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Brief report

Association between *COMT* Val158Met genotype and EEG alpha peak frequency tested in two independent cohorts

Cornelis P.M. Veth [a,b,*], Martijn Arns [c,d], Wilhelmus Drinkenburg [e], Willem Talloen [e], Pieter J. Peeters [e], Evian Gordon [f], Jan K. Buitelaar [b]

[a] Radboud University Medical Center, Department of Psychiatry, PO Box 9101, 6500 HB Nijmegen, The Netherlands
[b] Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Cognitive Neuroscience, PO Box 9101, 6500 HB Nijmegen, The Netherlands
[c] Research Institute Brainclinics, Bijleveldsingel 34, 6524 AD Nijmegen, The Netherlands
[d] Utrecht University, Department of Experimental Psychology, Utrecht, The Netherlands
[e] Janssen Research and Development, Pharmaceutical Companies of Johnson & Johnson, Turnhoutseweg 30, B-2340 Beerse, Belgium
[f] Brain Resource Limited, Level 12, 235 Jones St. Ultimo, NSW 2007, Australia

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ABSTRACT

This study could not confirm the association between the Catechol-O-Methyltransferase Val158Met polymorphism (*COMT*) and electroencephalographic (EEG) alpha peak frequency (APF) in two independent cohorts of 187 (96 depressed and 91 healthy participants) and 413 healthy participants. If *COMT* and APF play a role in depression or antidepressant treatment response, they do not have a shared pathway. We emphasize the importance of publishing null-findings for obtaining more accurate overall estimates of genetic effects.

1. Introduction

The functional polymorphism of Catechol-O-Methyltransferase Val158Met (*COMT*) strongly influences catecholamine (dopamine and norepinephrine) driven processes in prefrontal cortex and cortico-limbic brain connections (Lachman et al., 1996; Chen et al., 2004). Compared to the *COMT* ValVal genotype, carriers of the *COMT* Met allele have higher catecholamine levels in the prefrontal cortex. Additionally, higher catecholamine availability causes higher vigilance by higher corticolimbic reactivity (Goddard et al., 2010; Schellekens et al., 2012). Several studies investigated the 'Worrier–Warrier' hypothesis (Goldman et al., 2005; Stein et al., 2006), which states that *COMT* Met carriers (worriers) have enhanced cognitive performance but worse emotional processing, compared to the *COMT* ValVal genotype (warriors) (Enoch et al., 2003; Drabant et al., 2006; Williams et al., 2010). This modulation of emotional processing by *COMT* is thought to have a pivotal role in depression pathway and depression treatment mechanisms (Opmeer et al., 2010; Kocabas, 2012).

However, studies about the influence of *COMT* in depression (treatment) show inconclusive results (Niitsu et al., 2013). It is yet not known if the effects of *COMT* are mediated within a neurogenetic pathway. An appropriate neuroimaging method for finding such genetic effects is electroencephalograhic (EEG) alpha peak frequency (APF). APF is among the most heritable measures in the resting state EEG with an estimated heritability of 81% (Van Beijsterveldt and van Baal, 2002). APF is the frequency at maximum power within the alpha band (8–12 Hz) with a mean around 10 Hz in adults. APF is mostly assessed during resting state eyes closed condition, when alpha oscillations are prominently present (Steriade et al., 1990). APF reflects thalamocortical information exchange (Lopes Da Silva and Storm Van Leeuwen, 1977) and predicts cognitive performance (Klimesch, 1997) but also response to antidepressant treatments (Ulrich et al., 1984; Arns et al., 2012a, 2012b; Arns and Olbrich, 2014). These characteristics of APF might be explained by catecholamine regulation by *COMT* (Bazanova and Vernon, 2013).

Recently, a large effect of *COMT* on APF has been reported in a small population of healthy men ($n=21$), where the *COMT* MetMet

* Corresponding author at: Radboud University Medical Center, Department of Psychiatry, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 646201471.
E-mail address: cpmveth@gmail.com (C.P.M. Veth).

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genotype showed a 1.4 Hz faster APF than *COMT* ValVal (Cohen's D effect size (ES): −1.05) (Bodenmann et al., 2009).

Given this association of *COMT* with APF and the potency for personalizing treatment of depression, we hypothesized that *COMT* and APF share a pathway to antidepressant treatment response.

In this study, we attempted to replicate the association between *COMT* and APF with the use of general APF methods (Steriade et al., 1990). Furthermore, frontal APF was analyzed because *COMT* influences prefrontal catecholaminergic neurotransmission (Mier et al., 2010). Additionally, we took into account potential confounders such as brain region, ethnicity (Domschke et al., 2012), age, gender (Chiang et al., 2011) and diagnosis (depressed or healthy controls). Moreover, we analyzed effects of *COMT* on APF in two large independent cohorts.

2. Methods

In this study, two independent cohorts were used (see Supplementary material for detailed methodology and Cohort characteristics).

2.1. Cohort-1

Participants ($n=96$ depressed and $n=91$ healthy) were recruited in the area of Sydney and Adelaide (Australia). They were between 18 and 65 years old and mainly had a European ancestry ($n=104$). Participants were originally matched on gender, age and ethnicity and were screened for DSM-IV psychiatric disorders using the Mini-International Neuro-psychiatric Interview (Sheehan et al., 1998). Medication-free depressed participants were included if the depressive symptoms were not caused by other primary somatic causes or DSM-IV diagnoses. The Sydney West Area Health Service and the University of Sydney Human Research Ethics Committees approved the study.

2.2. Cohort-2

Healthy participants ($n=413$) between 18 and 65 years were obtained from the Brain Resource International Database administered by BRAINnet for scientific access (BRID; www.brainnet.net). All participants were recruited from metropolitan regions in the USA, Europe, and Australia. Screening procedures were identical as in Cohort-1. Healthy participants (European ethnicity) with complete *COMT* genotype and APF data were included. Independent Review Board (IRB) approval was obtained for all sites.

2.3. Electroencephalography

Participants in both cohorts underwent two-minute resting state EEG recordings using a standardized methodology (Brain Resource Ltd., Australia). Details of EEG procedures, reliability, validity and across site-consistency have been published elsewhere (Williams et al., 2005; Paul et al., 2007, Arns et al., 2008).

APF was defined as the frequency at frontal and parietal brain regions (Chiang et al., 2008), which was determined at the maximum value within the defined alpha band (6–12 Hz). For replication purposes APF at C3 was determined in Cohort-1 separately.

2.4. Genotyping

Genotyping was similar in both cohorts. Genomic DNA was extracted from cheek swab samples and *COMT* Val108/158Met genotypes were determined by polymerase chain reaction amplification and restriction fragment polymorphism analysis. Genotype group distributions in both cohorts were checked for accordance with Hardy–Weinberg equilibrium (Rodriguez et al., 2009).

2.5. Statistical analyses

Data were analyzed with SPSS (version 18.0, Chicago, IL). APF was modeled in a repeated measure ANOVA with region (Parietal and Frontal) as within subject factor and *COMT*, ethnicity, gender and diagnosis (Cohort-1) as between subject factor. For purpose of replication, APF at electrode C3 was added to the model for Cohort-1 as within subject factor. Age was added as covariate in all models. All two-way interactions with *COMT* were tested. Post hoc power calculations were made using the G*Power program (Faul et al., 2007).

3. Results

In both Cohorts the observed *COMT* genotype distributions were in agreement with expected values according to the Hardy–Weinberg equilibrium (*Cohort-1*: $P=0.83$; *Cohort-2*: $P=0.82$).

3.1. Cohort-1

Repeated measure models did not show a main effect of *COMT* on APF ($F_{2,162}=1.06$, $P=0.35$) and the effect size appeared very small: ES=0.01. There were no significant two-way interactions of *COMT* × region ($F_{4,344}=0.32$, $P=0.85$), *COMT* × gender ($F_{2,172}=0.06$, $P=0.95$), *COMT* × age ($F_{2,172}=1.23$, $P=0.30$), *COMT* × ethnicity ($F_{2,172}=1.35$, $P=0.26$) and *COMT* × diagnosis ($F_{2,172}=0.76$, $P=0.47$). Only age ($F_{1,309}=17.6$, $P<0.001$) and brain region ($F_{2,309}=8.57$, $P<0.001$) demonstrated significant associations with APF.

3.2. Cohort-2

There was no main effect of *COMT* on APF ($F_{2,406}=0.85$, $P=0.43$) with very small effect size (ES=0.00). There were no significant two-way interactions: *COMT* × gender ($F_{2,404}=0.37$, $P=0.69$), *COMT* × age ($F_{2,404}=2.19$, $P=0.11$) and *COMT* × region ($F_{2,404}=1.08$, $P=0.35$). Only age ($F_{1,406}=2.00$, $P=0.07$) and brain region ($F_{1,406}=4.39$, $P=0.09$) demonstrated associations with APF at trend level.

3.3. Posthoc analyses

Since we were unable to find the association between *COMT* and APF as found in the original study, we conducted the following tests to more closely replicate the Bodenmann et al. (2009) findings:

1. The above analyses repeated contrasting *COMT* ValVal vs. MetMet: No main effect of *COMT* on APF was found (*Cohort-1*: $F_{1,75}=0.82$, $P=0.37$; *Cohort-2*: $F_{1,205}=0.76$, $P=0.39$).
2. The above analyses repeated in a pooled subgroup ($n=22$) with identical inclusion criteria as used in the original study (healthy males aged 20–26): No main effect of *COMT* on APF was found ($F_{1,18}=2.01$, $P=0.17$).
3. Post-hoc power analyses showed that both cohorts had more than 90% power to detect effect sizes (ES) of COMT on APF smaller than 0.3.

4. Discussion

4.1. COMT, alpha peak frequency and response on antidepressive treatment

Both *COMT* genotype and APF are potential markers for antidepressant treatment response. Recently, an association between *COMT* and APF was reported with a large ES (ES = −1.05), suggestive of a neurogenetic pathway for antidepressant treatment response. However, we were unable to replicate this association between APF and *COMT* MetMet vs. ValVal homozygotes (Bodenmann et al., 2009; $n=21$) in two independent and large cohorts ($n_{cohort\text{-}1}=187$ and $n_{cohort\text{-}2}=413$). Post-hoc tests, in an identical subgroup as compared to the original study, and at the same electrode site (C3) also failed to find any association between *COMT* on APF. Finally, the ES from both cohorts were very small and post-hoc power analyses demonstrated our study was adequately powered to detect small to medium ES. Therefore, we

Table 1
Distribution and means (S.D.) of demographics and APF for each *COMT* genotype.

COMT Val158Met genotypes[b]			
Cohort-1($n=187$)[a]	ValVal($n=46$)	ValMet($n=95$)	MetMet($n=46$)
Age	34.0(14.6)	39.1(12.7)	40.1(13.8)
Gender (m/f)	17/29	34/61	21/25
Ethnicity (European/other)	24/22	48/47	32/14
Diagnosis (depressed/healthy)	25/21	49/46	22/24
Parietal APF (Hz)	9.8(0.9)	9.4(0.9)	9.3(1.2)
Frontal APF (Hz)	9.2(1.1)	8.9(1.1)	8.8(1.3)
Cohort-2($n=413$)	ValVal($n=89$)	ValMet($n=203$)	MetMet($n=121$)
Age (yrs)	41.6(15.2)	37.7(15.2)	38.0(13.7)
Gender(m/f)	44/45	101/102	64/57
Parietal APF(Hz)	9.6(0.9)	9.8(1.0)	9.7(0.9)
Frontal APF(Hz)	9.4(0.9)	9.6(1.1)	9.5(0.9)

[a] Values are given as means (S.D.) for string variables and the distribution for binary variables.
[b] Catechol-O-methyltranferase polymorphism genotypes: ValVal; ValMet; and MetMet. Genotype frequencies are in Hardy–Weinberg equilibrium.

were unable to confirm a neurogenetic pathway between *COMT* and APF.

4.2. Limitations

Our study used different EEG recordings compared to Bodenmann et al. (2009). We used a 26 channel EEG with linked ears as reference electrodes, whereas the original study used C3-A2 as a reference. However, validated accepted methods of resting state EEG and APF measures were used in our cohorts (Kondacs and Szabó, 1999; Näpflin et al., 2007). Both referencing methods use neutral mastoids as reference and therefore, it is very unlikely that differences in EEG referencing method explain the lack of results. Another difference is the use of a 5 min period of EEG measurement by the original study (our study used 2 min EEG recordings) and control for time of the day, and monitored sleep-wake of the participants. However, given the high heritability and reliability of APF, this difference in EEG conditions is also not likely to explain the contrast between our null-findings and the previous claim that *COMT* would have a large effect on APF. Moreover, we did not find any similar effect of *COMT* in two independent and larger populations, which strengthens the conclusion from our results.

4.3. Future directions

Recently, non-replication of genetic findings has been discussed. Small sample sizes, stratification and multiple testing may explain inter-study discrepancies. Large populations are needed and positive results have to be replicated to overcome publication bias (Ioannidis et al., 2006), as has been shown also elsewhere (Zoon et al., 2013; Spronk et al., 2013). We emphasize the importance of publishing null-findings, which will contribute to obtain more accurate overall estimates of genuine genetic effects. Table 1.

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Brain Resource Company (BRC, Australia) and Johnson & Johnson RRD (J&J, Belgium) sponsored this study, but analyses were not constrained by either party.

Conflict of interest

The authors have no declared conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2014.05.021.

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