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COMT Val$^{108/158}$Met polymorphism modulates task-oriented behaviour in children with ADHD

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Abstract

Context—It has been suggested that the symptoms of ADHD (inattention and/or hyperactivity/impulsivity), translate into deficits in task-oriented behaviour or problem-focussed activity. The fronto-subcortical dopamine and norepinephrine pathways have been implicated in ADHD, and one of the key modulators of these neurotransmitters in the prefrontal cortex is catechol-*O*-methyltransferase (COMT).

Objective—To examine the association of the *COMT* Val$^{108/158}$Met polymorphism with (1) task-oriented behaviour in children with ADHD, and (2) response of this phenotype to methylphenidate treatment.

Design, Setting, Participants—Children diagnosed with ADHD (n=212), were assessed using the Restricted Academic Situation Scale (RASS). The RASS uses a simulated academic environment within the research clinic, to assess the child's ability for independent, sustained orientation to a task of math problems.

Interventions—Each child was administered placebo and methylphenidate (0.5 mg/kg in a divided b.i.d. dose), each for a one-week period, in a double-blind, crossover trial. On day 3 of the respective treatment week, the child was administered placebo/ methylphenidate in the clinic, and the acute change in behaviour (before and 1 hour after treatment) was evaluated on the RASS.

Main Outcome Measure—The main outcome measure was the RASS score (number of behavioural events measured during a 15-minute time period), measured at four time points: before and after placebo/methylphenidate treatment. Analysis was carried out using mixed model analysis of variance.

Results—Significant main effects of *COMT* genotype [$F_{2,206} = 4.78$, $p = 0.009$] and treatment [$F_{1,206} = 45.22$, $p < 0.0001$] on task-oriented behaviour were observed. The *Met-Met* and *Val-Met* genotype groups had fewer behavioural events, and were more engaged in the math task, compared to the *Val-Val* group. No genotype by treatment interaction was observed.

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Conclusion—These results suggest that the *COMT* Val$^{108/158}$Met polymorphism modulates task-oriented behaviour, but it does not modulate the response of this behaviour to MPH treatment.

Keywords

COMT; task-oriented behaviour; methylphenidate; ADHD

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood behavioural disorders, affecting 8–12% of school-aged children worldwide.[1] It is characterised by symptoms of inattention and/or hyperactivity/impulsivity, with accompanying cognitive deficits. Neuropsychological studies have converged on the hypothesis that ADHD is associated with deficits in executive function (EF). EF encapsulates higher order neurocognitive control functions required to complete a defined goal. Children with ADHD usually exhibit deficits in working memory and planning, lack attentional and strategic flexibility, and fail to monitor their behaviour so as to align themselves with the task set out. Other findings point to key deficits in incentive, motivational and reward-related processing and suggest that these are largely independent from EF deficits. As described in the dual-pathway model by Sonuga-Barke (2002), the behavioural symptoms associated with ADHD (inattention and/or hyperactivity/impulsiveness), whether they arise from EF or motivational dysregulation, translate into problems with goal-oriented behaviours, affecting the quality and quantity of task or problem-focused activity.[2]

Neuropsychological, imaging and neuro-pharmacological studies have suggested that dysregulation of the fronto-subcortical circuits involved in EF and emotional/motivational processing of behaviours (reward-based behaviours, error prediction, and the choice between short- and long-term gains) are disrupted in ADHD.[3–6] While the dorso-lateral prefrontal cortex (PFC) plays a key role in memory-guided, goal-oriented behaviour, the anterior cingulate cortex and orbital frontal cortex are critical for the emotional control of behavioural output. Thus, it is possible that dysregulation of the fronto-subcortical circuits involved in EF (working memory, planning, inhibition, monitoring and execution of behaviour) and emotional/motivational processing of behaviours (reward-based behaviours, error prediction, and the choice between short- and long-term gains) may be, separately or jointly, disrupted in ADHD.

During performance of goal-oriented behaviour, the PFC neurons exhibit sustained activity possibly reflecting the active holding of goal-related information or the preparation of forthcoming actions.[7] Dopamine strongly modulates both this sustained (delay-period) activity and behavioural performance in working-memory tasks.[7–14] Recent studies in animals have suggested that, at therapeutic doses, psychostimulant medications used to treat ADHD symptoms preferentially increase the synaptic levels of dopamine and norepinephrine in the PFC.[15–18] In addition, several neuro-imaging studies in humans have shown that the administration of methylphenidate at therapeutic doses results in elevated dopamine levels in the brain,[19] activation of prefrontal cortex regions involved in emotional processing [20] and an increase in the saliency of assigned tasks.[20]

One of the key endogenous modulators of DA synaptic concentration in the PFC is the enzyme catechol-O-methyltransferase (COMT). COMT inactivates catecholamines by transferring a methyl group to the catechol nucleus. COMT is thought to be particularly important for the clearance of dopamine in the prefrontal cortex (accounting for >60% of total turnover), given the paucity of dopamine transporter in this region.[21, 22] Two variants are encoded by the COMT gene (mapped to chromosome 22q11), with two available transcription start sites. The short

variant is soluble and is found in the cytoplasm (s-COMT), while the longer variant is found to be membrane-bound (m-COMT). Within exon 4 of the COMT gene, a common single nucleotide polymorphism (C**G**TG versus C**A**TG) results in the presence of methionine or valine at codon 108 (in s-COMT) or codon 158 (in m-COMT). COMT containing valine at position 108/158 has been shown to have higher stability and approximately 2–4 fold higher activity than the met variant.[23, 24] Results of a recent study with healthy volunteers reported that the *COMT* Val$^{108/158}$Met polymorphism modulates brain activation in the PFC, with the *Val* allele being associated with inefficient prefrontal working memory response.[25] These findings suggest that the *COMT* Val$^{108/158}$Met polymorphism may be an excellent candidate to investigate for association with task-oriented behaviour and response of these behaviours to methylphenidate treatment, in children with ADHD.

We have examined the association between the *COMT* Val$^{108/158}$Met polymorphism and task-oriented behaviour and the response of this behaviour to methylphenidate treatment. Task-oriented behaviour was measured in the clinic, within a restricted academic situation. This simulated academic environment allows for the assessment of the child's behaviour when given an academic task (set of math problems, at a level of difficulty equivalent to the child's ability), in the absence of adult supervision. For each child, the assessment of task-oriented behaviours was performed on four occasions: before, and one hour after treatment with either placebo or methylphenidate, allowing us to study the association of the *COMT* Val$^{108/158}$Met polymorphism with task-oriented behaviour and its response to methylphenidate. These assessments were part of a two-week double-blind, placebo-controlled crossover trial with methylphenidate.

Methods

Subjects

Two hundred and twelve children (178 boys and 34 girls), between 6 and 12 years with a mean age of 9 years [SD=1.8], were recruited from the Disruptive Behaviour Disorders Program and the child psychiatry outpatient clinics at the Douglas Hospital in Montreal. They were referred to these specialized care facilities by schools, community social workers, family doctors and paediatricians. Each child was diagnosed with ADHD, using DSM-IV criteria, on the basis of a clinical interview, between the child, at least one parent, and a child psychiatrist. This clinical examination was supplemented with a structured clinical interview of parents using the Diagnostic Interview Schedule for Children-version IV (DISC-IV, parental report, Shaffer et al., 2000).[26] In the majority of cases, mothers were the primary informants.

Exclusion criteria included having an IQ less than 70, as measured with the Wechsler Intelligence Scale for Children-III (WISC-III),[27] Tourette syndrome, pervasive developmental disorder, and psychosis. The research protocol was approved by the Research Ethics Board of the Douglas Hospital. Parents were explained the study and provided written consent. Children were explained the study and gave their assent to participate.

Assessment of task-oriented behaviour in the clinic within a Restricted Academic Situation

The Restricted Academic Situation Scale (RASS) is a coding system, designed to observe and record the behaviour of a child when assigned a set of math problems (based on the child's current grade), during a simulated independent academic situation within a clinic setting.[28] It is an assessment of the child's ability for sustained attention to routine, repetitive academic work in the presence of potential distractions, with no adult supervision.[29] This scale has been used to discriminate between children with ADHD and normal controls as well as from those with conduct problems unrelated to ADHD.[30]

The Restricted Academic Situation was set up in a clinic playroom containing toys, a work table, chair and an intercom.[28] After allowing the child to play for 5 minutes, used as a habituation period, the child was given a set of math problems with instructions to complete as many problems as possible, not to leave the seat, and not to play with any of the toys in the room. The child's behaviour was then assessed from behind a one-way mirror over a 15 minute time period. Behavioural events were recorded at 30-second intervals according to five categories: *off-task* (looking away from the task sheet), *playing with objects* (touching any object not directly used in the task), *out of seat* (lifting buttocks off chair or moving chair), *vocalizing* (any vocal noise, whether task related or not), and *fidgeting* (repetitive, purposeless movements). The RASS score is the total number of recorded behavioural events in the 15-minute period.

Measuring response of task-oriented behaviour to methylphenidate treatment within a Restricted Academic Situation

A 2-week double-blind, placebo-controlled, within-subject (crossover) experimental design was used to assess the behavioural response to a fixed dose of MPH (0.5 mg/kg/day) as compared to placebo (PBO). However, before the trial was initiated, the child and parents participated in a week of baseline assessments, which also served as a wash-out period for children previously treated with MPH. During this time, the overall behaviour of the child was assessed using the comprehensive (113-item questionnaire) child behavioural checklist (CBCL). The CBCL was completed by the parent(s) of the affected child.

Following this wash-out period, subjects received one week of treatment with PBO and one week of treatment with 0.5 mg/kg of MPH in a divided b.i.d. dose (0.25 mg/kg, morning and noon). The order of PBO and MPH administration was determined by random assignment. PBO and MPH were prepared individually in opaque gelatin capsules in weekly blister packs by a pharmacist not otherwise involved in the study to maintain blind allocation of treatments. At the end of each week of treatment, the blister packs were collected and medication adherence was checked.

On day 3 of each week of treatment, the child was asked to come to the clinic and the RASS was conducted both before (pre-treatment) and 60 minutes after (post-treatment) the treatment was administered by the research staff. A different set of math problems were assigned for each assessment. Trained research personnel conducted the assessments. The inter-rater reliability was high, with intraclass correlation coefficient ranging from 0.97 to 0.99.

Assessment of motor activity during the restricted academic situation

Overall motor activity was estimated using actiwatch® actigraphy, while the child was performing the assigned task within the simulated academic situation. Actigraphy is the use of instrumentation sensitive to movement, such as an actiwatch®, to record activity over time. The actiwatch® is a small, rugged electronic device, worn on the non-dominant hand, which is sensitive to acceleration. With each subject movement, an accelerometer generates a variable voltage that is digitally processed. Movements $\geq 1/100^{th}$ of g are detected and recorded. The signal is integrated over a user-selected epoch (30 second time bin selected in this study) and a value expressed as "Activity Counts" is recorded in the instrument memory.

Molecular genetics

DNA was extracted from a blood sample, a buccal swab or saliva sample, if the child was amenable only to the latter. The *COMT* $Val^{108/158}$Met polymorphism was genotyped by PCR amplification and digestion of the PCR product with *Nla*III as previously described.[31]

Statistical analyses

Demographic and clinical characteristics of the three *COMT* genotype groups were compared using ANOVA or χ^2 tests as appropriate. Mixed model analysis of variance was used to analyse the data (SAS Mixed procedure, SAS version 6.12, SAS Institute Inc, Cary NC).[32] For the RASS, the dependant variable was the total RASS score (total number of behavioural events measured during a 15-minute time period), measured at four time points: before PBO treatment, after PBO treatment, before MPH treatment, and after MPH treatment. Five different main effects were assessed in the mixed model analysis: *COMT* genotype, time of assessment (week 1 or 2), administration of PBO/MPH (before *versus* after treatment), treatment (PBO *versus* MPH), and order of treatment (MPH administered in week 1- PBO in week 2, or reverse order, since the order was randomized in a double-blind trial). Two interaction effects were also investigated in the analysis: *COMT* genotype by treatment, treatment by administration. *COMT* genotype, time, administration, treatment with PBO and MPH, and order were fixed effects; individuals were random effects.

Identical analysis was conducted for the sub-scale scores for each of the domains within the RASS: *off-task, playing with objects*, *out of seat, vocalizing*, and *fidgeting*. For motor activity, the dependant variable was the total number of 30 second bins during which at least one movement was recorded by the actiwatch®. As with the RASS, motor activity was measured at four different time points: before and after PBO treatment, before and after MPH treatment. Mixed model analysis, as conducted with the RASS, was performed. Where significant association with *COMT* genotype was observed, post-hoc comparison between the different groups was conducted using the Tukey Honest Significant Difference Test.

RESULTS

The frequency of the *Val* allele was 53.1% and the *Met* allele was 46.9%. The genotype frequencies (19.8% *Met-Met*, 54.2% *Val-Met*, and 25.9% *Val-Val*) did not depart from Hardy Weinberg equilibrium ($\chi^2 = 2.67$, df = 2, p = 0.74). The three genotype groups did not differ with respect to their demographic characteristics (Table 1). The three groups were also similar with respect to incidence of comorbid disorders and overall number of behavioural symptoms on the CBCL.

Effect of methylphenidate and placebo on RASS scores

Mixed model analysis of variance showed a significant treatment by administration interaction with the RASS total score [$F_{1,209} = 155.2$, $p < 0.0001$] and with each of the dimensional scores (data not shown). Regardless of genotype, administration of placebo resulted in a significant deterioration in performance ($F_{1,209}=19.7$, $p<0.000$; Cohen's *d* effect size =0.22) whereas administration of methylphenidate resulted in a significant improvement in performance ($F_{1,209}=82$, $p<0.000$; Cohen's *d* =1.1) (Figure 1). In spite of the opposing effects of placebo and methylphenidate on the RASS score, a significant main effect of administration of treatment (before *versus* after MPH/PBO treatment) was observed [$F_{1,209} = 13.65$, $p = 0.0003$]. This significant administration effect is a reflection of the fact that methylphenidate treatment shows a much stronger effect (~5 times) in improving task orientation, vis-à-vis the negative effect of placebo treatment.

Association of *COMT* Val$^{108/158}$Met polymorphism with task-oriented behaviour

Mixed model analysis showed a significant main effect of *COMT* genotype on the total RASS score [$F_{2,207} = 4.85$, $p = 0.009$]. Post-hoc analysis showed that the *Met-Met* (p= 0.08) and *Val-Met* (p= 0.01) genotype groups had fewer behavioural events, and were more engaged in the math task, compared to the *Val-Val* group. The *Met-Met* and *Val-Met* genotype groups did not differ significantly from each other (p= 0.79), suggesting a recessive effect of the *Val* allele on

this phenotype (Figure 2). No significant genotype by treatment interaction was observed [$F_{2,207}$ = 1.64, p = 0.2], suggesting that *COMT* genotype does not modulate therapeutic response, at least at the dose of MPH tested (0.5 mg/kg).

The RASS score used above is a composite of the total number of behavioural events recorded in each of five categories: *off-task*, *playing with objects*, *out of seat*, *vocalizing*, and *fidgeting*. In order to better understand the relation of each of these behavioural categories to task-oriented behaviour, we explored the correlation of each of these behaviours to *off-task* behaviour, since this item likely has the best face validity with regard to orientation to task. The correlation with off-task behaviour was very high for *playing with objects* (r>0.9), intermediate for *out of seat* and *vocalisation* (0.4<r<0.5) and very low for fidgeting (r<0.1) (Table 2).

The association between *COMT* genotype and each of the five RASS behaviour categories was examined (Table 3). *COMT* genotype showed a strong association with those dimensions that are most representative of task engagement or problem-focused activity; *off task* behaviour [$F_{2,207}$ = 5.63, p = 0.004] and *playing with objects* [$F_{2,207}$ = 5.72, p = 0.004]. The *Val/Val* genotype group had higher scores (significantly higher behavioural problems) than the *Met* carriers on each of these measures. Only a trend of association was observed between *COMT* genotype and *out of seat* behaviour [$F_{2,207}$ = 2.68, p = 0.07]. *Vocalizing* ($F_{2,207}$ = 2.17, p = 0.12) and *fidgeting* ($F_{2,207}$ = 1.77, p = 0.17) were not associated with *COMT* genotype.

Association of *COMT* Val$^{108/158}$Met polymorphism with task-oriented behaviour in Caucasian subjects

Although the majority of children were of Caucasian origin and the ethnic distribution was not different between the three genotype groups, it is possible that the association observed between the *COMT* Val$^{108/158}$Met and RASS scores is due differences in unmeasured genetic factors. In order to correct for possible effects arising due to population stratification, the analysis was restricted to Caucasians only. Each of the effects of *COMT* genotype remained significant; total RASS score [$F_{2,184}$ = 5.12, p = 0.007]; *off task* behaviour [$F_{2,184}$ = 5.86, p = 0.003] and *playing with objects* [$F_{2,184}$ = 6.09, p = 0.003]. As before, a strong trend of association was observed with *out of seat* behaviour [$F_{2,184}$ = 3.07, p = 0.05] and no association with *vocalizing* ($F_{2,184}$ = 2.1, p = 0.12) and *fidgeting* ($F_{2,184}$ = 0.57, p = 0.57)

No association of *COMT* Val$^{108/158}$Met polymorphism with motor activity

In order to dissect the effect of non-specific motor hyperactivity from task-oriented behaviour (which likely includes additional important cognitive dimensions), actiwatch® measurements were analyzed. As with the RASS, a main effect of treatment [$F_{1,184}$ = 5.41, p = 0.02] and a treatment by administration interaction [$F_{1,178}$ = 33.21, p<0.0001] were observed. However, no association was observed between motor activity and *COMT* genotype; there was no main gene effect [$F_{2,196}$ = 1.99, p = 0.14] nor a gene by treatment interaction [$F_{2,184}$ = 0.77, p = 0.47]. These results suggest that the *COMT* Val$^{108/158}$Met polymorphism specifically modulates those dimensions of task-oriented behaviour or problem-focussed activity that are distinct from motor hyperactivity, either in their aetiology or in their expression.

DISCUSSION

Previous studies by several independent groups, as well as a recent meta-analysis (including both family-based and case-control studies), have concluded that there is no association between ADHD, considered as a clinical syndrome, and the *COMT* Val$^{108/158}$Met polymorphism.[33–38] However it has been suggested that polymorphisms within candidate genes are more likely to be associated with behavioural dimensions within the disorder.[39]

Indeed, the ADHD syndrome may result from disturbances of various behavioural dimensions that are unique for each affected child and that may be differentially represented in each sample. If a candidate gene is relevant for one or more of these behavioural dimensions, its effect may be difficult to identify, if the between-subject heterogeneity is not taken into consideration.

There is a large body of literature supporting the association between the *COMT* Val$^{108/158}$Met polymorphism and neurocognitive functions involving the dorsolateral PFC, in healthy adults as well as adult patients with psychotic disorders.[40, 41] In contrast, only a limited number of studies have examined the association with specific executive function domains in children with ADHD, in spite of compelling evidence implicating dorsolateral PFC dysfunction in the disorder. It is particularly difficult to extrapolate findings obtained in adult studies to complex childhood disorders, since it has been shown that the enzymatic activity of COMT in the dorsolateral PFC, shows considerable change over the developmental trajectory.[42] Previously, we and others have reported that the *COMT Val$^{108/158}$Met* polymorphism is not associated with performance on tests of executive function, including the Wisconsin Card Sorting Test, Tower of London, and Self-Ordered Pointing Task. One other study has reported the association between this polymorphism and two subtests of the Test of Everyday Attention for Children (*Walk Don't Walk* and *Sky Search Dual Task*).[43] In this study, the authors report that ADHD children with the *Val/Val* genotype showed better sustained attention than the *Met* carriers.

Here we have examined the association between the *COMT* Val$^{108/158}$Met polymorphism, treatment with methylphenidate, and task-oriented or goal-directed behaviour, in children with ADHD. Task-oriented behaviour was measured in a simulated academic situation, which offers the dual advantage that the child's behaviour can be assessed objectively within a clinical environment, while simulating a situation similar to homework time or independent study time in the classroom.[29] Each child was assessed on five dimensions (*off-task*, *playing with objects*, *out of seat*, *vocalizing*, and *fidgeting)*. The advantage therefore of using the Restricted Academic Situation Scale is that it offers a multi-dimensional, ecologically-relevant evaluation of the child's goal-oriented behaviour. Further, coupled with a placebo-controlled evaluation of the effect of methylphenidate, it may be of particularly important clinical relevance.

We observed that the *COMT Val$^{108/158}$Met* polymorphism modulates task-oriented behaviour in children with ADHD. Children in the *Met-Met* and *Val-Met* genotype groups had significantly lower total RASS scores (better behaviour in the simulated classroom) than children with the *Val-Val* genotype. Further examination of each of the RASS factors showed that the *COMT Val$^{108/158}$Met* polymorphism was specifically associated with “off-task” behaviour. In addition, a significant association was also observed with “playing with objects”, which was highly correlated with “off-task” behaviour. Analysis with each of these factors showed that children with *Met-Met* and *Val-Met* genotypes were more oriented to the assigned task and were less distracted than children with the *Val-Val* genotype. In order to disentangle this association further, we examined the effect of *COMT* genotype on motor activity, as measured by the number of 30 second intervals where there was activity in the non-dominant hand. No association was observed, which suggests that the *COMT Val$^{108/158}$Met* polymorphism modulates dimensions of task-oriented behaviour other than motor hyperactivity.

We model these results on the two-compartment tonic-phasic hypothesis of dopamine regulation.[44] Tonic DA is the low, background level of extrasynaptic dopamine (~5–20nM) which is regulated by baseline firing of the dopamine neurons, which in turn is regulated by inputs from glutamatergic afferents. Phasic DA, on the other hand, is the high-amplitude (μM concentrations), transient burst that occurs in response to a behavioural stimulus. Bilder et al (2004) have hypothesized that tonic DA regulates the stability of cortical activation states, via

its effect on dopamine receptor D1 stimulation.[45] Tonic D1 stimulation has thus been hypothesized to be important for maintaining stability by preventing "uncontrolled, spontaneous switches into high-activity states (i.e spontaneous activation of task-irrelevant representations)".[45] In contrast, phasic DA levels regulate the plasticity of these activation states, via D2 receptor function. Phasic DA levels are believed to be important for "updating" of information into the activation state.

The Val-containing COMT variant has been shown to have 3–4 times higher stability and enzymatic activity compared to the Met-containing variant. In the prefrontal cortex, COMT plays a critical role in the hydrolysis of dopamine, thereby regulating extracellular dopamine concentration. It is therefore expected that the Met-containing COMT variant would result in higher tonic DA in the PFC and concurrently higher stability of the activation state compared to the Val-containing COMT variant.[44] On a task like the RASS, which calls for stability of behaviour over the course of the test period, children with the *Met-Met* genotype are therefore expected to have higher tonic DA, therefore performing better than children having the *Val-Val* genotype. This is congruent with our findings.

In this study, task-oriented behaviour of the child was assessed in two treatment conditions, given placebo and methylphenidate, administered in a double-blind manner. The acute effect, following administration of the placebo or methylphenidate, was measured by conducting the assessment before and one hour-after the treatment. Methylphenidate has been shown to increase the level of extracellular dopamine in the brain, via blockage of dopamine as well as the norepinephrine transporters.[46–48] Positron emission tomography studies using [^{11}C]-labelled MPH, have shown that the peak brain concentration of MPH is achieved around 60 minutes after oral administration.[48] Hence the time frame (1 hour after administration) used in this study should be appropriate for studying the acute effect of MPH treatment. It has also been demonstrated that the median effective dose, i.e. the dose required to block 50% of the dopamine transporter, is 0.25mg/kg.[48] Thus at the dose administered in this study, at least 50% of the DAT is expected to be blocked.[49]

Measurement of task-oriented behaviour using the Restricted Academic Situation Scale showed a significant 2-way interaction between treatment (methylphenidate *vs.* placebo) and administration (before *vs.* after treatment). Placebo treatment resulted in a significant deterioration, whereas MPH treatment significantly improved task-oriented behaviour. It has been previously shown that MPH increases the saliency of a mathematical task in healthy adult subjects.[50] The rating of a mathematical task as "interesting", "exciting", "motivating", and "less tiresome" significantly increased with MPH treatment. Together with these findings, our results suggest that in children with ADHD, the saliency of a mathematical task is diminished as a result of administration of placebo, possibly as a result of boredom due to repetition of the task. This boredom effect is dramatically reversed with methylphenidate treatment, possibly as a result of increased dopamine neurotransmission in the prefrontal regions of the brain.

Our results further suggest that the *COMT* Val$^{108/158}$Met polymorphism does not modulate response of task-oriented behaviour with MPH treatment. Such a result might be expected, given that the 50% blockade of DA transporter is likely to have a substantially greater impact on DA availability compared to the effect of *COMT* genotype.

It is noted that these results were obtained with children diagnosed with ADHD. It would be important to further determine if the association between task-oriented behaviour and *COMT* genotype is specific to the ADHD disorder or is true of all children in the school-aged population. It may be predicted that the effect of instability would be greater with ADHD children, given their major deficits in task-orientation, such that small disruptions in DA levels are likely to have multiplicative effects on their capacity to orient to task. On the other hand,

the impact of MPH treatment would likely obscure differences related to genotype, since the methylphenidate-induced increase in DA levels would be substantially greater than the differences due to metabolism.

In conclusion, this is the first study investigating the role of the *COMT* Val$^{108/158}$Met polymorphism in task–oriented, ecologically-relevant behaviors related to ADHD. It also explores the role of this polymorphism in the response of these behaviors to methylphenidate in children with ADHD. It is also the largest study using the double-blind, placebo-controlled, crossover design for the evaluation of behavioral response to psychostimulants. In addition, the assessment tool used in this study was developed for children and was shown to be adequate for the evaluation of therapeutic response to medication in children with ADHD. The results of this study strongly suggest that children with the *Val/Val* genotype demonstrate poor task-oriented behavior. In this study, we did not identify a gene by treatment interaction, suggesting that this polymorphism modulates behavior relevant for ADHD but not the response of this behaviour to methylphenidate. If these profiles are confirmed in a larger group of patients, this may help in understanding the pathogenesis of this very common childhood disorder.

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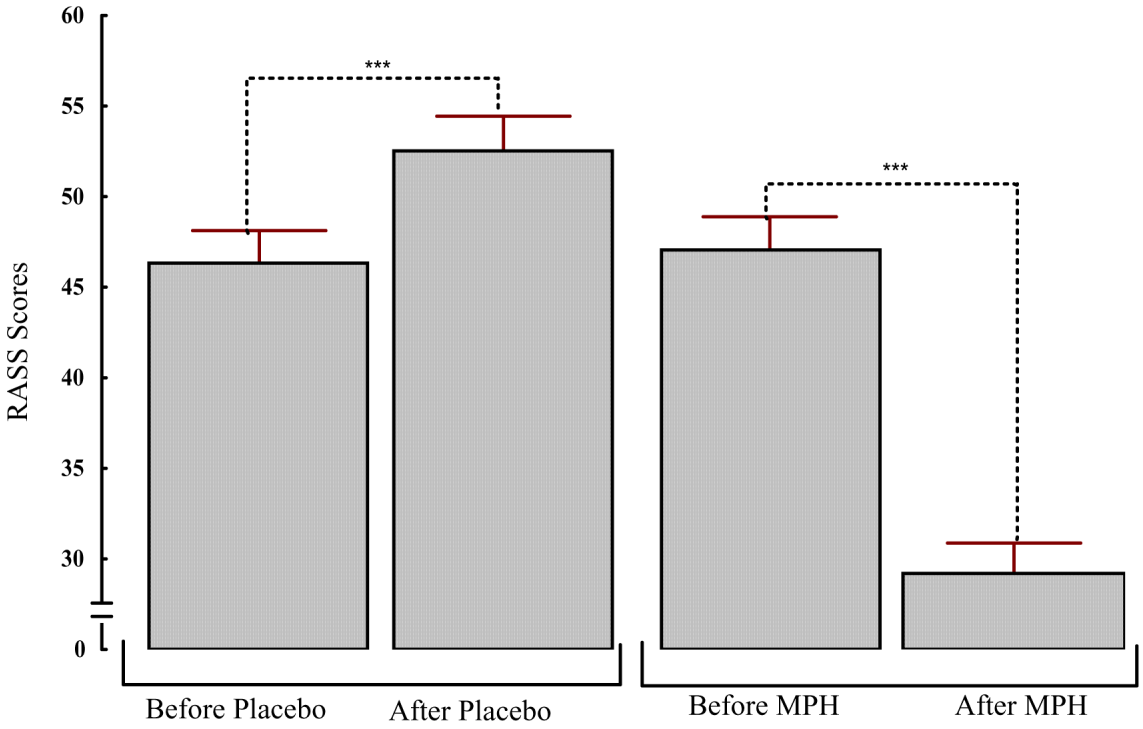

Figure 1.

Acute response of task orientation to placebo and methylphenidate as measured in the restricted academic situation.

Restricted Academic Situation Scale (RASS) scores (mean ± SE), before and one hour after treatment with placebo (2 left bars) or methylphenidate (2 right bars). ***: $p<0.000$. The RASS score is the total number of behavioural events measured over a 15 minute time period. Behavioural events were recorded at 30-second intervals according to five categories: off-task, fidgets, out of seat, vocalizes and plays with objects.

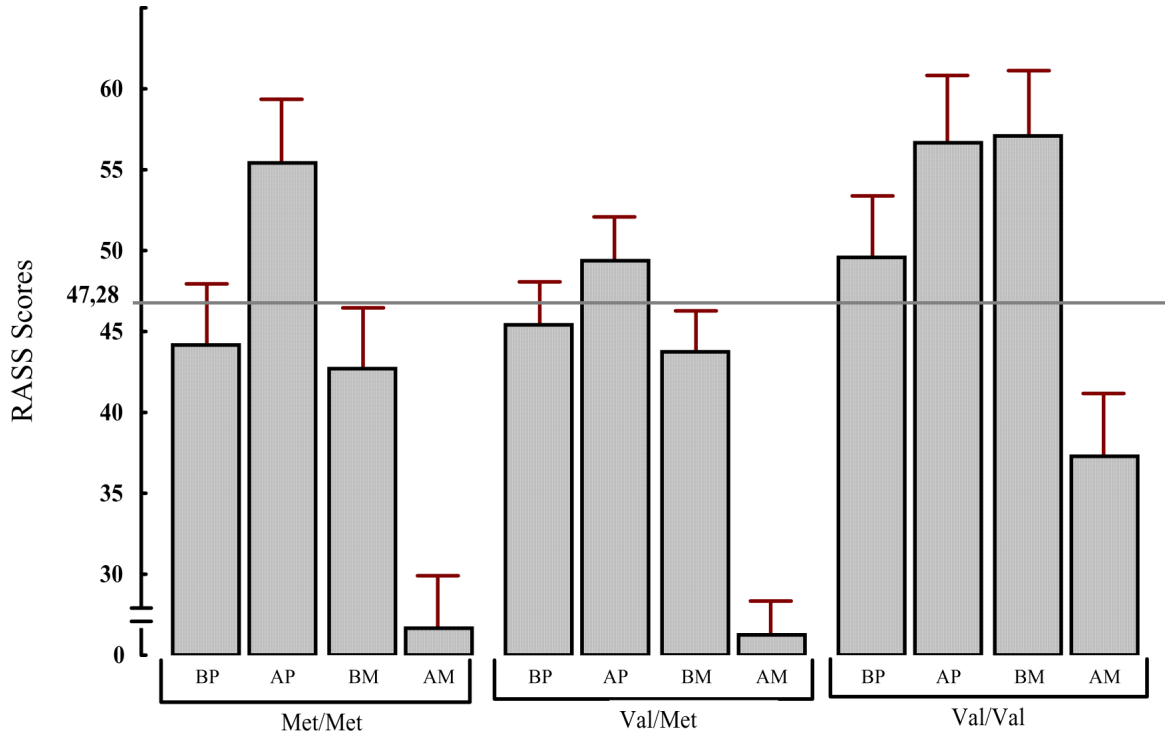

Figure 2.

Acute response of task orientation to placebo and methylphenidate as measured in the restricted academic situation in children with ADHD separated according to their genotype in the *COMT* (*Val*$^{105/158}$*Met*) polymorphism.

Restricted Academic Situation Scale (RASS) scores (mean ± SE) before administration of either placebo (BP) or methylphenidate (BM) and one hour after administration of either placebo (AP) or methylphenidate (AM) in the three genotype groups. Dashed line indicates the mean of the RASS calculated over the four measurement times (before and after placebo and methylphenidate).

Table 1

Demographic and clinical characteristics of children with ADHD separated according to their genotypes in the COMT Val$^{108/158}$Met polymorphism.

	***Met/Met* (n=42)**	***Val/Met* (n=115)**	***Val/Val* (n=55)**	**Statistic and p-value**
M/F (% males)	37/5 (88.1%)	93/22 (80.9%)	48/7 (87.3%)	χ^2=1.8, df=2, p=0.41
Age, yrs	9.1 (2.0)	9.0 (1.8)	8.9 (1.7)	$F_{2,209}$=0.1, p=0.9
Household income (% < $20,000 per yr)	40.5%	41.9%	41.8%	χ^2=0.02, df=2, p=0.99
Ethnic origin (Caucasian/other)	38/4	104/11	46/9	χ^2=1.9, df=2, p=0.39
WISQ-III full scale IQ	97.2 (14.1)	99.3 (14.5)	97.8 (13.1)	$F_{2,191}$=0.41, p=0.67
Comorbidity (%) with:				
CD	19.1%	36.6%	30.2%	χ^2=4.4, df=2, p=0.11
ODD	38.1%	40.4%	39.6%	χ^2=0.07, df=2, p=0.97
AD	38.5%	43%	57.5%	χ^2=3.71, df=2, p=0.16
MD	15.8%	12.9%	8.3%	χ^2=1.2, df=2, p=0.56
CBCL total score	68.3 (9)	70.4 (9.3)	69.7 (7.6)	$F_{2,202}$=0.91, p=0.4

Table 2

Correlation of "out of task" item of the RASS with the other four RASS items and with the total time of left hand movement during the 15 min of RASS observation as measured by the actiwatch. Correlation coefficients and p-values are provided for each of the four measurement occasions.

	Play with object	Out of seat	Vocalization	Fidgeting
Before placebo	0.92 p<0.000	0.48 p<0.000	0.43 p<0.000	0.09 p=.208
After placebo	0.91 p<0.000	0.54 p<0.000	0.42 p<0.000	0.00 p=.989
Before methylphenidate	0.91 p<0.000	0.48 p<0.000	0.43 p<0.000	−0.03 p=0.680
Before methylphenidate	0.90 p<0.000	0.45 p<0.000	0.44 p<0.000	0.03 p=0.711

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Table 3

Genotype effect of the COMT Val$^{108/158}$Met polymorphism with each individual item of the RASS and with the total time of left hand movement assessed by the actiwatch.

		BP	AP	BM	AM	F*	p*	ESP	ESM	ES COMT
Off task	*Val/Val*	13.7 (9.5)	15.4 (9.9)	15.1 (9.2)	10.0 (8.6)	5.63	0.004	−0.18	0.50	0.36
	Met+	11.6 (8.9)	13.4 (9.6)	10.4 (8.5)	6.4 (8.0)					
Play with object	*Val/Val*	11.0 (8.3)	13.4 (9.2)	13.3 (9.1)	7.6 (8.1)	5.72	0.004	−0.27	0.62	0.31
	Met+	8.9 (8.3)	11.0 (9.0)	9.8 (8.2)	5.1 (8.1)					
Out of seat	*Val/Val*	7.2 (7.9)	9.5 (8.9)	7.8 (7.8)	4.0 (6.4)	2.68	0.07	−0.21	0.21	0.10
	Met+	6.4 (7.7)	7.5 (8.2)	5.4 (6.7)	6.1 (7.6)					
Vocalization	*Val/Val*	5.6 (6.8)	7.0 (7.8)	7.1 (7.7)	4.8 (6.5)	2.17	0.12	−0.18	0.19	0.22
	Met+	4.9 (7.2)	6.1 (7.6)	5.1 (7.6)	2.2 (4.0)					
Fidgeting	*Val/Val*	12.0 (7.2)	11.3 (7.0)	13.8 (7.5)	8.9 (7.5)	1.77	0.17	0.07	0.65	−0.10
	Met+	13.4 (7.8)	13.0 (7.5)	13.8 (7.9)	8.8 (7.6)					

Values are mean (χSD). Cohen's *d* effect size of placebo (ESP), Methylphenidate (ESM) and COMT *Val$^{108/158}$Met* polymorphism [*Val/Val* genotype *vs. Met/Met+ Val/Met* genotypes *(Met+)*].

*The statistic is based on the mixed model analysis conducted with the three genotype groups.