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Impact of COMT val158met on tDCS-induced cognitive enhancement in older adults

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Abstract

Background: Previous studies suggest that genetic polymorphisms and aging modulate inter-individual variability in brain stimulation-induced plasticity. However, the relationship between genetic polymorphisms and behavioral modulation through transcranial direct current stimulation (tDCS) in older adults remains poorly understood.
Objective: Link individual tDCS responsiveness, operationalized as performance difference between tDCS and sham condition, to common genetic polymorphisms in healthy older adults.
Methods: 106 healthy older participants from five tDCS-studies were re-invited to donate blood for

genotyping of apoliproprotein E (APOE: ε4 carriers and ε4 non-carriers), catechol-*O*-methyltransferase (COMT: val/val, val/ met, met/met), brain-derived neurotrophic factor (BDNF: val/val, val/met, met/met) and KIdney/BRAin encoding gene (KIBRA: C/C, C/T, T/T). Studies had assessed cognitive performance during tDCS and sham in cross-over designs. We now asked whether the tDCS responsiveness was related to the four genotypes using a linear regression models.

Results: We found that tDCS responsiveness was significantly associated with COMT polymorphism; i.e., COMT val carriers (compared to met/met) showed higher tDCS responsiveness. No other significant associations emerged.

Conclusion: Using data from five brain stimulation studies conducted in our group, we showed that only individual variation of COMT genotypes modulated behavioral response to tDCS. These findings contribute to the understanding of inherent factors that explain inter-individual variability in functional tDCS effects in older adults, and might help to better stratify participants for future clinical trials.

1. Introduction

Given the increasing proportion of older adults in populations worldwide, the prevalence of people with age-associated cognitive decline is rising [1]. Therefore, strategies aimed at ameliorating this condition are of great interest. So far, numerous studies have used non-invasive brain stimulation (NIBS) in older adults to modulate brain activity during different cognitive tasks [2–4], accumulating evidence for large inter-individual variability in responsiveness to NIBS [5]. This highlights the importance of determining individual predictors of stimulation response. Here, variability in polymorphisms of genes known to be involved in molecular pathways that eventually affect cognitive functioning contribute to the magnitude of behavioral plasticity induced by NIBS protocols [6–8]. Four common polymorphisms have been most extensively studied in this context, i.e., apolipoprotein E (APOE), catechol-O-methyltransferase (COMT), brain-derived neuro- trophic factor (BDNF) and KIdney/BRAin encoding gene (KIBRA) [9–13].

With regard to age-related cognitive decline, Ɛ4 allele carriers of the APOE gene are known to show relatively disrupted lipid supply required for synaptic plasticity [14], and thus show faster age-related cognitive decline than APOE ε4 allele non-carriers [15]. Additionally, they are known to be at higher risk for developing Alzheimer's disease (AD) [16]. Healthy older COMT val carriers (i.e., with either one or two val alleles) show lower prefrontal dopamine levels [17] than met/met carriers, possibly related to lower performance in tasks involving visuospatial learning [18] episodic, and working memory [19–21]. BDNF effects on cognition are mixed, with evidence for lower processing speed and poorer recall memory in older met carriers, characterized by lower synaptic BDNF levels [22–24]. However, there is also evidence for superior working memory performance in those individuals compared to val/val carriers [25]. For KIBRA, animal studies have demonstrated that older C/C carriers express lower KIBRA protein, which negatively impacts hippocampal signaling pathways [26]. In humans, C/C carriers performed worse than T allele carriers in visuospatial learning [27,28], working and episodic memory tasks [29,30]. The ε4 allele of APOE has been found to be most strongly linked to risk for Alzheimer's disease (AD), but there is also evidence for a role of COMT, KIBRA and BDNF polymorphisms in AD development [31–35].

Only few studies have investigated the effect of genetic polymorphisms on the magnitude of behavioral modulation through transcranial direct current stimulation (tDCS) [36–38] or transcranial magnetic stimulation (TMS) in older adults [6,39]. For example, older APOE ε4 carriers showed similar modulation of recognition memory by repetitive TMS compared to non-carriers, but greater reduction of abnormal brain activation patterns [39]. The authors thus concluded higher compensatory neuromodulation in APOE ε4 carriers. Another recent working memory training study found greater tDCS-induced improvement of spatial memory in COMT val/val carriers compared to met carriers [36]. These genotype effects were expressed differently across different cognitive domains and stimulation intensities. In the same study, the

authors found no effects of BDNF genotype. In sum, recent evidence suggests that certain genetic polymorphisms which are implicated in age-related cognitive decline may also mediate responsiveness to NIBS protocols in older adults. However, due to a limited number of studies and heterogeneous methodological approaches, no clear picture has emerged so far [cf. 40].

In the present study, we aimed to address this question using the data of older participants from five previously conducted tDCS studies [41–45]. Participants were re-invited for an additional blood draw to perform genotyping. Original studies had been conducted in cross-over designs, using different cognitive tasks during anodal stimulation over cortices promoting the specific cognitive function under study (with contralateral supraorbital cathodes), including semantic word retrieval, visuospatial training and verbal episodic memory [42–46], compared to sham stimulation. We defined tDCS responsiveness as difference between task performance under tDCS and sham condition. We then explored if there were differences in responsiveness to stimulation between carriers of different alleles in four genes, i.e., APOE, COMT, BDNF, and KIBRA.

2. Materials and methods

2.1. *Overview*

Participants of five studies conducted by our group at the Department of Neurology at the Charité University Medicine, Berlin, Germany were included in the analyses [41–45], see Table 1 for an overview of included studies. All studies were conducted in a cross-over design and older participants performed a cognitive task during either anodal stimulation over cortices promoting the cognitive function under study (with contralateral supraorbital cathodes) or sham. Order of stimulation conditions was counterbalanced and sessions were separated by one week to three months. Studies were conducted in accordance with the Declaration of Helsinki and additional genetic testing was approved by the ethics committee of the Charit´e University Medicine in Berlin, Germany.

2.2. *Participants*

Participants from previous studies on tDCS-induced behavioral modulation in older adults were recruited for the genetic analyses (age range: 50–82 years, mean age: 67 years, standard deviation: 7 years). Here, 106 (out of a total of 124 participants recruited in the original studies) were available for blood draws to conduct genetic analysis. All subjects provided written informed consent prior to participation. For further information regarding baseline assessments, inclusion and exclusion criteria please see respective publications [41–45]. All subjects were right-handed according to Edinburgh Handedness Inventory [47], did not report any current or past psychiatric or neurological disorders or severe and untreated medical conditions.

2.3. *tDCS*

tDCS was administered via a battery-driven stimulator (neuroConn DC-Stimulator Plus; neuroCare Group GmbH, Munich, Germany) with a constant current of 1 mA and 10 s fade-in at the beginning and 10 s fade-out at the end of the stimulation. Electrodes were inserted into saline-soaked sponges. In detail, electrode sponges were soaked with approximately 10 ml saline (0.9 % NaCl solution) using a syringe [48] aiming to assure constant wetness while avoiding leakage [49,50]. Rubber bands were used to attach electrodes to the head [49]. Participants were asked about tightness and instructed to report drift. All investigators were

trained to control the position of electrodes, sponge wetness, and impedances at the beginning and end of each experimental session. Cleaning of equipment was performed as recommended in the manufacturer's manual: After each session, rubber electrodes and band were cleaned with water, with 90 % alcohol solution and then dried. In addition, we validated the polarity and current output of the stimulation devices. For a current intensity of 1000 μA, voltage values lay between
2.99 and 5.97 V, corresponding to current intensities between 990 and
997.78 μA, thus amounting to a maximum deviation of 1 % (range: 0.22–1 %). For electrode positions, electrodes sizes, and stimulation durations, see Table 1. During sham, stimulation was ramped down after 30 s.

In order to simulate the electric field distribution of each of the applied stimulation protocols, we performed computational modeling analysis on an MNI brain using SimNibs [51–53]. Field strengths (as indexed by 95th percentile of field magnitudes, given in V/m) were similar between electrode montages (ranging from 0.137 to 0.144 V/m) (Fig. 1).

2.4. Cognitive paradigms

Cognitive paradigms included semantic word generation, visuospatial memory and verbal associative learning tasks. Detailed descriptions of task parameters are described in the respective studies [41–45].

Table 1
Overview of the studies included in the analysis.

		[43]	[44]	[45]	[42]	[41]
N (total)	124	20	18	20	32	34
N (genetics)	106	17	13	15	29	32
Electrode montage[1]	anode	Left IFG (FC5)	Left M1 (C3)	Right TP (T6)	Right TP (T6)	Left TP (CP5)
	cathode	Right SO (Fp2)	Right SO (Fp2)	Left SO (Fp1)	Left SO (Fp1)	Right SO (Fp2)
Electrodes sizes (in cm^2)	anode	5 × 7	5 × 7	6.5 × 6.5	5 × 7	5 × 7
	cathode	10 × 10	10 × 10	9.5 × 9.5	10 × 10	10 × 10
Current intensity		1 mA	1 mA	1 mA	1 mA	1 mA
Stimulation duration		20 min	30 min	20 min	20 min	20 min
Cognitive Paradigm		Semantic word retrieval	Semantic word retrieval	Visuospatial memory	Visuospatial memory	Verbal episodic memory

[1] Location of the anode-cathode on the surface of the head (EEG 10–20 positions). IFG, inferior frontal gyrus. M1, sensorimotor. TP, temporoparietal.

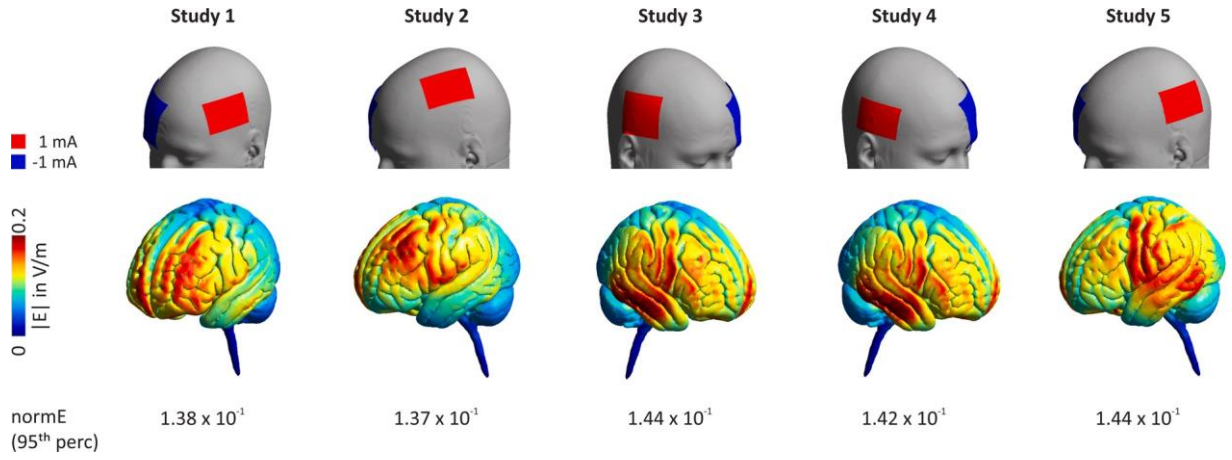

Fig. 1. Electric field distribution for each of the applied stimulation protocols simulated on an MNI head using SimNibs [51–53]. Field strengths (as indexed by 95th percentile of field magnitudes, given in V/m) were similar between electrode montages (ranging from 0.137 to 0.144 V/m).

Briefly, in the semantic word generation task participants were required to generate word exemplars of visually presented categories (e.g., animals, musical instruments). Number of errors were recorded as dependent variable (for the present study, percentage of correct answers were computed). In the visuospatial memory task, subjects were required to recall previously learned locations of buildings. The primary outcome was percentage of correct answers generated immediately after the learning phase. In the verbal associative learning task, subjects were required to recall previously learned pseudoword-picture pairs and the percentage of correct answers generated immediately after the learning phase was used as dependent variable. The difference between task performance under tDCS minus task performance under sham variable that will be referred to as "tDCS responsiveness" from now on was generated.

Semantic fluency task [43,44]: During this task, which was performed during simultaneous magnetic resonance imaging, subjects were presented with six semantic categories, and for each category, there were 10 consecutive trials (a total of 60 trials) with a duration of 3.8 s per trial. After the category presentation, subjects were instructed to generate exemplars for each category. Following each trial, a black screen replaced the stimulus for 2.2 s. An alternating baseline condition was presented between the task block (five consecutive trials where subjects were instructed to say the word "rest"). Two independent raters blinded to the stimulation condition scored the recorded verbal responses of each subject. Errors referred to incorrect answers, repetitions (or synonyms) and omissions. Stimulation was applied during the entire task duration. Main outcome was percentage of correct answers.

Visuospatial memory [42,45]: The task included a learning phase and a recall phase. In the learning phase, subjects were presented with a street map containing one building (3 s) and were instructed to decide whether the building was positioned in the correct location or not by pressing one of the two response buttons. During the learning phase, a total number of 30 buildings were learned and each building was shown more frequently at the "correct" than at the "incorrect" location. After the learning phase, four sessions of cued recall were performed. During these recall sessions, the street map was presented together with three possible building locations and subjects had to press a button for the correct location. Learning success was evaluated immediately after the learning phase (immediate recall; primary outcome), at the evening of the same day learning day (at least 6 h later), one day later, and one week later (delayed recall referring to the secondary outcome). Stimulation was applied during the learning phase. Main outcome was

percentage of correct responses.

Verbal associative learning [41]: The task started with a learning phase during which pseudoword-picture pairs were presented visually. This visual presentation consisted of 30 pseudowords and 30 pictures of objects of daily life. Random matching of 30 "correct" pairing was applied. The learning phase included five training blocks with 120 trials each. "Correct" pairings were presented ten times in total and "incorrect" pairings were presented only once. In addition, each picture was matched ten times with different "incorrect" pseudowords. An auditory spoken pseudoword was followed by the picture that lasted for 200 ms. During this time, subjects were instructed to press a button to answer whether the pairing was "correct" or "incorrect". The learning phase was followed by a retrieval phase where visually presented objects were replaced by corresponding spoken German words. Stimuli count and trial timing were similar as the learning phase. Learning success was assessed by the accuracy in the retrieval "transfer" block. Stimulation was applied during the learning phase. Main outcome was percentage of correct responses.

2.5. Blood extraction and genotyping

DNA extraction was performed using the whole blood sample using a minikit (Qiagen, Hilden, Germany) and was stored at -80 ◦C until analysis. Single nucleotide polymorphism (SNP) genotyping was conducted on four different genes that have previously been shown to be involved in cognitive function [11,12,54,55]; apoliproprotein E (apoE) rs429358 and rs7412, catechol-O-methyltransferase (COMT) rs4680, brain-derived neurotrophic factor (BDNF) rs6265, and KIdney/BRAin encoding gene (KIBRA) rs17070145. Genotyping was performed using the iPLEX Gold Sequenom MassARRAY system and a predesigned Taqman assay (from applied biosystems) at the laboratory of Dan Rujescu (University of Halle). Detailed polymerase chain reaction (PCR) mix and genotyping procedure have been described previously [56]. Table 2 details the behavioral and the genotypic characteristics of the studies included in the analysis.

2.6. Statistical analysis

We used IBM SPSS v24 to conduct all statistical analysis. A multiple linear regression model was used to analyze the association of genetic polymorphisms with responsiveness to tDCS, adjusted for possible confounders. In order to correct for study variability and stimulation order effects, and knowing that age, sex and baseline task performance are crucial factors that might interact with genetic polymorphisms [10,48], we adjusted for "task domain", "sex", "stimulation order", "age", and "sham performance". The variance of the dependent variable (difference between tDCS and sham condition) was standardized to ensure comparability across studies. Therefore, the difference was divided by the standard deviation of the difference, for each participant and each study, to yield standard deviations of 1 in each study. In order to assess the effect of genetic polymorphisms on sham performance per se, an additional linear regression model was conducted, adjusted for "task domain", "sex", "order of stimulation condition", "age". In both analyses' information on COMT, BDNF and KIBRA polymorphisms were entered as nominal variables depending on the allele composition of each gene (COMT: val/val, val/met, met/met; BDNF: val/val, val/met, met/met; KIBRA: TT, CT, CC) while APOE was entered as a dichotomous variable (ε4 carriers, non-carriers). A two-sided significance level of alpha = 0.05 was used.

Table 2 Demographic and genetic characteristics of study participants.

	n	[43]		[44]		[45]		[42]		[41]	
		Study 1		**Study 2**		**Study 3**		**Study 4**		**Study 5**	
		N	%	n	%	n	%	N	%	n	%
N		17		13		15		29		32	
Age (mean/SD)	67/7	69/6		69/4		66/7		70/7		63/7	
Age range		59-76		61-77		50-77		55-82		51-80	
Sex											
Male	56	9	16	6	11	6	12	15	27	19	34
Female	52	8	15	7	13	9	19	14	27	13	25
Sham performance (mean/SD)	0.73/ 0.16	0.89/ 0.05		0.85/ 0.08		0.55/ 0.14		0.69/ 0.18		0.73/ 0.11	
APOE											
ε4 carriers	28	2	7	3	10	3	14	12	41	8	28
ε4 non-carriers	78	15	19	10	13	12	16	17	22	24	30
COMT											
val/val (G/G)	21	4	19	1	5	3	14	6	29	7	33
val/met (G/A)	50	8	15	8	15	6	15	14	27	14	27
met/met (A/A)	35	5	14	4	11	6	17	9	26	11	31
BDNF											
val/val (C/C)	70	12	17	8	11	12	17	19	27	19	27
val/met (C/T)	32	5	15	5	15	3	12	8	24	11	33
met/met (T/T)	4	0	0	0	0	0	0	2	50	2	50
KIBRA											
C/C	58	8	13	7	12	8	17	16	27	19	32
C/T	35	7	20	6	17	6	17	7	20	9	26
T/T	13	2	15	0	0	1	8	6	46	4	31

Values reported are mean/standard deviation and absolute value. %: percentages per study number.

3. Results

3.1. Association of tDCS responsiveness with genetic polymorphisms

Linear regression showed an effect of COMT polymorphism on tDCS responsiveness (partial $\eta^2 = 0.067$, $p = 0.041$), indicating that tDCS responsiveness was higher in participants with COMT val/val genotypes ($\beta = -0.69$, 95 %-CI: -1.23, -0.16, $p = 0.012$). There was an effect of sham performance on tDCS responsiveness, in the direction of higher responsiveness with lower sham performance ($\beta = -0.14$, 95-%CI: -0.24, -0.03, partial $\eta^2 = 0.072$, $p = 0.009$). There were no substantial effects of age ($\beta = 0.01$, 95-%CI: -0.02, 0.04, partial $\eta^2 = 0.003$, $p = 0.553$), sex (females compared to males: $\beta = 0.14$, 95-%CI: -0.23, 0.51, partial $\eta^2 = 0.06$, $p = 0.456$) and session order (tDCS first vs. sham first: $\beta = 0.12$, 95 %-CI: -0.27, 0.51, partial $\eta^2 = 0.004$, $p = 0.542$) on tDCS responsiveness. Additionally, there were no substantial effects of APOE, BDNF and KIBRA polymorphisms on tDCS responsiveness (all partial $\eta^2<0.04$, see Table 3 and Fig. 2).

Table 3

Summary of linear regression model with tDCS responsiveness as dependent variable (n = 106), additionally adjusted for task domain.

		95% CI for B			
	B	Lower	Upper	p	Eta^2
Age	0.01	-0.02	0.04	0.533	0.003
Sex (males, ref: females)	0.14	-0.23	0.51	0.456	0.006
Session order (sham first, ref: tDCS first)	0.12	-0.27	0.51	0.542	0.004
Sham performance	-0.14	-0.24	-0.21	**0.009**	0.072
APOE ε4 carriers (ref: ε4 non-carriers)	-0.31	-0.71	0.14	0.165	0.021
COMT (ref: met/met)				**0.041**	0.067
val/val (G/G)	-0.69	0.14	1.16	**0.012**	
val/met (G/A)	-0.40	-0.13	0.68	0.112	
BDNF (ref: val/val)				0.311	0.025
val/met (C/T)	0.36	-0.06	0.74	0.481	
met/met (T/T)	0.63	-1.17	0.76	0.238	
KIBRA (ref: C/C)				0.829	0.004
C/T	-0.09	-0.48	0.31	0.778	
T/T	-0.18	-0.49	0.65	0.576	

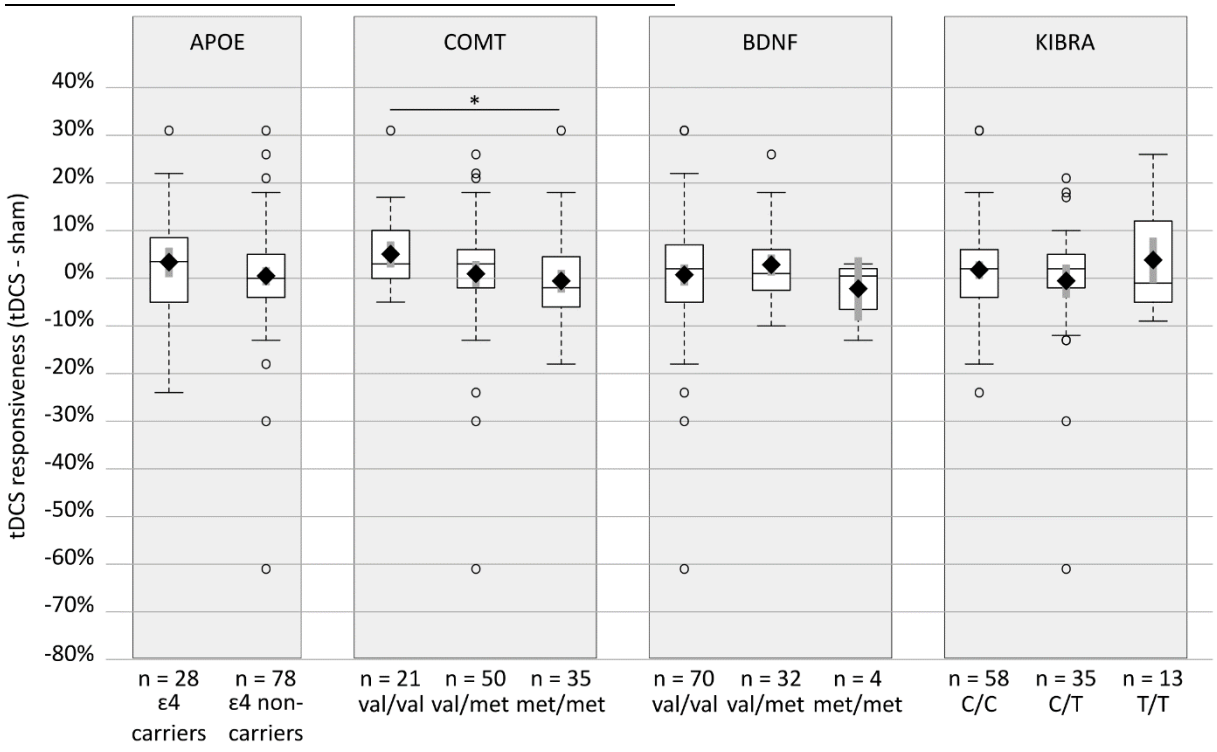

Fig. 2. Boxplots of tDCS responsiveness (in difference of % correct responses between anodal and sham) for the respective gene polymorphisms. There was a substantial effect of COMT on tDCS responsiveness: subjects with COMT val/val genotype showed higher tDCS responsiveness compared to subjects with COMT met/ met genotype. Means are shown as diamonds; error bars represent 95 % confidence intervals. * $p < 0.05$.

3.2. *Association between sham performance and genetic polymorphisms*

Linear regression showed an effect of age on sham performance (β = -0.005, 95 %-CI: -0.01, -0.001, p = 0.010), indicating that cognitive performance was lower in participants with higher age. There were no effects of sex (females compared to males: β = 0.02, 95-%CI: -0.03, 0.07, p = 0.372) and session order (tDCS first vs. sham first: β = 0.006, 95 %-CI: -0.05, 0.06, p = 0.827) on sham performance. Additionally, there were no substantial effects of APOE, COMT, BDNF and KIBRA polymorphism on sham performance (see Table 4 and Fig. 3).

4. Discussion

In the present study, we aimed to link tDCS responsiveness to genetic polymorphisms of APOE, COMT, BDNF and KIBRA in healthy older adults. tDCS responsiveness was higher in participants with COMT val/ val genotypes compared to COMT met/met carriers. Our exploratory comprehensive analysis of several studies that applied tDCS over different sites during different cognitive tasks in older adults suggests that COMT polymorphisms may contribute to the benefit an individual will gain from tDCS.

Table 4
Summary of linear regression model with sham performance as dependent variable (n = 106), additionally adjusted for task domain.

		95% Wald CI		
	beta	Lower	Upper	p
Age	-0.005	-0.01	-0.001	**0.010**
Sex (female)	0.02	-0.03	0.07	0.372
Session order (sham first, ref: atDCS first)	0.006	-0.05	0.06	0.827
APOE ε4 carrier (ref : ε4 non-carrier)	0.006	-0.05	0.06	0.827
COMT (ref: met/met)				
val/val (G/G)	-0.01	-0.08	0.06	0.864
val/met (G/A)	-0.01	-0.07	0.04	0.700
BDNF (ref: val/val)				
val/met (C/T)	0.03	-0.03	0.09	0.281
met/met (T/T)	0.09	-0.04	0.22	0.179
KIBRA (ref: C/C)				
C/T	-0.002	-0.06	0.05	0.932
T/T	0.04	-0.04	0.11	0.358

The effects of COMT polymorphisms on tDCS effects has been investigated more widely. Previous evidence suggested an impact of COMT polymorphism on NIBS-induced task performance modulation in healthy young and older adults [6,36,37,57,58]. For example, in young adults, inhibitory effects of prefrontal tDCS during a parametric Go/No-Go test were only observed in COMT val/val carriers [57]. Another study reported detrimental effects of tDCS on parametric Go/No-Go test in met/met carriers as compared to COMT val carriers [37]. Recently, Stephens et al. [36] evaluated group differences of

prefrontal tDCS effects with regard to genetic factors in an analysis of multiple study samples of older adults who performed different working memory tasks combined with varying tDCS protocols. The authors found no overall main effect of COMT polymorphism on immediate working memory performance. However, with regard to long-term training gains after one month, val/val carriers exhibited a higher benefit compared to met carriers. The results further indicated differences between genetic groups depending on tDCS intensity and task domain, suggesting that the impact of COMT status on tDCS-induced cognitive enhancement may be even more complex. Our results corroborate and complement these previous findings by showing that COMT val/val carriers showed higher tDCS responsiveness compared to met/met carriers. By assessing within-subject differences in tDCS effects, we were able to delineate the impact of COMT status also on immediate "online" behavioral effects across different cognitive tasks.

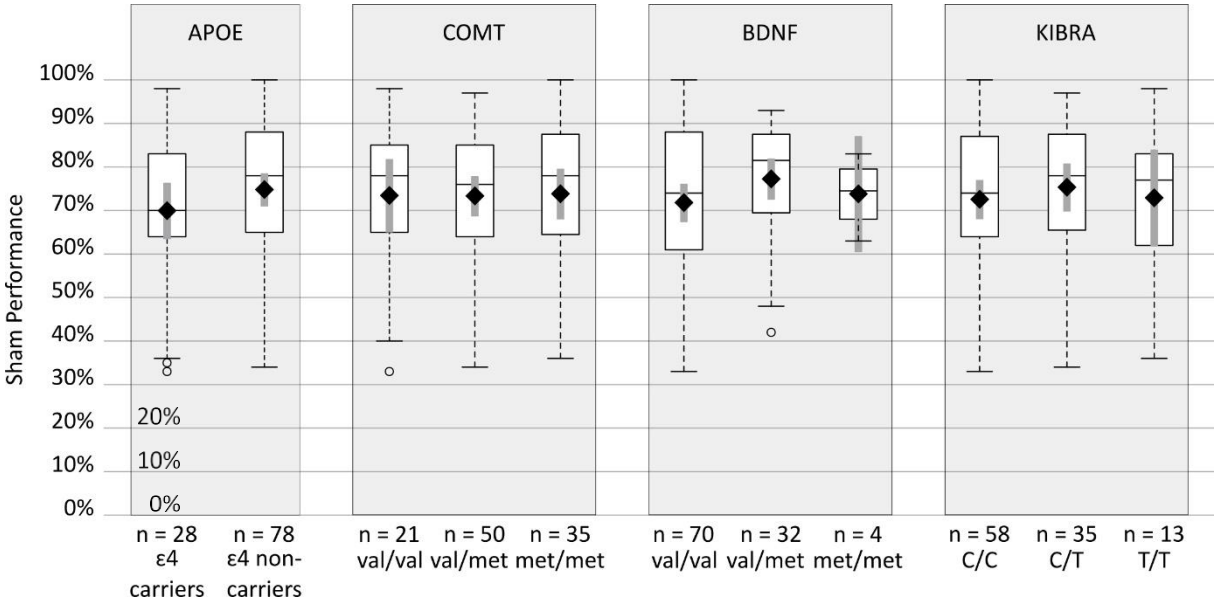

Fig. 3. Boxplots of sham performance (in % correct responses), divided by gene polymorphisms. There was no substantial effect of APOE, COMT, BDNF and KIBRA genetic polymorphism on sham performance. Means are shown; error bars represent 95 % confidence intervals.

While cellular mechanisms of tDCS have been discussed to involve LTP induction [59,60], it has been suggested that tDCS may increase frontal dopamine levels [61,62]. COMT polymorphism impacts dopamine metabolism preferably in the frontal cortex (for review [11]). According to the inverted-U shape hypothesis, dopamine levels should be present in an intermediate concentration to allow optimal cognitive functioning with both suboptimal and supraoptimal levels being detrimental for cognitive performance (for review [38]). In line with this hypothesis, we speculate that tDCS may have resulted in more "optimal" dopamine levels in val carriers compared to met carriers [63,64]. Interestingly, normal aging has been associated with decreased dopaminergic signaling [65,66] and upregulation of dopaminergic activity with levodopa restored memory formation in older adults [66]. As such, older adults might be particularly sensitive to the effects of plasticity-inducing techniques that act upon dopamine level increase [36,67,68].

In sum, we found an increased tDCS-induced enhancement of cognitive performance in COMT val carriers compared to met/met carriers. Nevertheless, we remain cautious about relating this enhancement to differences in dopamine levels, and future studies are needed to confirm this speculation at the molecular level.

With regard to the effect of APOE, BDNF and KIBRA on NIBS-induced plasticity, previous findings have been heterogeneous, suggesting that they depend on stimulation parameters, internal factors, or both [6,7,36, 69].

We did not find significant differences in tDCS responsiveness between APOE ε4 carrier and APOE ε4 non-carrier. Only few previous studies, applying TMS in older adults, have suggested that APOE ε4 carrier status may affect responsiveness to NIBS [39,70]. Pena-Gomez et al. showed that while APOE status did not affect behavioral effects of repetitive TMS on memory function, it modulated stimulation effects on task-related brain network activation in older adults with mild memory dysfunction [39]. As such, APOE may show no perceptible changes on the behavioral level [71]. In line with Stephens et al. [36], we did not find differences between BDNF genotype groups of healthy older adults in tDCS-induced cognitive enhancement. Likewise, KIBRA genotype groups did not differ with regard to tDCS-induced effects, as also observed in a previous study [6]. These findings imply that APOE, BDNF and KIBRA polymorphisms might not have a crucial impact on tDCS-induced performance modulation in aging. However, the non-significant results for both APOE and for BDNF may be also be due to small sample sizes in the respective genotype groups in our study.

Further evaluation of the interaction of genetic status on the four polymorphisms described here with other internal (such as additional cognition-relevant polymorphisms) and external factors (such as task domain or stimulation parameters) will increase the understanding and translational value of NIBS-induced modulation [36]. The exact mechanisms underlying the genotype-dependent differences in NIBS responsiveness remain elusive and need to be addressed in human studies combining behavioral tDCS effects with brain imaging that assess potential differences in neural network organization in older individuals with varying genotypes.

Noteworthy, defining a responder is a critical and also challenging task not only in brain stimulation research, but in medicine in more general terms [36,72,73]. Choosing a threshold that reflects individual change of clinical importance has been discussed as a possibility to define responsiveness [36,72,73]. To define "response to treatment", previous studies have for example used exact cut-off values, known to be clinically relevant, or individual change values (e.g., from pre to post treatment) to categorize subjects in responders and non-responders [36, 74–77]. The definition of responders by such cut-offs or pre-post change values is not possible in our cross-over study [73]. Two recent tDCS studies implementing a cross-over design have related performance under the active stimulation condition to performance under the reference condition [37,57]. In the present study, we used a similar regression approach which has also been recommended as the most reliable statistical analysis for "external responsiveness" [73]. Nevertheless, our results remain exploratory and should be supported by large clinical trials in the future. Following such confirmation, these findings will guide the search for alternative therapeutic approaches for "non-responders" (such as different stimulation types and modalities, or even different interventional approaches altogether).

5. Limitations

In order to increase statistical power and obtain a larger number of participants, we decided to pool participants from different studies. However, overall sample size is still considered moderate. Due to data pooling, we could not distinguish between effects of polymorphisms on different cognitive domains (executive functions, visuospatial, and episodic memory) and stimulation parameters (electrode montage, stimulation protocol, and duration). Rather, we focused on the overall effect of genetic polymorphisms, independent of cognitive domains or stimulation parameters. However, despite the variability in study parameters which may prevent us to infer which study is driving the effect, the association observed between tDCS response and COMT in this analysis of multiple studies and cognitive domains may actually argue for a more general COMT effect. Further, as all studies in our comprehensive analysis applied tDCS with 1 mA, our observations are limited to a modulation of genetic status with this particular stimulation intensity. The use of a fixed 1 mA stimulation intensity may further be a major source of variability, given individual

differences in brain physiology and head and brain anatomy [78–80]. Future studies should explore whether individuals with "genotypes reducing likelihood to respond" would benefit from different stimulation parameters [36], also taking into consideration individual differences in brain anatomy. In addition, the use of the conventional tDCS setup has shown a low spatial resolution [3,81]. However, several studies have proven this approach to induce performance improvements [4,41,82–85]. Further, the interaction of tDCS with ongoing brain activity (performing a task) may induce more focal effects on the neurophysiological level [86,87]. Lastly, we tested only older adults above the age of 50 years, so conclusions may not transfer to other age groups. However, as aging affects not only gene expression, but also effects of plasticity-inducing techniques [19, 88–90], our aim was specifically to elucidate the modulating impact of genetic polymorphisms on tDCS-effects in older age.

6. Conclusion

The present study points towards an impact of COMT carrier status on behavioral responsiveness to tDCS in healthy older adults, suggesting that individual genotype may be considered as a factor contributing to variability in tDCS effects. Interestingly, the data showed that individuals carrying alleles previously linked to lower cognition (i.e., COMT val) showed higher tDCS-induced behavioral response. The present study remains exploratory and further investigations with larger sample sizes are mandatory to confirm our observations and extend the understanding of the underlying mechanisms. This may pave the way for the ultimate goal of stratifying participants to a particular intervention, based on specific genotypes as well as additional variables (individualized tDCS approaches).

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CRediT authorship contribution statement

Dayana Hayek: Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Daria Antonenko:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **A. Veronica Witte:** Investigation, Writing - original draft. **Sophie M. Lehnerer:** Investigation, Data curation, Project administration. **Marcus Meinzer:** Investigation, Funding acquisition, Writing - original draft. **Nadine Külzow:** Investigation, Formal analysis. **Kristin Prehn:** Investigation, Formal analysis. **Dan Rujescu:** Methodology, Resources. **Alice Schneider:** Methodology, Formal analysis, Resources. **Ulrike Grittner:** Methodology, Formal analysis, Resources. **Agnes Flöel:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that no competing interests exist.

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