodin, M.; Wang, P.P.; Aleman, D.; McDonald-McGinn, D.; Zackai, E.; Moss, E.Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. *Genet. Med.,* **2001**, *3*, 34-39.

[118] Sergeant, J.A.; Geurts, H.; Oosterlaan, J.How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behav. Brain Res.,* **2002**, *130*, 3-28.

[119] Shaw, P.; Eckstrand, K.; Sharp, W.; Blumenthal, J.; Lerch, J.P.; Greenstein, D.; Clasen, L.; Evans, A.; Giedd, J.; Rapoport, J.L. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc. Natl. Acad. Sci. USA,* **2007**, *104*, 19649-19654.

[120] Maia, T.V.; Cooney, R.E.; Peterson, B.S. The neural bases of obsessive–compulsive disorder in children and adults. *Develop. Psychopathol.,* **2008**, *20*, 1251-1283.

[121] Huyser, C.; Veltman, D.J.; de Haan, E.; Boer, F. Paediatric obsessive–compulsive disorder, a neurodevelopmental disorder? Evidence from neuroimaging. *Neurosci. Amp. Biobehav. Rev.,* **2009**, *33*, 818-830.

[122] Watkins, L.H.; Sahakian, B.J.; Robertson, M.M.; Veale, D.M.; Rogers, R.D.; Pickard, K.M.; Aitken, M.R.; Robbins, T.W. Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychol. Med.,* **2005**, *35*, 571-582.

[123] Welsh, M.C.; Pennington, B.F.; Ozonoff, S.; Rouse, B.; McCabe, E.R. Neuropsychology of early-treated phenylketonuria: specific executive function deficits. *Child. Dev.,* **1990**, *61*, 1697-1713.

[124] Diamond, A. Consequences of Variations in genes that affect dopamine in prefrontal cortex. *Cereb. Cortex,* **2007**, *17*, i161-i170.

[125] Cullen, A.E.; Dickson, H.; West, S.A.; Morris, R.G.; Mould, G.L.; Hodgins, S.; Murray, R.M.; Laurens, K.R. Neurocognitive performance in children aged 9-12years who present putative antecedents of schizophrenia. *Schizophr. Res.,* **2010**, *121*, 15-23.

[126] Messias, E.L.; Chen, C.-Y.; Eaton, W.W. Epidemiology of schizophrenia: review of findings and myths. *Psychiatric Clin. North Am.,* **2007**, *30*, 323-338.

[127] Lewandowski, K.E.; Shashi, V.; Berry, P.M.; Kwapil, T.R. Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.,* **2007**, *144B*, 27-36.

[128] Maynard, T.M.; Haskell, G.T.; Peters, A.Z.; Sikich, L.; Lieberman, J.A.; LaMantia, A.S. A comprehensive analysis of 22q11 gene expression in the developing and adult brain. *Proc. Natl. Acad. Sci. USA,* **2003**, *100*, 14433-14438.

[129] Tunbridge, E.M.; Weickert, C.S.; Kleinman, J.E.; Herman, M.M.; Chen, J.; Kolachana, B.S.; Harrison, P.J.; Weinberger, D.R. Catechol-o-methyltransferase enzyme activity and protein expression in human prefrontal cortex across the postnatal lifespan. *Cereb. Cortex,* **2007**, *17*, 1206-1212.

[130] Liu, B.; Song, M.; Li, J.; Liu, Y.; Li, K.; Yu, C.; Jiang, T. Prefrontal-related functional connectivities within the default network are modulated by COMT val158met in healthy young adults. *J. Neurosci.,* **2010**, *30*, 64-69.

[131] Shaw, P.; Wallace, G.L.; Addington, A.; Evans, A.; Rapoport, J.; Giedd, J.N. Effects of the Val158Met catechol-O-methyltransferase polymorphism on cortical structure in children and adolescents, *Mol Psychiatry,* **2009**, *14*, 348-349.

[132] Diamond, A.; Briand, L.; Fossella, J.; Gehlbach, L. Genetic and Neurochemical Modulation of Prefrontal Cognitive Functions in Children. *Am. J. Psychiatry,* **2004**, *161*, 125-132.

[133] Davidson, M.C.; Amso, D.;erson, L.C.; Diamond, A. Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia,* **2006**, *44*, 2037-2078.

[134] Barnett, J.H.; Heron, J.; Goldman, D.; Jones, P.B.; Xu, K.Effects of catechol-O-methyltransferase on normal variation in the cognitive function of children. *Am. J. Psychiatry,* **2009**, *166*, 909-916.

[135] Wahlstrom, D.; White, T.; Hooper, C.J.; Vrshek-Schallhorn, S.; Oetting, W.S.; Brott, M.J.; Luciana, M. Variations in the Catechol O-methyltransferase polymorphism and prefrontally guided behaviors in adolescents. *Biol. Psychiatry,* **2007**, *61*, 626-632.

[136] Weickert, C.S.; Webster, M.J.; Gondipalli, P.; Rothmond, D.; Fatula, R.J.; Herman, M.M.; Kleinman, J.E.; Akil, M. Postnatal alterations in dopaminergic markers in the human prefrontal cortex. *Neuroscience,* **2007**, *144*, 1109-1119.

[137] Staiti, A.M.; Morgane, P.J.; Galler, J.R.; Grivetti, J.Y.; Bass, D.C.; Mokler, D.J. A microdialysis study of the medial prefrontal cortex of adolescent and adult rats, *Neuropharmacology,* **2011**, *61*, 544-549.

[138] Jacobs, E.; D'Esposito, M. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. *J. Neurosci.,* **2011**, *31*, 5286-5293.

[139] Dumontheil, I.; Roggeman, C.; Ziermans, T.; Peyrard-Janvid, M.; Matsson, H.; Kere, J.; Klingberg, T. Influence of the COMT genotype on working memory and brain activity changes during development. *Biol. Psychiatry,* **2011**, *70*, 222-229.

[140] Voelker, P.; Sheese, B.E.; Rothbart, M.K.; Posner, M.I. Variations in catechol-O-methyltransferase gene interact with parenting to influence attention in early development. *Neuroscience,* **2009**, *164*, 121-130.

[141] Kent, K.; Pelham, W.; Molina, B.; Sibley, M.; Waschbusch, D.; Yu, J.; Gnagy, E.; Biswas, A.; Babinski, D.; Karch, K. The academic experience of male high school students with ADHD. *J. Abnormal Child. Psychol.,* **2011**, *39*, 451-462.

[142] Diamond, A. Biological and social influences on cognitive control processes dependent on prefrontal cortex. *Prog. Brain Res.,* **2011**, *189*, 319-339.

[143] Diamond, A.; Lee, K. Interventions shown to aid executive function development in children 4 to 12 years old. *Science,* **2011**, *333*, 959-964.

[144] Bosia, M.; Bechi, M.; Marino, E.; Anselmetti, S.; Poletti, S.; Cocchi, F.; Smeraldi, E.; Cavallaro, R. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neurosci. Lett.,* **2007**, *417*, 271-274.

[145] Gothelf, D.; Hoeft, F.; Ueno, T.; Sugiura, L.; Lee, A.D.; Thompson, P.; Reiss, A.L. Developmental changes in multivariate neuroanatomical patterns that predict risk for psychosis in 22q11.2 deletion syndrome. *J. Psychiatr. Res.,* **2011**, *45*, 322-331.

[146] Campbell, L.E.; Azuma, R.; Ambery, F.; Stevens, A.; Smith, A.; Morris, R.G.; Murphy, D.G.M.; Murphy, K.C. Executive functions and memory abilities in children with 22q11.2 deletion syndrome. *Aust. NZ J. Psychiatry,* **2010**, *44*, 364-371.

[147] Schaer, M.; Debbané, M.; Bach Cuadra, M.; Ottet, M.-C.; Glaser, B.; Thiran, J.-P.; Eliez, S. Deviant trajectories of cortical maturation in 22q11.2 deletion syndrome (22q11DS): A cross-sectional and longitudinal study. *Schizophr Res.,* **2009**, *115*, 182-190.

[148] Simon, T.J.; Bish, J.P.; Bearden, C.E.; Ding, L.; Ferrante, S.; Nguyen, V.; Gee, J.C.; McDonald-McGinn, D.M.; Zackai, E.H.; Emanuel, B.S. A multilevel analysis of cognitive dysfunction and psychopathology associated with chromosome 22q11.2 deletion syndrome in children. *Dev. Psychopathol.,* **2005**, *17*, 753-784.

[149] Gothelf, D.; Eliez, S.; Thompson, T.; Hinard, C.; Penniman, L.; Feinstein, C.; Kwon, H.; Jin, S.; Jo, B.; Antonarakis, S.E.; Morris, M.A.; Reiss, A.L. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nat. Neurosci.,* **2005**, *8*, 1500-1502.

[150] Bearden, C.E.; Jawad, A.F.; Lynch, D.R.; Sokol, S.; Kanes, S.J.; McDonald-McGinn, D.M.; Saitta, S.C.; Harris, S.E.; Moss, E.; Wang, P.P.; Zackai, E.; Emanuel, B.S.; Simon, T.J. Effects of a functional COMT polymorphism on prefrontal cognitive function in patients with 22q11.2 deletion syndrome. *Am. J. Psychiatry,* **2004**, *161*, 1700-1702.

[151] Diamond, A.; Prevor, M.B.; Callender, G.; Druin, D.P. Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. *Monogr. Soc. Res. Child. Dev.,* **1997**, *62*, i-v, 1-208.

[152] Diamond, A.; Ciaramitaro, V.; Donner, E.; Djali, S.; Robinson, M.B. An animal model of early-treated PKU. *J. Neurosci.,* **1994**, *14*, 3072-3082.

[153] Enns, G.M.; Koch, R.; Brumm, V.; Blakely, E.; Suter, R.; Jurecki, E. Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence, *Mol. Genet. Metab.,* **2010**, *101*, 99-109.

[154] Leuzzi, V.; Pansini, M.; Sechi, E.; Chiarotti, F.; Carducci, C.; Levi, G.; Antonozzi, I. Executive function impairment in early-treated PKU subjects with normal mental development. *J. Inherit. Metab. Dis.,* **2004**, *27*, 115-125.

[155] MacDonald, A.; Gokmen-Ozel, H.; van Rijn, M.; Burgard, P. The reality of dietary compliance in the management of phenylketonuria. *J. Inherit. Metab. Dis.,* **2010**, *33*, 665-670.

[156] Sengupta, S.; Grizenko, N.; Schmitz, N.; Schwartz, G.; Bellingham, J.; Polotskaia, A.; Stepanian, M.T.; Goto, Y.; Grace, A.A.; Joober, R. COMT Val108/158Met Polymorphism and the Modulation of Task-Oriented Behavior in Children with ADHD. *Neuropsychopharmacology,* **2008**, *33*, 3069-3077.

[157] Eisenberg, J.; Mei-Tal, G.; Steinberg, A.; Tartakovsky, E.; Zohar, A.; Gritsenko, I.; Nemanov, L.; Ebstein, R.P. Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): Association of the high-enzyme activity val allele with adhd impulsive-hyperactive phenotype. *Am. J. Med. Genet.,* **1999**, *88*, 497-502.

[158] Bellgrove, M.A.; Domschke, K.; Hawi, Z.; Kirley, A.; Mullins, C.; Robertson, I.H.; Gill, M. The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. *Exp. Brain Res.,* **2005**, *163*, 352-360.

[159] Viggiano, D.; Vallone, D.; Ruocco, L.A.; Sadile, A.G. Behavioural, pharmacological, morpho-functional molecular studies reveal a hyperfunctioning mesocortical dopamine system in an animal model of attention deficit and hyperactivity disorder. *Neurosci. Biobehav. Rev.,* **2003**, *27*, 683-689.

[160] Pliszka, S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child. Adolesc. Psychiatry,* **2007**, *46*, 894-921.

[161] Agster, K.L.; Clark, B.D.; Gao, W.J.; Shumsky, J.S.; Wang, H.X.; Berridge, C.W.; Waterhouse, B.D. Experimental strategies for investigating psychostimulant drug actions and prefrontal cortical function in ADHD and related attention disorders. *Anat. Rec. (Hoboken),* **2011**, *294*, 1698-1712.

[162] Wilens, T.E. Effects of methylphenidate on the catecholaminergic system in attention-deficit/hyperactivity disorder. *J. Clin. Psychopharmacol.,* **2008**, *28*, S46-S53.

[163] Kereszturi, E.; Tarnok, Z.; Bognar, E.; Lakatos, K.; Farkas, L.; Gadoros, J.; Sasvari-Szekely, M.; Nemoda, Z. Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.,* **2008**, *147B*, 1431-1435.

[164] Tunbridge, E.M.; Harrison, P.J. *Importance of the COMT Gene for Sex Differences in Brain Function and Predisposition to Psychiatric Disorders Biological Basis of Sex Differences in Psychopharmacology*; Neill, J.C.; Kulkarni, J.; Eds.; Springer Berlin, Heidelberg, **2011**, pp. 119-140.

[165] Shifman, S.; Bronstein, M.; Sternfeld, M.; Pisanté-Shalom, A.; Lev-Lehman, E.; Weizman, A.; Reznik, I.; Spivak, B.; Grisaru, N.; Karp, L.; Schiffer, R.; Kotler, M.; Strous, R.D.; Swartz-Vanetik, M.; Knobler, H.Y.; Shinar, E.; Beckmann, J.S.; Yakir, B.; Risch, N.; Zak, N.B.; Darvasi, A. A highly significant association between a COMT haplotype and schizophrenia. *Am J. Hum. Genet.,* **2002**, *71*, 1296-1302.

[166] Talkowski, M.E.; Kirov, G.; Bamne, M.; Georgieva, L.; Torres, G.; Mansour, H.; Chowdari, K.V.; Milanova, V.; Wood, J.; McClain, L.; Prasad, K.; Shirts, B.; Zhang, J.; O'Donovan, M.C.; Owen, M.J.; Devlin, B.; Nimgaonkar, V.L. A network of dopaminergic gene variations implicated as risk factors for schizophrenia. *Hum. Mol. Genet.,* **2008**, *17*, 747-758.

[167] Karayiorgou, M.; Altemus, M.; Galke, B.L.; Goldman, D.; Murphy, D.L.; Ott, J.; Gogos, J.A. Genotype determining low catechol-O-

methyltransferase activity as a risk factor for obsessive-compulsive disorder. *Proc. Natl. Acad. Sci.,* **1997**, *94*, 4572-4575.

[168] Pooley, E.C.; Fineberg, N.; Harrison, P.J. The met158 allele of catechol-O-methyltransferase (COMT) is associated with obsessive-compulsive disorder in men: case-control study and meta-analysis. *Mol. Psychiatry,* **2007**, *12*, 556-561.

[169] Biederman, J.; Kim, J.W.; Doyle, A.E.; Mick, E.; Fagerness, J.; Smoller, J.W.; Faraone, S.V. Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD: a preliminary study. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.,* **2008**, *147B*, 1511-1518.

Received: November 9, 2011 **Revised: January 25, 2012** **Accepted: January 26, 2012**

PMID: 22483296