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The COMT Val¹⁵⁸Met polymorphism does not modulate the after-effect of tDCS on working memory

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Abstract

Transcranial direct current stimulation (tDCS) can alter cortical excitability, neural plasticity, and cognitive-behavioral performance; however, its effects are known to vary across studies. A partial account of this variability relates to individual differences in dopamine function. Indeed, dopaminergic manipulations alter the physiological and cognitive-behavioral effects of tDCS, and gene polymorphisms related to dopamine have predicted individual response to online tDCS (i.e., stimulation overlapping with the critical task). Notably, the role of individual differences in dopamine has not yet been properly assessed in the effect of offline tDCS (i.e., stimulation prior to the critical task). We investigated if and how the COMT Val¹⁵⁸Met polymorphism (rs4680) modulates the after-effect of prefrontal tDCS on verbal working memory (WM). One hundred and thirty-nine participants were genotyped for the COMT Val¹⁵⁸Met polymorphism and received anodal-over-left, cathodal-over-right (AL-CR), cathodal-over-left, anodal-over-right (CL-AR), or sham stimulation over the dorsolateral prefrontal cortex in a between-subjects, pretest–posttest study design. WM was assessed using the N-back task. The results provide no evidence that the COMT polymorphism impacts the after-effect of prefrontal tDCS on WM. Taken together with previous findings on dopamine and tDCS interactions, the results of the present study suggest that (a) indirect markers of dopamine (such as COMT) are differently related to online and offline effects of tDCS, and (b) findings from studies involving pharmacological manipulation should be generalized with caution to findings of inter-individual differences. In sum, we argue that state (i.e., a manipulation of) and trait (i.e., baseline) differences in dopamine may exert different effects on online and offline tDCS.

KEYWORDS

COMT, dopamine, individual differences, transcranial direct current stimulation, working memory

Abbreviations: AL-CR, Anodal-over-left, cathodal-over-right; CL-AR, Cathodal-over-left, anodal-over-right; COMT, Catechol-O-methyltransferase; DA, Dopamine; dlPFC, Dorsolateral prefrontal cortex; PFC, Prefrontal cortex; RT, Reaction time; tDCS, Transcranial direct current stimulation; WM, Working memory.

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1 | INTRODUCTION

Recent research has increasingly focused on the idea that noninvasive brain stimulation can serve as an effective tool to investigate and possibly enhance the neuromodulation of cognitive-behavioral performance. Of the available techniques, transcranial direct current stimulation (tDCS) is a popular method of transiently enhancing performance or augmenting the gains from extended training. tDCS alters cortical excitability (Nitsche & Paulus, 2000) and at longer stimulation periods affects neural plasticity (Nitsche & Paulus, 2001; Nitsche, Nitsche, et al., 2003), by inducing a polarity-dependent shift in the resting membrane potential of cortical neurons. It has been questioned whether these physiological changes translate to reliable effects on cognition (Horvath, Forte, & Carter, 2015a; Horvath, Forte, & Carter, 2015b; Mancuso, Ilieva, Hamilton, & Farah, 2016), but reviews on this issue often suffer many limitations that prevent an unequivocal answer (Antal, Keeser, Priori, Padberg, & Nitsche, 2015). Notwithstanding the variability in results that might be explained by methodological differences across studies, it has been suggested that individual differences in dopamine (DA) function within and across studies might partially account for variable effects of tDCS (Li, Uehara, & Hanakawa, 2015; Wiegand, Nieratschker, & Plewnia, 2016). In the present study, we explore this idea by investigating whether a genetic predisposition toward higher or lower prefrontal DA activity predicts the effect of tDCS on verbal working memory (WM).

There is converging evidence that DA indeed has an important impact on tDCS effects. Pharmacological stimulation of DA receptors has nonlinear effects on tDCS-induced neuroplasticity, and blockage of DA receptors can eliminate effects on plasticity entirely (Fresnoza, Paulus, Nitsche, & Kuo, 2014; Fresnoza, Stiksrud, et al., 2014; Kuo, Paulus, & Nitsche, 2008; Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010; Monte-Silva et al., 2009; Nitsche et al., 2006, 2009). These studies point to an inverted-U-shaped relationship between DA activity and tDCS effects (Wiegand et al., 2016), as low and high, but not moderate, stimulation of DA receptors abolished tDCS-induced changes in neuroplasticity (Fresnoza, Paulus, et al., 2014; Monte-Silva et al., 2010). However, moderate DA enhancement did strengthen long-term depression-like effects of cathodal tDCS, while it converted after-effects of anodal tDCS from long-term potentiation to long-term depression-like effects (Kuo et al., 2008; Monte-Silva et al., 2010). An inverted-U-shaped relationship is also observed in studies of pre-existing differences rather than artificially induced changes in DA function, with results varying depending on the type of stimulation and experimental task conditions. Using the COMT Val¹⁵⁸Met polymorphism to estimate individual differences in prefrontal DA, it was shown that tDCS impaired cognitive flexibility

in individuals with high DA activity who received excitatory stimulation during task performance (Plewnia et al., 2013). In contrast, tDCS impaired response inhibition in individuals with low DA activity who received inhibitory stimulation during the task (Nieratschker, Kiefer, Giel, Krüger, & Plewnia, 2015).

These results were conceptually mirrored in a recent study examining the effect of a modest dopaminergic manipulation on the cognitive-behavioral effects of tDCS (Jongkees, Sellaro, et al., 2017). Stimulation was combined with administration of L-tyrosine, the biochemical precursor of L-dopa and DA, to transiently enhance DA activity. Results showed that prefrontal tDCS impaired performance on the N-back task when L-tyrosine was combined with excitatory stimulation of the left dorsolateral PFC (dlPFC), whereas it trend-wise enhanced performance when L-tyrosine was combined with inhibitory stimulation of the left dlPFC. The authors speculated that DA and tDCS might interact on cortical excitability such that an increase in DA combined with excitatory stimulation results in overexcitability of the cortex, whereas combined with inhibitory stimulation it might serve to promote cortical signal-to-noise ratio. Together with the aforementioned studies, these findings highlight a state-dependency of tDCS effects, with the type of stimulation interacting with the individual dopaminergic activity state.

To account for these behavioral findings, it has been proposed that tDCS might bring an individual closer to or further away from an optimal level of dopaminergic signaling (Nieratschker et al., 2015; Plewnia et al., 2013; Wiegand et al., 2016), which would be consistent with animal literature demonstrating that tDCS can enhance DA release (Tanaka et al., 2013). Specifically, individuals with an already optimal level of signaling, such as those with high prefrontal DA activity due to genetic predisposition or L-tyrosine administration, might be pushed toward a sub-optimal, too high level of activity that results in impaired performance when they receive excitatory stimulation. Conversely, individuals with a lower-than-optimal level of signaling due to low prefrontal DA activity might show impaired performance when that activity is further reduced by inhibitory stimulation. In brief, an individual's initial position on the inverted-U curve relating DA and performance would determine whether a shift toward the right or left on the curve (due to excitatory or inhibitory stimulation, respectively) enhances or impairs performance.¹

¹It is noteworthy that this interaction between tDCS and DA might not necessarily reflect a direct impact of the former on the latter, but might instead be mediated by tDCS-induced changes in levels of glutamate and GABA (Bachtar, Near, Johansen-Berg, & Stagg, 2015; Kim, Stephenson, Morris, & Jackson, 2014; Stagg et al., 2009).

1.1 | The present study

This line of reasoning has been applied primarily to online effects of tDCS, that is, stimulation *overlapping* with the critical task. In the present study we investigated whether this hypothesis extends to offline tDCS as well, that is, stimulation *prior* to the critical task. Whereas online effects are attributed mainly to a modulation of cortical excitability, offline effects reflect changes in neural plasticity (Nitsche & Paulus, 2000; Nitsche, Nitsche, et al., 2003). Both can be sensitive to DA, with the interaction between DA and online tDCS being mediated partially by interacting effects on task-induced activity (Bortoletto, Pellicciari, Rodella, & Miniussi, 2015; Mattay et al., 2003). On the other hand, the interaction with offline tDCS might be mediated by effects on N-methyl-D-aspartate (NMDA) receptors which drive neuroplasticity via long-term potentiation and depression (Gurden, Takita, & Jay, 2000; Huang, Simpson, Kellendonk, & Kandel, 2004; Spencer & Murphy, 2000). Given that a DA manipulation has previously altered the cognitive-behavioral after-effect of tDCS (Jongkees, Sellaro, et al., 2017), and individual baseline differences in DA have predicted online effects of tDCS (Nieratschker et al., 2015; Plewnia et al., 2013), it is conceivable that these individual differences predict the after-effects of offline tDCS as well. We were interested in the effects on WM in particular, because this process is the most-often investigated process in tDCS studies. Hence a demonstration that individual differences modulate the after-effects of tDCS on WM—or a lack of such a modulation—would have implications for a majority of the existing tDCS literature.

Following the only two available studies on individual differences in DA and cognitive-behavioral effects of prefrontal tDCS (Nieratschker et al., 2015; Plewnia et al., 2013), we assessed genetic predisposition toward higher or lower dopaminergic signaling in the prefrontal cortex (PFC) using the COMT Val¹⁵⁸Met polymorphism. The COMT enzyme is responsible for degradation of extracellular DA, and differences in thermolability of the enzyme determined by different COMT polymorphisms affect the rate at which DA is degraded (Weinshilboum, Otterness, & Szumlanski, 1999). Carriers of the Val allele have a less thermolabile enzyme that results in faster degradation and, consequently, lower concentrations of DA, whereas carriers of the Met allele have a more thermolabile enzyme that results in slower degradation and, consequently, higher concentrations of DA. The COMT polymorphism relates to prefrontal DA activity in particular (Karoum, Chrapusta, & Egan, 1994) due to a relative lack of DA transporters in the PFC as compared to their abundance in the striatum (Lewis et al., 2001). Consistent with a lower prefrontal DA concentration, Val-carriers demonstrate less efficient cortical

processing (Egan et al., 2001; Mattay et al., 2003) and worse behavioral performance during WM tasks (Goldberg et al., 2003), but also better task-switching performance as compared to Met-carriers (Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010). Most important for our purposes, this polymorphism has previously predicted the effect of prefrontal tDCS on cognitive-behavioral performance (Nieratschker et al., 2015; Plewnia et al., 2013), making it the most obvious marker of individual differences in DA for this study's purpose.

Considering tDCS effects likely vary depending on experimental parameters such as electrode placement and stimulation duration, we opted for a stimulation montage and duration of which the after-effects are known to be sensitive to a mild DA manipulation (Jongkees, Sellaro, et al., 2017). Electrodes were placed over dlPFC in a bilateral bipolar-balanced montage (Nasseri, Nitsche, & Ekhtiari, 2015). This montage previously enhanced WM in antidepressant-free patients with major depressive disorder (Oliveira et al., 2013). Of particular relevance to our purposes, in healthy adults this type of stimulation has been shown to interact with a dopaminergic manipulation on WM (Jongkees, Sellaro, et al., 2017) in a manner that is similar to studies on individual differences in DA and cognitive-behavioral effects of online tDCS (Nieratschker et al., 2015; Plewnia et al., 2013).

In brief, 139 participants were genotyped for the COMT Val¹⁵⁸Met polymorphism and received either anodal-over-left, cathodal-over-right (AL-CR) dlPFC stimulation, cathodal-over-left, anodal-over-right (CL-AR) or sham stimulation in a between-subjects, sham-controlled, pre-test–posttest study design. Based on previous findings (Jongkees, Sellaro, et al., 2017; Nieratschker et al., 2015; Plewnia et al., 2013), we expected individuals with high dopaminergic signaling, that is Met-carriers, to demonstrate worse WM performance after receiving excitatory stimulation (AL-CR) over the left dlPFC—as compared to sham stimulation—whereas individuals with low dopaminergic signaling, that is Val-carriers, were expected to demonstrate worse WM performance after receiving inhibitory stimulation (CL-AR) over the left dlPFC. The inverted-U-curve proposed by (Wiegand et al., 2016) also suggests that Val-carriers may potentially benefit behaviorally from a slight increase in dopaminergic signaling due to excitatory stimulation (i.e., being shifted right and upwards on the inverted-U-curve). Notwithstanding these hypothesized findings, it is important to consider that pharmacological manipulations do not necessarily mimic the effects of natural variation in a neurotransmitter system (cf. Boy et al., 2011), pointing to the possibility that COMT-tDCS interactions do not necessarily mirror the interaction between dopaminergic manipulations and tDCS. This is a significant possibility in light of the fact that no published

study has yet demonstrated a role for individual differences in DA in the after-effects of tDCS on WM. This suggests DA-tDCS interactions might vary or not apply to every type of stimulation and/or experimental task, as our results will indeed indicate.

2 | MATERIALS AND METHODS

2.1 | Ethical approval

The study conformed to the ethical standards of the declaration of Helsinki and the protocol was approved by the local ethical committee (Leiden University, Institute for Psychological Research).

2.2 | Participants

One hundred and thirty-nine right-handed undergraduate students participated in a study on tDCS and memory after providing written informed consent. Participants were randomly assigned to one of the three stimulation groups (AL-CR, CL-AR, or sham). Nine participants were identified as performance outliers as described in the Results section, leaving a total of 130 participants for further analysis. The stimulation groups did not differ with respect to age, $F(2, 127) = 0.079$, $p = 0.924$, gender, $\chi^2(N = 130) = 2.492$, $p = 0.288$, or genotype distribution, $\chi^2(4, N = 130) = 1.059$, $p = 0.901$, see Table 1 for group demographics. All participants were screened individually using the Mini International Neuropsychiatric Interview (MINI), a short, structured interview of approximately 15 min that screens for several psychiatric disorders and drug use (Sheehan et al., 1998), and has been used previously in neuromodulation research (Jongkees, Immink, & Colzato, 2017; Jongkees, Sellaro,

et al., 2017). Participants were included if they met the following criteria: (a) between 18 and 30 years; (b) no history of neurological or psychiatric disorders; (c) no history of substance abuse or dependence; (d) no chronic or acute medication; (e) no implants such as pacemakers or any kind of metal in the body, nor any skin conditions, for safety reasons concerning tDCS. One exception was hormonal contraceptive use in females, which was required to limit fluctuations in hormone levels that can influence DA function and confound group differences (Colzato & Hommel, 2014; Czoty et al., 2009; Jacobs & Esposito, 2011). All participants met these criteria. Before the study, participants were informed of the procedure and potential side-effects of tDCS (i.e., itching, stinging or burning sensation from the electrodes, reddening of the skin and headache). None of the participants reported major side-effects.

2.3 | Genotyping

Genetic material to determine COMT genotype was collected using buccal swabs, which were analyzed by the company BaseClear (The Netherlands). The SNP Val¹⁵⁸Met of the COMT gene (rs4680) was genotyped using Applied Biosystems (AB) TaqMan technology. All genotypes were scored by two independent readers by comparison to sequence-verified standards. For COMT Val¹⁵⁸Met, three genotype groups were established: Val/Val homozygotes, Val/Met heterozygotes, and Met/Met homozygotes. COMT genotype was available in all participants.

Genotype distribution for COMT Val¹⁵⁸Met polymorphism in our Dutch healthy population was 30 Val/Val homozygous subjects (23.08%), 60 Val/Met heterozygous subjects (46.15%), and 40 Met/Met homozygous subjects (30.77%). All resulting genotype frequencies from our cohort of participants did not deviate from Hardy–Weinberg equilibrium ($p = 0.415$).

2.4 | N-back task

WM performance was assessed using the N-back task (Kane, Conway, Miura, & Colflesh, 2007), which is predominantly used in tDCS studies on WM (Au et al., 2016; Fregni et al., 2005; Hoy et al., 2013; Mylius et al., 2012; Ohn et al., 2008; Oliveira et al., 2013; Teo, Hoy, Daskalakis, & Fitzgerald, 2011; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011). As in the study on L-tyrosine and tDCS (Jongkees, Sellaro, et al., 2017), a letter-based N-back task was used to assess verbal WM (Colzato, Jongkees, Sellaro, & Hommel, 2013). To prevent potential ceiling effects induced by repeated practice in a pretest–posttest design, a 2-back and 4-back condition was included in each pretest and posttest.

Stimuli were presented in the middle of a computer screen with a refresh rate of 60 Hz and a 800 × 600 resolution using

TABLE 1 Group demographics

	AL-CR	CL-AR	Sham
<i>N</i>			
Met/Met	16	11	13
Val/Met	20	21	19
Val/Val	12	8	10
Gender F:M			
Met/Met	9:7	7:4	9:4
Val/Met	15:5	11:10	15:4
Val/Val	8:4	6:2	8:2
Age in years			
Met/Met	21.1 (3.1)	22.1 (2.3)	21.5 (2.8)
Val/Met	22.4 (2.9)	21.3 (2.7)	21.4 (2.5)
Val/Val	22.5 (2.9)	23.1 (3.9)	22.7 (3.2)

Standard deviation in parentheses.

E-Prime 2.0 software. Participants were comfortably seated approximately 50 cm from the screen while wearing headphones. On each trial, participants were required to indicate whether the currently shown letter was the same or different (i.e., match or mismatch) as compared to the letter shown N trials prior to the current one. Responses were given using the 'z' and 'm' buttons of a QWERTY keyboard for targets (i.e., matches) and nontargets (i.e., mismatches), respectively. Mapping of response buttons to targets and nontargets was not counterbalanced across participants to prevent differences in response-mapping across genotypes. After an incorrect or belated response (latency longer than 1,000 ms), a brief tone was presented to signal the error. Both the 2-back and the 4-back conditions consisted of two blocks of 51 + N trials. For example, a 2-back block consisted of 53 trials. Regardless of the WM load condition, each block comprised 21 targets and 30 nontargets. All participants performed the 2-back condition first and then the 4-back condition, and each N-back condition was preceded by 17+ N practice trials (7 targets and 10 targets).

2.5 | Transcranial direct current stimulation

In line with a previous study on offline tDCS, WM, and DA by Jongkees, Sellaro, et al. (2017), two electrodes of 35 cm² (5 × 7 cm) were placed over dlPFC in a bilateral bipolar-balanced montage (Nasseri et al., 2015), that is in symmetrical positions. For each individual participant, the dlPFC was located using the international 10/20 system for placing electrodes on the scalp (Jasper, 1958). As such, for the AL-CR montage the anode and cathode were placed over F3 and F4, respectively, whereas this placement was reversed for the CL-AR montage. In the sham condition, half of participants received the AL-CR montage and the other half received the CL-AR montage.

Stimulation consisted of a current of 1,000 μ A delivered by a DC Brain Stimulator Plus (NeuroConn, Ilmenau, Germany), a device complying with the Medical Device Directive of the European Union (CE-certified). The current was built up during a fade-in of 10 s, after which stimulation lasted for precisely 15 min and then ended with a 10 s fade-out. Sham stimulation was exactly the same but lasted for 15 s instead of 15 min, thus providing a similar initial sensation as active stimulation. The after-effects of 15 min of tDCS typically last 30–60 min, whereas stimulation of only a few seconds produces no changes in cortical excitability or plasticity (Nitsche et al., 2008).

The experience of side-effects due to tDCS was assessed through self-report ratings for the following symptoms: (a) headache, (b) neck pain, (c) nausea, (d) muscle contractions in the face or neck, (e) stinging sensation under the electrodes, (f) burning sensation under the electrodes, and (g) a nonspecific, uncomfortable feeling. Consistent with previous

studies, the most prominent side-effects were stinging and burning sensations under the electrodes (Bikson, Datta, & Elwassif, 2009), although no participants voiced major complaints.

2.6 | Procedure

Participants gave written consent upon entering the laboratory. After filling in a questionnaire assessing their general health, they completed a pretest of the N-back task, which took on average 20 min. Subsequently, the tDCS montage was mounted on the participants' scalp and stimulation was started. During the 15 min of stimulation, when participants were not required to do anything, buccal swabs were taken to determine COMT genotype. Following stimulation, the tDCS electrodes were removed and participants completed the posttest of the N-back, which was identical in structure to the pretest and took on average 20 min. In total, the procedure took approximately 90 min.

2.7 | Statistical analysis

Aside from parameters such as hit rate and correct rejections, we were interested in target sensitivity, indexed by d' prime derived from signal detection theory (Swets, Tanner, & Birdsall, 1961). This measure combines hit rate and false alarms to provide an index of the ability to discriminate targets from nontargets, with higher scores indicating more selective and correct reporting of targets. d' prime was calculated, and perfect scores were corrected for, as described earlier (Colzato et al., 2013).

First, each group (i.e., each combination of stimulation type and COMT polymorphism) was checked for outlier performance (below or above 3 times the group's interquartile range) on d' prime, hit rate, correct rejections, and reaction time (RT). In order to test the hypothesis that the COMT polymorphism modulates the effect of tDCS on WM performance, a repeated-measures analysis of variance (rmANOVA) was conducted with time (pretest vs. posttest) and WM load (2-back vs. 4-back) as within-subject factors and type of stimulation (AL-CR vs. CL-AR vs. sham) and COMT genotype (Val/Val vs. Val/Met vs. Met/Met) as between-subject factors. Separate analyses were performed for d' prime, hit rate, correct rejections, and RT for targets and nontargets.

3 | RESULTS

Four participants were identified as outliers based on either pretest or posttest d' prime scores, three additional participants were identified as outliers based on hit rate or correct rejections, and another two participants were identified as outliers based on RT. This left a total of 130 participants for

TABLE 2 N-back scores

	AL-CR		CL-AR		Sham	
	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
2-back						
d' prime						
Met/Met	1.96 (0.51)	2.39 (0.49)	1.81 (1.14)	2.65 (0.97)	1.73 (0.38)	2.36 (0.68)
Val/Met	1.98 (0.61)	2.55 (0.71)	1.78 (0.59)	2.42 (0.79)	2.24 (0.80)	2.88 (0.98)
Val/Val	1.72 (0.62)	2.30 (0.55)	2.26 (0.72)	2.87 (0.53)	1.83 (0.50)	2.30 (0.81)
Hit rate in %						
Met/Met	84.1 (9.4)	89.9 (6.1)	79.9 (13.4)	91.1 (8.8)	83.2 (8.5)	91.2 (5.6)
Val/Met	86.1 (8.4)	91.8 (8.9)	83.8 (7.8)	90.4 (7.1)	88.5 (10.0)	92.6 (7.4)
Val/Val	80.6 (9.7)	88.7 (3.8)	89.9 (6.1)	96.7 (2.2)	86.2 (7.1)	89.5 (8.5)
Correct reject. in %						
Met/Met	80.5 (5.2)	83.7 (6.6)	76.2 (15.3)	83.8 (10.7)	75.5 (6.3)	79.5 (11.4)
Val/Met	78.6 (8.4)	82.5 (7.9)	75.5 (11.1)	82.0 (12.0)	78.7 (12.3)	86.0 (11.8)
Val/Val	77.8 (11.3)	83.2 (9.9)	80.0 (9.4)	81.9 (11.2)	74.2 (8.6)	80.3 (11.4)
RT _{Target} in ms						
Met/Met	598 (75)	554 (76)	583 (48)	550 (57)	589 (53)	548 (52)
Val/Met	610 (51)	589 (57)	593 (73)	568 (67)	613 (73)	593 (54)
Val/Val	615 (50)	591 (73)	626 (73)	601 (69)	618 (55)	600 (75)
RT _{Nontarget} in ms						
Met/Met	558 (85)	502 (71)	560 (95)	495 (72)	526 (75)	482 (79)
Val/Met	543 (94)	480 (81)	545 (73)	499 (64)	506 (51)	458 (61)
Val/Val	522 (59)	495 (73)	535 (82)	461 (60)	540 (86)	486 (77)
4-back						
d' prime						
Met/Met	1.55 (0.87)	2.17 (0.70)	1.37 (0.88)	1.96 (0.91)	1.53 (0.61)	2.02 (0.63)
Val/Met	1.65 (0.58)	2.26 (0.60)	1.52 (0.54)	2.27 (0.81)	1.90 (0.58)	2.64 (0.80)
Val/Val	1.22 (0.37)	1.69 (0.55)	1.72 (0.28)	2.28 (0.42)	1.62 (0.56)	2.26 (0.62)
Hit rate in %						
Met/Met	57.9 (17.0)	65.6 (14.8)	54.8 (16.6)	57.6 (18.8)	57.3 (14.0)	64.1 (15.2)
Val/Met	58.5 (11.4)	64.3 (12.9)	60.8 (12.7)	65.4 (17.9)	62.8 (11.9)	71.8 (14.2)
Val/Val	54.0 (13.2)	63.3 (19.1)	57.4 (11.8)	63.7 (9.8)	56.4 (12.1)	63.1 (14.7)
Correct reject. in %						
Met/Met	89.1 (7.6)	94.5 (5.3)	86.4 (11.5)	93.9 (7.0)	89.0 (7.9)	94.0 (4.1)
Val/Met	90.3 (7.1)	95.8 (4.7)	87.5 (7.1)	95.6 (3.3)	92.5 (5.5)	96.5 (5.0)
Val/Val	85.4 (8.4)	89.0 (5.4)	92.5 (4.9)	96.7 (3.1)	91.7 (4.7)	96.7 (2.2)
RT _{Target} in ms						
Met/Met	595 (72)	573 (43)	616 (81)	589 (94)	605 (79)	567 (64)
Val/Met	601 (70)	572 (91)	623 (100)	563 (108)	575 (53)	531 (62)
Val/Val	593 (61)	524 (63)	583 (61)	541 (47)	600 (43)	542 (66)
RT _{Nontarget} in ms						
Met/Met	588 (83)	528 (78)	566 (69)	524 (76)	551 (74)	504 (74)
Val/Met	578 (62)	533 (56)	583 (51)	529 (61)	596 (69)	548 (67)
Val/Val	570 (79)	524 (72)	622 (23)	563 (68)	610 (72)	552 (78)

Average N-back scores with standard deviation in parentheses.

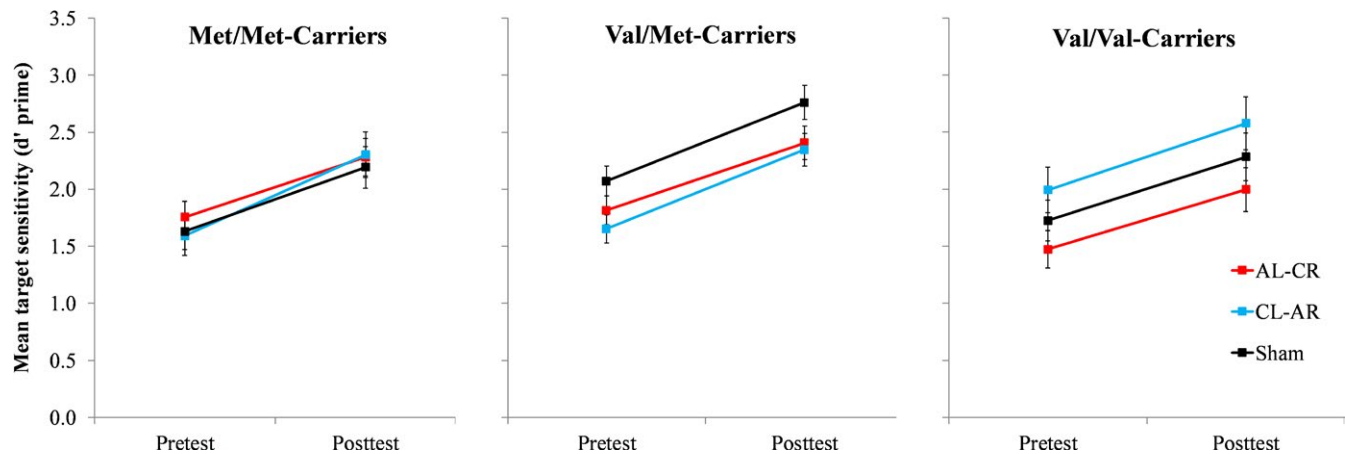


FIGURE 1 d' prime scores as a function of time (pretest vs. posttest), stimulation group (anodal-over-left, cathodal-over-right vs. cathodal-over-left, anodal-over-right vs. sham), and COMT genotype (Met/Met vs. Val/Met vs. Val/Val). [Colour figure can be viewed at wileyonlinelibrary.com]

subsequent analyses. See Table 2 for an overview of group scores on the N-back, and see Figure 1 for a depiction of the d' prime score results.

None of the dependent variables (d' prime, hit rate, correct rejections, and RT) demonstrated a main effect of stimulation ($ps \geq 0.406$), an interaction between time and stimulation ($ps \geq 0.494$), or a three-way interaction involving load ($ps \geq 0.252$), suggesting that tDCS did not modulate N-back performance when disregarding COMT genotype. Only RT to nontargets revealed a main effect of COMT, $F(2, 121) = 3.43$, $p = 0.036$, partial $\eta^2 = 0.054$, with Val homozygotes demonstrating higher RT than Met homozygotes ($M = 591$ vs. 557 ms, $p = 0.012$) but not Val/Met heterozygotes ($M = 577$ ms, $p = 0.286$), nor was there a significant difference between Met homozygotes and heterozygotes ($p = 0.068$). All other measures revealed no main effect of COMT ($ps \geq 0.140$), nor an interaction with time ($ps \geq 0.465$) or a three-way interaction involving load ($ps \geq 0.211$).

Most important to the present study, no measures demonstrated a significant three-way interaction between time, stimulation and COMT ($ps \geq 0.476$) or a four-way interaction involving load ($ps \geq 0.505$) except for RT to targets $F(4, 121) = 2.67$, $p = 0.036$, partial $\eta^2 = 0.054$. To disentangle this four-way interaction, we first computed difference scores for pretest and posttest RT and then separately submitted 2-back and 4-back scores to the ANOVA with stimulation and genotype as between-subject factors. This revealed no significant interaction between stimulation and COMT for either the 2-back, $F(4, 121) = 1.53$, $p = 0.198$, or the 4-back, $F(4, 121) = 1.03$, $p = 0.394$.

To obtain further evidence for a lack of an interaction between COMT and stimulation, we performed post hoc comparisons using nonparametric Mann–Whitney's U tests for the two main hypotheses. Specifically, previous studies predicted Met homozygotes would demonstrate impaired performance

following AL-CR stimulation as compared to sham, whereas Val homozygotes would become impaired following CL-AR stimulation as compared to sham. Difference scores for pretest and posttest for each dependent variable were computed separately for the 2-back and 4-back, but none of the comparisons demonstrated significant stimulation group differences, $ps \geq 0.326$. As such, the results do not point toward a modulation of tDCS after-effects on WM by the COMT genotype.

4 | DISCUSSION

The present study investigated whether the after-effect of prefrontal tDCS is modulated by individual differences in DA function. To this end, participants were genotyped for the COMT Val¹⁵⁸Met polymorphism to estimate prefrontal DA activity and completed tests of WM performance before and after tDCS over the dlPFC. Although a mild DA manipulation previously modulated the after-effect of tDCS on WM (Jongkees, Sellaro, et al., 2017), the current results indicate this modulation does not extend to pre-existing differences in—rather than a manipulation of—DA activity. Although the results contrast with two previous studies on COMT genotype and *online* effects of prefrontal tDCS on performance (Nieratschker et al., 2015; Plewnia et al., 2013), we do not take our results to undermine previous studies. Instead, we argue our results add to them by highlighting two important implications for future studies on tDCS.

First, whereas previous studies looked at an interaction between COMT and *online* effects of tDCS (i.e., stimulation overlapping with the critical task), the present study examined *offline* effects of tDCS (i.e., stimulation *prior* to the critical task). Online effects of tDCS are likely to reflect transient changes in cortical excitability (Nitsche & Paulus, 2000), whereas offline effects of tDCS are related to changes in synaptic plasticity

(Nitsche & Paulus, 2001; Nitsche, Nitsche, et al., 2003). As such, the present results combined with previous findings indicate that the COMT genotype might differentially affect tDCS-induced changes in cortical excitability and neural plasticity. Although the present study implies this distinction exclusively at a behavioral level of results, future studies might investigate whether online and offline effects on physiology are also differently affected by COMT genotype. An impact of DA primarily online rather than offline tDCS would notably contrast with the glutamatergic and GABAergic systems, which instead have been shown to be relevant for the offline but not online effects of tDCS (Nitsche, Fricke, et al., 2003).

Second, the results underscore a need for caution when generalizing results from pharmacological manipulation of a neurotransmitter system to results from pre-existing baseline differences in that system. Whereas administration of DA's precursor L-tyrosine did modulate the after-effect of prefrontal tDCS on WM (Jongkees, Sellaro, et al., 2017), this pattern of results was not mirrored by the COMT genotype as shown in the present study. Although it is possible that similar effects are observable on a physiological level, for example, the directionality of change in cortical excitability and neuroplasticity, the impact of genetic predisposition might not be large enough to immediately produce detectable differences at the behavioral level. On the one hand, this might be explained by the possibility that pharmacological manipulation induces larger changes in a neurotransmitter system that more easily cross a threshold at which behavioral changes are observed. As such, it might be that the smaller effect of COMT genotype requires longer periods of stimulation, repeated stimulation, and/or larger sample sizes to become apparent. On the other hand, it is possible that manipulation of a neurotransmitter system exerts different physiological and behavioral effects than naturally occurring variation in that system (cf. Boy et al., 2011), leading to different interactions between DA and the psychophysiology of tDCS.

Notably, in neither this study or the study on L-tyrosine (Jongkees, Sellaro, et al., 2017) did tDCS have a main effect on WM. Two important factors that have possibly contributed to this null-finding are (a) a perhaps underpowered sample size when considering each possible combination of COMT genotype and type of stimulation, and (b) the fact that the present study involved bilateral stimulation of dlPFC, whereas previous studies often report behavioral effects when placing the target electrode over left dlPFC and the reference over the contralateral orbital region. This implies that the behavioral effects of bilateral dlPFC stimulation as used in the present study might be somewhat less reliable, although significant effects with this particular type of stimulation on WM have been reported previously (Oliveira et al., 2013). In this regard, it is important to consider that tDCS effects can require several sessions to become behaviorally observable, by presumably strengthening the consolidation of practice between sessions (Au, Karsten, Buschkuehl, &

Jaeggi, 2017; Au et al., 2016). As such, a single-session might not be able to capture effects of COMT genotype offline tDCS. However, of particular relevance to the present study is the fact that L-tyrosine was shown to modulate the effect of single-session bilateral tDCS, whereas the COMT genotype did not as reported here. In light of the possibility that COMT effects might be smaller than pharmacological manipulation of DA, future studies could examine whether COMT genotype does predict effects of tDCS following multiple sessions of stimulation, and as mentioned before, whether these effects are different for online and offline tDCS (Mancuso et al., 2016).

Regardless of the exact underlying mechanism, the differential effect of L-tyrosine and COMT on tDCS after-effects on WM cannot be attributed to methodological differences between studies such as type of montage or duration of stimulation, which were identical in both studies (Jongkees, Sellaro, et al., 2017). One notable difference is that the present study includes a pretest of WM performance, which might have produced a learning effect that obscured tDCS-induced changes in performance and their interaction with COMT. Although a pretest was necessary to exclude the possibility that results were driven by baseline differences due to COMT genotype, the present study cannot definitively rule out that a learning effect accounts for the different results across studies. One method of alleviating the issue of ceiling effects in future studies might be to use adaptive N-back tasks (Au et al., 2016; Jaeggi, Buschkuehl, Shah, & Jonides, 2014), which potentially lessen the obscuring effect of practice in static N-back versions.

Furthermore, although the current study assessed WM both before and after tDCS in order to rule out baseline group differences, it should be noted that the critical comparisons of the different genotypes and stimulation groups were still between-subjects in nature. That is, each individual received one form of stimulation (AL-CR, CL-AR, or sham), thus preventing a within-subjects comparison of individual response to different types of tDCS. Although the present study opted for a between-subjects design in this regard in order to prevent magnifying the practice effects inherent in a pretest–posttest design, future studies should strive to compare different types of stimulation in a within-subjects manner. In particular, it would be useful to genotype participants prior to behavioral testing in order to allow counterbalancing of the order of stimulation types within each genotype.

Lastly, it should be acknowledged that tDCS literature so far—the present study included—has focused primarily on the COMT genotype as a predictor of DA and tDCS interactions. Although COMT's influence on prefrontal DA activity is likely to be highly relevant for tDCS applied to the PFC, it is important to note that other dopaminergic genes might play an influential role as well—particularly in the investigation of tDCS and WM. For example, dopaminergic activity in the basal ganglia is known to play an important role in

the input-gating mechanism that controls access of information to WM (Chatham & Badre, 2015; Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2006; O'Reilly, 2006). In this regard, it is noteworthy that an animal study has demonstrated that anodal tDCS can enhance DA activity in the basal ganglia, particularly the striatum (Tanaka et al., 2013). As such, it is possible that DA and tDCS might have interacting effects on WM performance not only via prefrontal but also striatal dopaminergic systems. We therefore recommend future studies to extend their investigations to include dopaminergic genes related to striatal DA activity, such as the DA transporter DAT1 (Shumay, Chen, Fowler, & Volkow, 2011; van de Giessen et al., 2009) and DRD2 (Hirvonen et al., 2009) polymorphisms. Indeed, DA transporters are far more abundant in the basal ganglia than PFC, and thus the DAT1 polymorphism is most closely related to dopaminergic activity in the basal ganglia (Lewis et al., 2001; Shumay et al., 2011; van de Giessen et al., 2009). Similarly, DA D2 receptors are up to 11 times more prevalent in basal ganglia than PFC (Camps, Cortés, Gueye, Probst, & Palacios, 1989), and drugs with a particular affinity for the D2 receptor have previously been demonstrated to impact effects of tDCS over the frontal cortex (Fresnoza, Stiksrud, et al., 2014; Monte-Silva et al., 2009; Nitsche et al., 2006). Taken together, it is therefore possible that the DAT1 and DRD2 genotypes modulate the cognitive-behavioral effects of tDCS and we strongly recommend future studies to take this possibility into consideration.

To conclude, the present study demonstrates a lack of evidence for an impact of COMT genotype on the after-effect of single-session prefrontal tDCS on WM. In doing so, this study indicates that (a) DA might differentially modulate the effects of online and offline tDCS, and (b) more generally, tDCS results obtained in pharmacological studies should be generalized with caution to studies of individual differences in neurotransmitter function.

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CONFLICT OF INTEREST

Author MAN is a member of the Advisory Board of Neuroelectrics. The other authors declare no conflicts of interest.

DATA ACCESSIBILITY

The primary data can be accessed from www.dataverse.nl.

AUTHORS' CONTRIBUTION

BJJ, MAN, and LSC designed the study; BJJ and AAL carried out data collection; FBY performed modeling of the electrical current flow; BJJ wrote the first draft of the manuscript; and all authors revised and approved the final manuscript.

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