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The impact of Val108/158Met polymorphism of catechol-O-methyltransferase on brain oscillations during working memory

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Abstract

This study investigated whether catechol-O-methyltransferase (COMT) Val/Met polymorphism was associated with variation in event-related desynchronization/synchronization (ERD/ERS) of responses during working memory (WM). 11 Val/Val and 11 Met/Met homozygous participants underwent magnetoencephalography (MEG) while performing a WM task. In contrast to small effects behaviourally, during the delay period Val/Val individuals showed lower ERS in the gamma band (Hz 30–50) in frontal regions, increased ERS in the alpha band (Hz 8–12) in the right frontal and parietal regions and increased ERD in the beta band (Hz 14–30) in the left fronto-temporal regions as compared with Met/Met homozygous individuals. During the response period Val/Val participants showed greater beta ERD in the prefrontal and parietotemporal regions. These results demonstrate that COMT genotype has a strong impact on brain responses (oscillatory activity) during WM performance likely a consequence of compensatory activity during the delay and response periods.

Keywords

Dopamine; Genetics; Frontal lobe; Event-related desynchronization (ERD); Event-related synchronization (ERS); Human memory

1. Introduction

A common Val (108/158) Met substitution within the COMT gene results in the Val allele exhibiting significantly greater enzyme activity than the Met allele [6]. Given the preferential role of COMT in prefrontal dopamine degradation [31], this polymorphism is

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thought to exert its effects on cognition by modulating dopamine signaling in the frontal lobes [9]. Several studies show it accounts for a small but significant proportion of variance in prefrontal-mediated cognitive function in humans [12] and in mice [20]. Individuals homozygous for the COMT Val allele perform relatively poorly across a wide range of cognitive tasks including executive function [9] and working memory (WM) [12]. However, little is known about the gender-specific effects of the COMT genotype and the association of COMT genotype with neural network activation states that mediate WM maintenance [3,24].

One approach to clarify the role of COMT in cognition is examination of neurophysiological parameters that reflect the basic neural mechanisms underlying task performance. Neuroimaging studies have consistently shown that COMT genotype affects measures of brain activation during task performance with Val-carriers, relative to Met-carriers, showing decreases in overall efficiency and reduced performance (i.e., prefrontal hyperactivation) under conditions where the groups are matched on task performance [10]. However, neuroimaging methods lack the subsecond temporal resolution to examine the precise time course of cognitive processes.

Recently many studies have examined the effects of COMT genotype on electrophysiological responses that can be observed in wideband ERP waveforms with subsecond temporal resolution [4]. However, the ERP reflects averaged electrical neural activity originating from multiple brain sources and is the result of superimposition of many event-related oscillations and thus is physiologically complex [14]. In contrast, isolation of specific oscillations allows a more granular dissection of brain electrical responses than wideband ERP waveforms. Two kinds of factors determine the properties of brain oscillations: the intrinsic membrane properties of the neurons and the dynamics of synaptic processes; the modulating influences from general or local neurotransmitter systems [22]. Therefore, brain oscillations are closely related to basic mechanisms of brain activation and are expected to be more directly associated with underlying genomic variation than a highly variable ERP phenotype. Compared to studies with complex neurophysiological traits, which frequently include a large number of participants, electrophysiological studies of brain oscillations afford investigations with smaller sample sizes [25].

WM studies employing electroencephalogram band power as a measure of brain activity have revealed a close relationship between WM and oscillations in theta [13] alpha [18] beta [21] and gamma [26] frequency ranges in healthy humans during the performance of cognitive tasks. Several studies have shown that EEG power in different frequency bands is a highly heritable trait [28]. Thus oscillations represent an important intermediate phenotype for studying behavioral traits and brain network structure. However little is known about which genes contribute to EEG power differences. A close link between brain oscillations and dopamine could be inferred from studies showing changes in dopamine levels are associated with significant amplitude changes in oscillatory activity [11,17]. These studies suggest that dopamine stabilizes cortical microcircuits by increasing slow wave synchrony and enhancing the power of gamma oscillations in prefrontal cortex in response to stimuli.

Very few studies have examined the effects of the COMT genotype on EEG activity during performance on executive tasks [25], and the influence of COMT on brain oscillations during a WM task is unknown. Previous studies provide little insight into the specific task components that may be preferentially sensitive to effects of COMT genotype. The Sternberg task allows for the isolation of cognitive subprocesses (encoding, maintenance and retrieval) involved in WM, and thus may help clarify the relationship between COMT genotype and neurocognitive functioning. Several studies have demonstrated that the association between the COMT polymorphism and WM is particularly pronounced under conditions that place significant demands on WM [9]. Therefore, an increase in WM load might be a promising research parameter in explorations of the effect of COMT genotype on cognitive subprocesses of WM.

Here we used whole-brain magnetoencephalography (MEG) to localize oscillatory activity changes in simultaneously active cortical areas during the performance of a modified version of the Sternberg task. Our goal was to examine the influence of COMT genotype on EEG activity during a task that requires prefrontal activity. We reasoned that COMT genotype might influence cortical oscillatory activity during WM performance. One way to assess cortical oscillatory activity is the event-related desynchronization/synchronization approach in which a relative decrease in the power of any given frequency band is called event-related desynchronization (ERD) and a relative increase in the power is called event-related synchronization (ERS).

1.1. Participants

Recruitment of study participants and genetic analyses, as part of the Clinical Brain Disorders Branch Sibling Study has previously been described [9]. Participants with significant medical conditions that might affect central nervous system function, histories of head trauma, or alcohol or other drug abuse within the past 6 months were excluded. Blood samples were collected and DNA extracted. The COMT Val158Met genotype was determined using assays on demand from ABI as previously described [20]. Twenty-two healthy volunteers in this study were prospectively selected based on their genotypes; 11 homozygous Val/Val allele carriers (6 males; mean age 35.2 years, SD 8.3; mean education years 16.5, SD 2.0) and 11 homozygous Met/Met allele carriers (7 males; mean age 33.7 years, SD 6.8; mean education years 16.6, SD 1.8). Robust statistical differences in COMT have been observed in homozygous individuals with the Val/Val or Met/Met genotypes [10]. Therefore, heterozygous phenotypes were not included. The study was conducted according to the guidelines of the internal review board at the National Institute of Mental Health.

1.2. Behavioral procedures

We employed a modified version of the Sternberg memory task used in our earlier work [1]. The task consisted of an encoding phase (2 s) during which a set of letters was presented, followed by a delay period (6 s) when a fixation point appeared in the centre of the screen, and a response period (2 s) during which a single letter probe was presented for 1 s. This was followed by an inter-trial interval of 1s during which no stimuli were presented. Participants were instructed to press a button as quickly and accurately as possible according to whether the probe had been present (positive probe) or absent (negative probe) in the

preceding string. Working memory demand was manipulated by varying the number of letters (set size: 5 and 8). The control task followed the identical structure except that letters were substituted with a set of horizontal left and right arrows pointing towards the center of the screen, which were presented followed by a single arrow pointing either to the left or to the right, to which a button in the corresponding direction was to be pressed. The experimental and control blocks (each comprising three trials) were alternated. Therefore, three consecutive working memory trials were alternated with three consecutive control trials. There were 24 blocks in total, thus resulting in 72 trials for each load type.

1.3. Image acquisition procedures

MEG signals were recorded in a magnetically shielded room using a helmet-shaped CTF with 275-channel whole head system (CTF Systems Inc., Coquitlam BC, Canada). Stimuli were presented to participants via presentation software (www.neurobs.com). MRIs were acquired on a 1.5 Tesla GE scanner with 124 sagittal slices (thickness 1.5 mm). In order to co-register the MRI and MEG data three fiducial markers were placed on the MRI at the same locations used during MEG data acquisition.

1.4. MEG analysis

All analyzes were performed using the CTF MEG Software package using methods previously reported [1]. Briefly, MEG signals were sampled at a rate of 600 Hz, third gradient balancing was applied to remove the background magnetic signal, and then high-pass filtered at 0.61 Hz. All raw data were reviewed by visual inspection and trials that contained artifacts were rejected. The data were divided into four frequency bands: theta (4–7 Hz), alpha (8–12 Hz), beta (14–30 Hz), and gamma (30–50 Hz). For analysis of brain activity, only trials on which responses were correct were included. We derived brain shape models by first stripping the skull from the structural data. The brain shape was used for forward modeling of the MEG signals. Synthetic aperture magnetometry (SAM) was used to reconstruct whole brain volumes in each frequency band. We used dual-state imaging, in which the normalization of active state (memory task) is computed using real brain noise, a so-called control state (control task). The amplitude was obtained by computing a *pseudo-F* ratio between the power in the active and the control state. Band power changes were expressed as the percentage of a decrease (ERD) or increase (ERS) in band power. In the case of ERS, the *pseudo-F* value is derived from the formula $A/C - 1$, where A is the source power in the active state and C is the source power in the control state. For ERD, the formula is $-((C/A) - 1)$. A calculation of source power was performed for 7.5 mm³ voxels throughout the brain volume.

To define the spatio-temporal sequence of those cerebral regions active during different phases of the experiment, the SAM analyzes were performed on the entire active epochs (encoding, delay and retrieval). Trials were segmented using a sliding 500 ms time window with 100 ms increments and compared to the corresponding time window in the control task. The SAM volumes were then normalized to Z -scores. The effects of genetic polymorphisms on the evoked oscillations were tested with an analysis of variance (ANOVA) design with genotype as between-subjects variable and load as the within-subjects variable. Participants were treated as a random factor and genotype was treated as fixed effect in a mixed

model. Planned contrast analyzes (Val/Val versus Met/Met; low versus high memory load; genotype $\times$ memory load) were modeled as contrast statements ($-1\ 1$) within the ANOVA. Statistical analyzes were computed at each time window over the course of experiment and for each frequency band. The random permutation analyzes were performed for each time window to take care of the problem that the voxels are not computed independently. Random permutation analysis performed an ANOVA over and over with shuffled data to build up a distribution of statistical values for each voxel. These values were used to calculate corrected P -values that more accurately reflect the per-voxel statistics [1].

To analyze the group data in a common anatomical space the structural data and SAM volumes were aligned into Talairach space using Analysis of Functional NeuroImages (AFNI) [7]. All reported effects in these analyzes were reliable at the $P < 0.05$ level unless otherwise indicated. Demographic variables were examined in a series of χ^2 and t -test analyzes. Group differences and Group $\times$ set size interactions were tested for accuracy (% correct), reaction time (RT) by means of ANOVA. To examine correlations between brain activity and behavioral performance we used a region of interest (ROI) approach [1].

2. Results

2.1. Behavioral data

The genotype subgroups (11 Val/Val and 11 Met/Met participants) did not differ significantly in age, male/female ratio and education years (all $P > 0.05$). In the Met–Met group average performance was 82.6 (SD 3.8) and 80.5 (SD 4.2) at low and high memory load respectively. In the Val–Val group average performance was 81.5 (SD 4.5) and 80.3 (SD 4.8) at low and high load respectively. On correct answers, repeated measures ANOVA revealed no main effect of genotype ($F(1,20) = 1.22$, $P > 0.73$), and no difference in accuracy as a function of load ($F(1,20) = 5.55$, $P > 0.92$), and nor a significant interaction between genotype and load ($F(1,20) = 6.22$, $P > 0.8$). In the Met–Met group average reaction times were 773 (SD 188) and 907 ms (SD 185) at low and high memory load respectively. In the Val–Val group average reaction times were 815 (SD 191) and 914 ms (SD 195) at low and high memory load respectively. Repeated measures of ANOVA revealed no main effect of genotype ($F(1,20) = 1.01$; $P = 0.9$), but participants responded more slowly with increasing memory load ($F(1,20) = 6.72$ $P < 0.02$), but there was not a significant interaction between genotype and load ($F(1,20) = 0.02$; $P = 0.9$). We correlated RTs in the low and high load WM conditions with beta ERDs values from several cortical areas observed during the response period. We did not find evidence of the hypothesized positive RT-ERDs relationship (i.e., better performance (short RTs) associated with less cortical activation) probably due to the small sample size. However, the correlation between performance and beta ERDs from left prefrontal area was in the expected (positive) direction ($r = 0.40$).

2.2. MEG data

The average number of trials without artifacts was 30 for the low memory load condition and 29 for the high memory load condition. A significant main effect of genotype during the delay period was observed in the gamma frequency range in the left frontal regions from 4000 to 5200 ms after stimulus onset, where less ERS responses were found in the Val/Val

relative to Met/Met group ($F(1,20)$, $P < 0.03$, corrected). Greater beta ERD responses during the delay period were observed from 2000 to 3000 ms and from 4700 to 5100 ms after stimulus onset in the left frontal and parietotemporal regions in the Val/Val relative to Met/Met group ($F(1,20)$, $P < 0.01$, corrected). Additionally, from 7100 to 7900 ms after stimulus onset in the right prefrontal and parietal regions greater alpha ERS responses were observed in the Val/Val than in the Met/Met group ($F(1,20)$, $P < 0.01$, corrected) (Fig. 1). There was no main effect of the COMT polymorphism in the theta frequency ($F(1,20)$, $P > 0.05$). A significant interaction between genotype and memory load was found in the beta range in the left prefrontal and temporal regions peaking at 4700 ms ($F(1,20)$, $P < 0.01$, corrected) and in the alpha range in the right prefrontal regions peaking at 7700 ms ($F(1,20)$, $P < 0.01$, corrected) after stimulus onset. The Val/Val group displayed a significant increase of activation from low to high WM load in both alpha and beta frequencies ($P < 0.01$); the Met/Met group did not exhibit such an increase in activation ($P > 0.05$). During the response period a significant main effect of genotype was present in the left prefrontal regions and left parietal areas where greater ERD responses were found in the Val/Val relative to Met/Met group from 8300 to 8700 ms ($F(1,20)$, $P < 0.01$, corrected), but there was no interaction between genotype and memory load ($F(1,20)$, $P > 0.05$).

3. Discussion

The major findings of this study were that Val homozygotes, as compared to Met homozygotes, exhibited less ERS in the gamma frequency in the left prefrontal areas, increased ERD in the beta band in the left frontal-parietotemporal regions and increased ERS in the alpha frequency in the right prefrontal-parietal regions during the delay period of the Sternberg Task. During the response period Val homozygotes showed increased ERD responses within the beta range in prefrontal-parietotemporal regions.

The enhancement in gamma power during the retention interval of a delayed match-to-sample task has been often interpreted as an indicator of the formation of neural assemblies involved in the maintenance of WM information [18,26]. In our study, Val/Val homozygous participants exhibited lesser magnitude of the gamma ERS in early latencies of the maintenance period suggesting reduced activation within the prefrontal network compared to Met/Met homozygous individuals. This attenuation of the gamma band power is consistent with the abnormal oscillations proposed to underlie some disorders associated with cortical dopaminergic deficiency such as Parkinson's disease and schizophrenia [11,17]. Cortical dopamine is thought to modulate the excitability of intrinsic GABAergic and glutamatergic cortical neurons, considered to be critical for establishing gamma frequency oscillations. Particularly, dopamine effects appear to be mediated by D1 receptor stimulation, which likely enhances *N*-methyl-D-aspartate (NMDA) conductance of both pyramidal neurons and inhibitory interneurons responsible for generating those oscillations [5,30]. Therefore, modification of gamma oscillations by COMT polymorphism points toward abnormal dopamine–glutamate interactions within prefrontal networks. The differences between the two genetic groups were not apparent in performance but appeared from ERS/ERD patterns. Such a result is probably because participants were able to activate enough processing resources to succeed in the task and this mobilization of processing resources clearly appeared on ERS/ERD patterns in the lower frequencies.

Several studies have reported beta ERD responses in frontal regions in association with WM maintenance [1,21]. It has been suggested that transition from local gamma oscillations to oscillatory activity in the beta range would modulate the network synaptic efficiency and promote the rehearsal of representation of the stimulus during WM [18,27]. These studies reported increased beta power during the delay phase of WM tasks suggesting that beta activity reflected activation of larger distributed networks. However, beta energy decrease is generally considered an indicator of cortical activation reflecting small neuronal assemblies working in a relatively independent manner during cognitive processes [22]. An increased ERD in the beta frequency could be a consequence of the involvement of a larger network or more cell assemblies in information processing. Previous studies revealed that factors contributing to such an enhancement are more efficient task performance and more effort and attention in patients and the elderly [15,22]. Thus, it is conceivable that the greater magnitude of beta ERD during the delay observed in the Val homozygotes indicates that the memory task place higher working memory demands on them as compared to Met homozygotes.

Alpha oscillatory activity reflects reverberating activity in thalamo-cortical and cortico-cortical circuits [19]. Enhanced alpha power in the prefrontal cortex has been often interpreted as a correlate of frontal executive processes [18]. Alternatively alpha ERS reflects an inhibition of brain areas no longer involved in task completion once the capacity limits of WM are reached or exceeded and alternative strategies are needed and utilized [16]. The capacity limits of WM may have been stressed in Val homozygotes at the end of the delay period, and enhanced alpha ERS may reflect deactivation of the right prefrontal networks not directly involved in maintenance. This interpretation is consistent with a recent study that found Val homozygotes had relative increased power in frontal regions within the alpha range; whereas, Met homozygotes had attenuated power in the alpha band during executive processing although the task performance did not show significant differences between Val/Val and Met/Met groups [25]. Our results are also consistent with recent experimental data demonstrating that alpha oscillations were enhanced in the prefrontal cortex of subhuman primates during learning by the dopamine D1 receptor antagonist [23]. Our present results are also in line with a report of exacerbated alpha ERS in patients with schizophrenia and their non-schizophrenic co-twins during WM maintenance suggesting that the capacity limits of WM were most probably exceeded in patients and their siblings relative to healthy controls [2].

There is also evidence for an involvement of dopamine in theta oscillations. Dopamine from the ventral tegmental area modulates the hippocampal-prefrontal theta coherence which is a central mechanism underlying WM [8]. Based on these findings, we might expect a significant impact of COMT genotype on oscillatory brain activity in theta. However, we did not find differences between the two genotype groups in the evoked theta responses. Task differences may be a factor in variable findings related to theta frequency signals, and there is evidence that theta oscillations are generated in the anterior cingulate cortex that is involved in complex cognitive tasks [13]. Thus, it is conceivable that the role of COMT in the cingulate remains minimal during the performance of a simple cognitive task such as the Sternberg task. During retrieval, beta ERD responses were significantly greater in the prefrontal cortex and parietotemporal regions in Val than in Met homozygotes. It has

been suggested that beta ERD responses during the recognition stage of delayed matching-to-sample tasks reflect active memory search processes [21], and recent data suggest that dopamine may be particularly important in this specific aspect of cognitive control [29]. Therefore, one possible explanation is that increase of beta ERD responses in the Val/Val group might reflect covert neurophysiological changes in the efficiency of memory retrieval, such that for Val/Val individuals higher neural activation may be required to achieve optimal response discriminability.

The main limitation of this study is the small sample size which can lead to spurious positive findings. However, in contrast with traditional studies in which ERS/ERD responses are calculated in reference to a prestimulus baseline we used a separate control task as a baseline, since it is well known that the ERS/ERD responses are influenced by the absolute frequency power in the prestimulus interval. From a statistical point of view we employed statistical tests that do not assume equal variance between groups. Moreover, to ensure the most stable value possible to describe the ERS/ERD responses a mean amplitude measure computed over a relatively long time window at any frequency was used.

4. Conclusion

In conclusion, the present data show a strong impact of COMT genotype on an electrophysiological correlate of prefrontal circuits functioning during WM. Val/Val participants showed smaller gamma ERS, greater alpha ERS and beta ERD during the delay and greater beta ERD during the retrieval likely reflecting changes in the efficiency of prefrontal and parietotemporal circuits during WM. Neurophysiological approaches such as the present one are valuable tools to further elucidate the impact of genetic variation on functional brain activation.

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HIGHLIGHTS

- Influence of COMT polymorphisms on brain oscillatory activity during working memory.
- Study is conducted using a neuroimaging technique with high temporal resolution: MEG.
- The spatiotemporal distribution of ERD/ERS is identified.
- COMT polymorphisms modulate brain oscillations within prefrontal cortical networks.

Fig. 1.

The upper panels present gamma (30–50 Hz) event-related synchronization (ERS) in the Met–Met (A) and Val–Val groups (B) during the maintenance phase (4000–5200 ms) of the task ($P < 0.01$). ERS in the left frontal area was more prominent in the Met–Met than in the Val–Val. (C) Significant difference in the gamma power is shown in the left frontal area (VAL < MET; $P < 0.03$). (D) A significant increase in beta (14–30 Hz) event-related desynchronization (ERD) is shown in the left frontal areas in Val–Val group relative to Met–Met group during the maintenance phase (4700–5100 ms) ($P < 0.01$). (E) A significant increase in alpha (8–12 Hz) ERS in the right frontal–parietal areas is shown in the Val–Val group relative to Met–Met group during the maintenance phase (7100–7900 ms) ($P < 0.02$). (F) A significant increase in beta ERD is shown in left frontal–parietal areas in the Val–Val group relative to the Met–Met group during the retrieval phase (8300–8700 ms) ($P < 0.01$). Red color coding indicates a task related power increase; blue color coding indicates a task related power decrease. The figure shows data rendered onto a Talairach-space surface template.