

## Research article

# Baseline delayed verbal recall predicts response to high definition transcranial direct current stimulation targeting the superior medial frontal cortex

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## ABSTRACT

Anodal high definition transcranial direct current stimulation (HD-tDCS) targeting the pre-supplementary motor area/dorsal anterior cingulate cortex (pre-SMA/dACC) has recently been shown to improve verbal retrieval deficits in veterans with chronic traumatic brain injury (TBI) (Motes et al., 2020), but predictors of treatment response are unclear. We hypothesized that baseline delayed verbal recall, a sensitive measure for post-TBI chronic cognitive decline, would predict therapeutic effects of HD-tDCS targeting the pre-SMA/dACC for verbal retrieval deficits. Standardized verbal retrieval measures were administered at baseline, immediately after and 8 weeks after treatment completion. We applied mixed generalized linear modeling as a *post-hoc* subgroup analysis to the verbal retrieval scores that showed significant improvement in Motes et al. (2020) to examine effects of active stimulation across the groups with baseline-intact delayed recall ( $N = 10$ ) and baseline-impaired delayed recall ( $N = 8$ ), compared to sham ( $N = 7$ ). Individuals with impaired baseline delayed recall showed significant improvement (compared to baseline) in both category fluency and color-word inhibition/switch, while individuals with intact delayed recall showed significant improvement only in color-word inhibition/switch. Baseline delayed verbal recall may therefore be considered as a predictor for future electromodulation studies targeting frontal structures to treat TBI-related verbal deficits.

## 1. Introduction

There are approximately 2.5 million Traumatic Brain Injury (TBI)-related emergency room visits in the U.S. each year [44]. An estimated 15% of mild TBI and 65% of moderate to severe TBI patients report chronic cognitive deficits [46,36]. Word finding (verbal retrieval) difficulty is one of the most frequent complaints, for which there are as yet no broadly accepted effective treatments [12]. Among various non-invasive brain stimulation methods, transcranial direct current stimulation (tDCS) has proven its safety and shown promising results in improving chronic TBI-related cognitive deficits [8,33,39]. Even though

tDCS has been reported to improve verbal retrieval performance in healthy subjects [57,42,28,45,6] and aphasic patients [43,38,63], the use of tDCS to treat verbal retrieval deficits in TBI has rarely been systematically examined.

tDCS is generally thought to be dose and polarity dependent such that anodal stimulation induces a subthreshold facilitatory effect and increases cortical excitability, while cathodal stimulation usually exerts the opposite effect at lower current [16]. Previous tDCS studies to enhance verbal retrieval have used different stimulating electrode montages overlying several brain regions including the left inferior frontal and superior temporal gyri, which are thought to play central

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roles in language processing [45,38]. Another plausible target is the superior medial frontal cortex, encompassing the pre-supplementary motor area (pre-SMA) and the dorsal anterior cingulate cortex (dACC), as these brain regions play roles in word production and retrieval of lexico-semantic information, facilitated by close functional and structural connectivity to the striatum and thalamus [19,20,60]. One study, which used an anodal High Definition montage (HD-tDCS) targeting the dorsomedial frontal regions (pre-SMA/dACC) to treat chronic TBI-related verbal retrieval deficits, reported improved verbal retrieval functions, including immediate effects on verbal memory and retrieval (e.g., Delis-Kaplan Executive Function System, D-KEFS, Color-Word Interference Test that requires verbal retrieval with increased inhibitory control), as well as delayed effects (8 weeks after treatment) on category fluency [39]. HD-tDCS effects over the pre-SMA/dACC were speculated to modulate the underlying verbal retrieval circuits that mediate changes in verbal fluency and executive functions during inhibition and switching.

Given the heterogeneous nature of TBI and its consequences [18,50,25], it has been difficult to predict response to tDCS treatment. We hypothesized that delayed verbal recall could be tested as a predictor for HD-tDCS response. Delayed verbal recall has been demonstrated to be the most sensitive cognitive function to be impaired with TBI and to have larger effect sizes than do other memory measures including immediate recall, visual memory, or recognition memory [5,61] (in two meta-analysis studies [56,25]). This not only applies to the acute/sub-acute phases of TBI but also to the chronic phase, as impairment on verbal memory persists or even worsens while impairment in other cognitive functions may recover overtime [56,13]. It has been shown that delayed recall depends more on frontal lobe (especially the pre-frontal cortex) function than does recognition memory [51,22], and unstructured word list learning (as used in the current study) demands even more frontal lobe involvement than does story learning [55]. Verbal recall also bears more direct relationship to verbal retrieval in general than does non-meaningful non-verbal (e.g., visual) memory [5] given that semantic and phonological information, dependent on the frontal and temporal lobe structures, are often necessitated for verbal recall. These frontal and temporal cortices as well as white matter structures are susceptible to injury from TBI of all severities [41,50,27]. Another benefit of using delayed recall as a baseline predictor is that it is not dependent on the speed of answer production, which could be confounded by the commonly reduced speed of processing in TBI [25].

It has been shown that integrity of the underlying neural circuit may predict tDCS effectiveness in disorders of consciousness including those incurred through TBI [53]. Better pre-treatment phonemic fluency, which depends on frontal lobe function, has also been shown to predict anti-depressant response to tDCS [35]. Given that Motes et al. [39] have reported improvement in category fluency and two D-KEFS measures (color-word inhibition, color-word inhibition/switch) in response to HD-tDCS, we focused on those outcome measures. We thus sought to use baseline delayed verbal recall performance to separate those who underwent active HD-tDCS to test if they responded differentially to active intervention. We hypothesized that baseline delayed verbal recall would serve as a proxy of either structural or functional integrity of the frontal and temporal lobes as a consequence of TBI, and that intact baseline delayed verbal recall supports better responsivity to HD-tDCS intervention in verbal retrieval deficits. This was a *post-hoc* subgroup analysis based on extension of the existing dataset from Motes et al. [39].

## 2. Material and methods

### 2.1. Participants

US military veterans from Operations Enduring Freedom, Iraqi Freedom, and New Dawn were referred for treatment for cognitive dysfunction secondary to TBI. Participants eligible for HD-tDCS had subjective word finding difficulties confirmed by objective measures

including at least one verbal retrieval assessment (phonemic fluency, category fluency, picture naming, verbal list learning) of a T-score less than 40 or that was greater than one standard deviation (SD) below the average score. Exclusion criteria included a history of seizures and intracranial implants (e.g. coils, plates, clips, etc.). Eligible participants were assigned to the active or sham condition with 2:1 ratio. A total of 25 participants completed the baseline and post HD-tDCS intervention assessments (N = 18 in the active group, mean age of  $41.1 \pm 8.7$  years; N = 7 in the sham group, mean age of  $39.9 \pm 8.6$  years) (Table 1). Retrospective concussion history, using the Ohio State TBI Identification Method [9], did not significantly differ between the groups (Table 1). Written informed consent was obtained, and the study was conducted in accordance with the ethical standards of the Helsinki declaration (1964) and approved by the Institutional Review Board of the University of Texas at Dallas.

### 2.2. Study protocol

We used a prospective, single-blinded (to subjects) design. Potential subjects were screened and tested at baseline for their eligibility [39]. Neuropsychological assessment was administered at baseline (T0). Within a week after baseline assessment, eligible participants underwent 10 daily sessions of 20-minute HD-tDCS over a period of 2 weeks. Verbal retrieval measures (detailed in the next section) were primary outcomes and were assessed within a week after completion of HD-tDCS (T1, immediate post). For a subset of subjects (11 active and 5 sham subjects), verbal retrieval measures were also performed to evaluate sustaining effects 8 weeks (T2) after completion of HD-tDCS. Of note, the efficacy trial was reported recently and the current study comprised secondary and *post hoc* analyses that we did not intend to be considered as part of the clinical trial [39]. We did not have the capacity to blind the administrator of HD-tDCS at that time (of note, those who administered neuropsychological testing were blinded to group assignment) and we have been able to do that in our more recent studies.

**Table 1**  
Patient demographics and TBI history.

	Active (N = 18)			Sham (N = 7)
	All	Intact-recall (N = 10)	Impaired-recall (N = 8)	
Demographics: mean (SD)				
Age at test (yr)	41.1 (8.7)	41.1 (10)	41 (7.6)	39.9 (8.6)
Gender	15 M / 3F	7 M / 3F	8 M	7 M
Race	16C/2H	8C	8C/2H	6C/1H
Education (yr)*	15.9 (2.2)	16.7 (2.5)	15 (1.2)	14.1 (1.3)
TBI history: subject number (percentage)				
+ TBI w/ LOC	17 (94%)	9 (90%)	8 (100%)	6 (85.7%)
+ TBI w/ LOC > 30 min	6 (33%)	3 (30%)	3 (37.5%)	3 (42.9%)
+ blast TBI	12 (66.7%)	7 (70%)	5 (62.5%)	6 (85.7%)
Depression/Anxiety measures: mean (SD)				
BAI <sup>a</sup>	10.4 (6.3)	9.8 (5.9)	11.3 (7)	10.3 (8.4)
BDI-II	20.5 (11.8)	18.9 (11.4)	22.5 (12.8)	15.9 (13)

C: Caucasian, H: Hispanic; LOC: loss of consciousness.

BDI: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory.

SD: Standard Deviation.

\*  $p < 0.05$  using 2-tailed independent sample T tests comparing active (all) and active-intact to sham.

<sup>a</sup> N = 6 in sham.

### 2.3. Neuropsychological assessment

The Neuropsychological Battery consisted of: (1) verbal retrieval measures—Controlled Oral Word Association Test (COWAT; using F-A-S letters) [10], Category Fluency Test (using animal or fruit) [10], Boston Naming Test (BNT) [24]; (2) other cognitive measures—Rey Auditory Verbal Learning Test (RAVLT) [48], Digit Span Forwards and Backwards [62], Trail Making Test: A and B [47], Delis-Kaplan Color-Word Interference Test (DKEFS) [11]. No significant difference was found between the active and sham groups at baseline (Table 2). In order to test our hypothesis that baseline delayed verbal recall would affect HD-tDCS responsivity, we separated the active HD-tDCS group (N = 18) into intact (N = 10) versus impaired (N = 8) baseline delayed recall groups. Individuals who underwent active HD-tDCS were assigned to the impaired group if they performed at baseline less than or equal to 1 SD below the normative mean in the delayed recall score during RAVLT (Table 2). Although we found baseline differences between active-intact and active-impaired groups in category fluency and D-EKFS color-word inhibition/switch, no significant difference at baseline was found between (1) the active-intact and sham groups, and (2) the active-impaired and sham groups (Table 2).

### 2.4. HD-tDCS procedure

The HD-tDCS montage targeting the pre-SMA/dACC consisted of Fz for the central anodal electrode and FP1, FP2, F7, and F8 for the return (cathodal) electrodes (i.e., five circular Ag/AgCl electrodes 1 cm radius with conductive gel, Compumedics Quik-Gel Electrolyte). The electrode positions are based on a subset of the international standard 10–10 system and a battery-driven, wireless multichannel transcranial current source generated the stimulation current (Neuroelectronics, Starstim®). Cap size was selected based on head measurements for placement of

electrodes according to the International 10/10 Placement System. The positions of the selected electrodes on the caps conform to the International Placement System. The cap was positioned so that the center of the FPz electrode sat above the nasion at 10% of the distance between the nasion and inion for each subject. For subjects with different head circumferences, we had caps of small (49–54 cm), medium (54–57 cm), and large sizes (>57 cm) as recommended by the manufacturer (subject N = 0, 7, 11, respectively for each cap size; subject N = 7 with missing cap size information). Other than the above measures, we did not additionally verify positioning of each individual electrode. The electrodes were cleaned, sanitized, re-used, and replaced with new ones when there were signs of wearing off (e.g., high impedance, visual inspection, etc.). During a stimulation protocol, the impedance was monitored every second by the experimenter. At any instant, if the impedance exceeded 20 kOhm in any stimulation electrode, the stimulation protocol was aborted to protect the subject from the high voltages generated. At each session, active HD-tDCS was ramped up over 60 sec until it reached 1 mA, maintained at 1 mA for 20 min, and then ramped down to 0 mA over 60 s. Sham current was ramped up over 60 sec until it reached 1 mA, then ramped down to 0 mA over 60 s until being switched off and left off for 20 min. Pain/discomfort level was evaluated before and after each session, which did not show increased pain/discomfort after stimulation protocol. We did not attempt to combine HD-tDCS with training, so subjects were told to sit and stay alert, and they were not allowed to nap with the supervision of a research personnel. They did not engage in any directed mental activity but were allowed to chat casually with the experimenter.

### 2.5. Rationale for HD-tDCS parameters

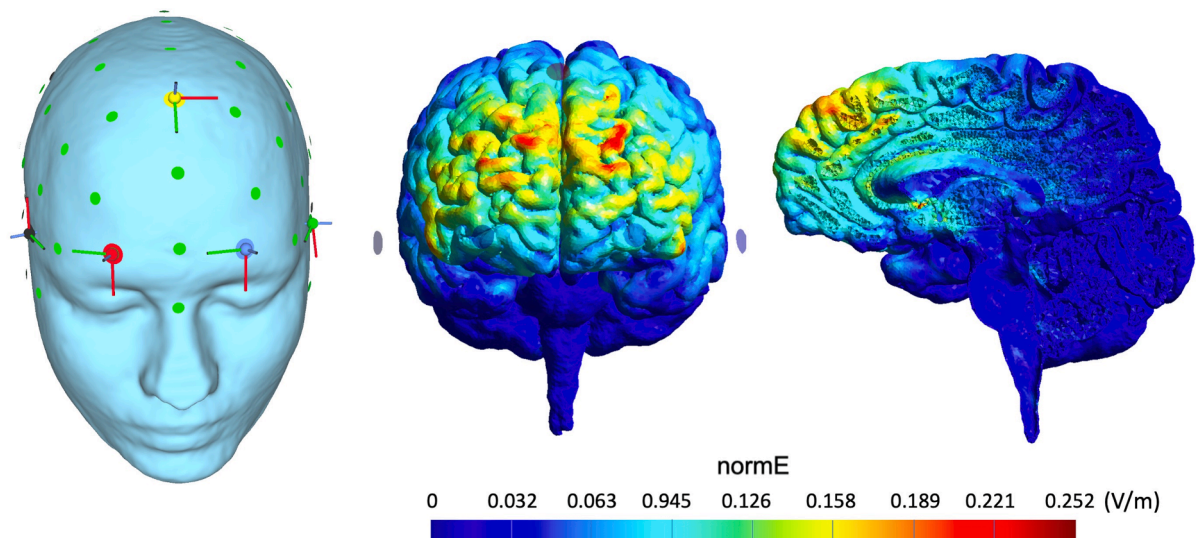
This protocol has been examined in previous research conducted in our lab revealing effect targeting frontal structures [54,21]. This montage has been reported in previous studies and was designed to target the dorsomedial prefrontal cortex with the electric field most concentrated in the pre-SMA/dACC [39,54]. There are several parameters that may warrant further clarification regarding this HD-tDCS protocol. (1) We had estimated normalized electric field based on a standard head model to simulate the intensity and distribution of our HD-tDCS montage (using the free software SimNIBS [52]). This model took into account the size of the HD-tDCS electrodes and their 10–10 EEG positions. The focus of the stimulation was concentrated in the prefrontal gyrus with maximal electric field of 0.252 (normalized electric field in units of Volt per meter, V/m) in the superior medial prefrontal gyrus, anatomically matching the pre-SMA (anterior and medial part of Brodmann Area 6) and dACC (Fig. 1). The peak electric field (normE) of 0.252 V/m is well within the wide range of the simulated peak electric fields based on HD-tDCS 4 × 1 ring montage reported in the literature (0.14 V/m using 2 mA in [58]; 0.8 V/m using 1 mA in [29]; 15 to 0.29 V/m using 1 mA based on different head models in [15]). It has been recognized that HD-tDCS has lower peak intensity than conventional tDCS [15]. Nevertheless, in a study by Kuo et al. [29], HD-tDCS induced longer-lasting effects in motor cortex excitability than conventional tDCS even when peak intensity was lower (0.08 V/m with HD-tDCS compared to 0.22 V/m with conventional tDCS). Still, (HD-)tDCS dose-response function is complex and likely not linear, depending on the indications and outcome measures under investigation [8,15,17]. It is also possible that the effects obtained could be due to peripheral stimulation [1], so even with low amplitude it is possible to induce an effect. Furthermore, the head model used depends on several parameters that can be modified (cerebrospinal fluid, thickness of the skull, conductivity of different tissues). Each model takes into account different parameters that makes it difficult to compare studies directly. For now, we demonstrated that at least 1 mA anodal HD-tDCS targeting the pre-SMA/dACC was beneficial based on this protocol. (2) We continued to use 1 mA for our protocol in that when more than 1 mA was delivered (up to 2 mA), subjects tended to experience more tingling and

**Table 2**  
Baseline neuropsychological data: mean (SD).

	Active (N = 18)			Sham (N = 7)
	All	Intact-recall (N = 10)	Impaired-recall (N = 8)	
MOCA <sup>a</sup>	26.1 (3.3)	27 (2.2)	25.1 (4.2)	23.9 (4.4)
COWAT (total)	44.3 (13.6)	45 (14.2)	43.4 (13.7)	40.6 (11.6)
Category fluency (total)	20.8 (6.6)	23.7 (6.1)	17.3 (5.6)*	23.3 (5.5)
BNT total	55.9 (2.6)	55.9 (3.2)	56 (1.5)	56.1 (8.9)
Digit span-forward (longest)	6.9 (1.9)	6.5 (1.2)	7.4 (2.6)	6.7 (1.3)
Digit span-backward (longest)	5.6 (1.6)	5.5 (1.3)	5.8 (2)	5 (1.8)
TMT A (sec)	30.9 (11.8)	27.5 (8.6)	35.3 (14.2)	31.9 (8.9)
TMT B (sec)	73.6 (26.9)	65.3 (23.9)	84 (28.3)	102.6 (88.8)
D-KEFS inhibition (sec)	54.8 (11.9)	53 (11.9)	57.4 (12.4)	68.7 (26.5)
D-KEFS inhibition-switch (sec)	68.6 (17)	60.5 (12)	78.6 (17.5)*	80.1 (47.5)
RAVLT delayed recall (item)	8.9 (4.4)	12.3 (7.4)	4.6 (2.3)**	7.4 (5.3)

MOCA: Montreal Cognitive assessment; COWAT: Controlled Oral Word Association Test; BNT: Boston Naming Test; TMT: Trail Making Test; D-KEFS: Delis-Kaplan Executive Function System; RAVLT: Rey Auditory Verbal Learning Test. \*  $p < 0.05$ , \*\*  $p < 0.01$ , for group comparisons (active intact vs impaired) using 2-tailed independent sample T tests. None was significant in any measure for group comparisons of (1) active (all) vs sham, (2) active intact vs sham, and (3) active impaired vs sham.

<sup>a</sup> N = 8 active-intact, N = 7 in active-impaired.



**Fig. 1.** HD-tDCS montage and simulated electric field. HD-tDCS is applied using a 1:4 montage, with the anodal electrode at Fz (1 mA) and four cathodal electrodes at FP1, FP2, F7, F8 (0.25 mA each). Normalized electric field is simulated to represent its intensity and distribution based on an individual example head model (methods and head model based on SimNIBS [52]). The focus of HD-tDCS is located to the medial superior part of the prefrontal gyrus with a peak electric field of 0.252 (normalized electric field in units of Volt per meter) in the pre-Supplementary Motor Area (pre-SMA) and the dorsal Anterior Cingulate Cortex (dACC).

discomfort over the electrode sites which was thought to be related to the small electrode size (1 cm radius). In the current study no one dropped out because of pain or intolerance. The use of the stimulator and the conductive gel may contribute to the reason why 2 mA (that we tested) was not well tolerated. Although failure to limit use of electrodes could affect tolerance, as routine we visually inspected (signs of wearing off), checked (impedance), and replaced electrodes as necessary. Lower tolerance to 2 mA still occurred even when new electrodes were used, so electrode quality due to overuse should not be the main reason. However, our current study was not designed to test these factors. (3) We used 60 s to ramp up current for both active and sham conditions. Though not systemically examined, subjects from our previous studies reported tingling sensation up to 60 s which then dissipated in the active condition. In order to make subjective experience during the sham condition as close as to the active condition, we continued to adopt 60 s ramp up time. In addition, increasing the ramp-up time (typically 60 s in our protocol) made the electrical current tolerable. Admittedly there could be potentially minimal dosing during sham HD-tDCS as a result.

## 2.6. Statistical analysis

We used mixed generalized linear modeling (mixed GLM) which utilizes the restricted maximum likelihood (REML) method implemented in IBM SPSS Statistics 26.0 to include subject as a random factor in addition to fixed factors including Time ( $T1_{\text{change}}$ ,  $T2_{\text{change}}$ ) and Subgroup (active intact-group, active impaired-group, sham group) with their 2-way interaction.  $T1$  and  $T2$  indicate immediate-post and 8 weeks-post intervention, respectively. The outcome measures were verbal retrieval measures that were previously reported significant (category fluency, D-KEFS color-word inhibition, D-KEFS color-word inhibition/switch; see [39]). We used Shapiro-Wilk tests to check if data conformed to normal distribution before statistical analyses were performed. Percent change [ $T1_{\text{change}}$ : (Post-immediate score – Baseline score)/Baseline score]  $\times$  100 and  $T2_{\text{change}}$ : (Post-8 weeks score – Baseline score)/Baseline score  $\times$  100] for D-KEFS color-word inhibition scores conformed to normal distribution ( $p = 0.588$ ). Logarithmic transformation [ $T1_{\text{change}}$ : Log (Post-immediate score) – Log (baseline score) and  $T2_{\text{change}}$ : Log (post-8 weeks score) – Log (baseline score)] for category fluency and D-KEFS color-word inhibition/switch scores conformed to normal distribution ( $p = 0.307$  and  $0.231$ , respectively). All estimates were performed using Kenward-Roger approximation due to

smaller sample conditions at confidence level of 95% (IBM SPSS Statistics 26.0). Co-variance structure for repeated measures was based on first-order autoregression. Significant results were reported with  $p < 0.05$ .

## 3. Results

Group average percent and logarithmic changes in the three outcome measures at  $T1$  and  $T2$  are reported in Table 3 and Fig. 2. Although there was significant post-intervention improvement from  $T1$  to  $T2$  consistent across groups,  $F(1,20) = 10.642$ ,  $p = 0.004$ , likely representing practice effects, post-intervention change in category fluency differed significantly between groups,  $F(2,23) = 5.855$ ,  $p = 0.009$ . *Post hoc* comparisons showed significant group differences based on the 95% confidence intervals in the active-impaired group (0.137, 95% CI: 0.064 to 0.209) compared to the active-intact group (–0.003, 95% CI: –0.059 to 0.054), though not to the sham group (–0.008, 95% CI: –0.081 to 0.065) groups (boxplot with individual scores in Fig. 2a). The active-impaired group also showed significant post-intervention improvement in category fluency while the other two groups did not (Fig. 2a). For D-KEFS color-word inhibition/switch, post-intervention change across groups differed by marginal significance,  $F(2,20) = 3.278$ ,  $p = 0.059$ . *Post hoc* comparisons did not reveal significant group differences in post-intervention change for color-word inhibition/switch performance, but both the active-impaired (–0.119, 95% CI: –0.185 to –0.053) and active-intact (–0.063, 95% CI: –0.115 to –0.011) groups demonstrated significant post-intervention improvement compared to baseline, while the sham group (–0.007, 95% CI: –0.07 to 0.057) did not (boxplot with individual scores in Fig. 2b). The main effect of time and the time  $\times$  group interaction were not significant ( $p = 0.182$  and  $0.502$ , respectively). No main effects or interactions were significant for D-KEFS color-word inhibition (all  $p$ 's  $> 0.05$ ; see values in Table 3).

## 4. Discussion

First, we found that category fluency improved post-active intervention only in individuals with impaired delayed recall at baseline. This was further corroborated by a significant difference in the post-intervention change in the impaired compared to intact group. Second, D-KEFS color-word inhibition/switch improved in individuals with or without impaired baseline delayed verbal recall post active HD-tDCS



**Table 3**

Model estimates post intervention: mean (95% confidence interval).

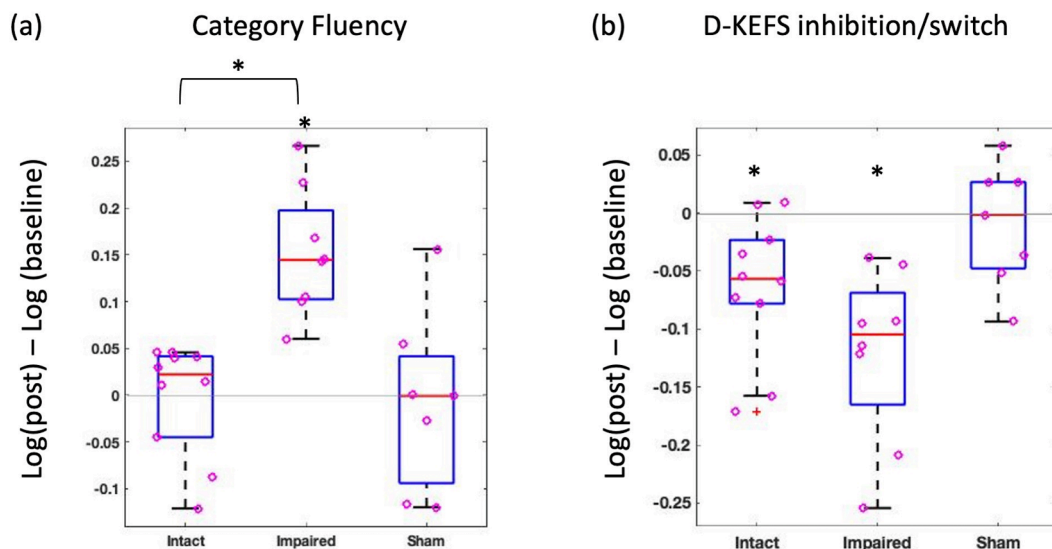
Time points	Active intact (N = 10)		Active impaired (N = 8)		Sham (N = 7)	
	$\Delta T1$	$\Delta T2$	$\Delta T1$	$\Delta T2$	$\Delta T1$	$\Delta T2$
Category fluency (total items)*	-0.047 (-0.113 to 0.019)	0.042 (-0.033 to 0.116)	0.055 (-0.024 to 0.134)	<b>0.218</b> <b>(0.113 to 0.324)</b>	-0.035 (-0.114 to 0.045)	0.019 (-0.087 to 0.124)
D-KEFS inhibition (total time)^	-7.8 (-20.6 to 4.9)	<b>-15.3</b> <b>(-29.4 to -1.2)</b>	-6.8 (-23.2 to 9.7)	-2.6 (-25.3 to 20.2)	-2.1 (-17.4 to 13.1)	-12.7 (-30.5 to 5.1)
D-KEFS inhibition/switch (total time)*	-0.057 (-0.115 to 0.001)	<b>-0.069</b> <b>(-0.133 to -0.005)</b>	<b>-0.112</b> <b>(-0.181 to -0.043)</b>	<b>-0.126</b> <b>(-0.216 to -0.036)</b>	0.03 (-0.039 to 0.099)	-0.043 (-0.124 to 0.038)

\* Log transform change.

^ Percentage change (%).

Bolded scores represent significant difference at follow-up compared to baseline.

SD: standard deviation.



**Fig. 2.** Boxplots for Category Fluency (a) and D-KEFS color-word inhibition/switch (b) performance in all three groups. Y-axis is based on individual scores using logarithmically transformed difference between post-intervention time points (collapsed over two follow ups) and the baseline. Noted that in (a), the higher the scores, the more words generated compared to baseline; whereas in (b), the lower the scores, the faster (more improved) the performance compared to baseline. For plotting purposes, missing data were replaced by subgroup means. The horizontal line (in red) inside of each box represents the sample median; the top and bottom edges of each box (in blue) represent the upper and lower quartiles, respectively; the whiskers represent the minimum and maximum values that are not outliers; outliers ( $>1.5$  interquartile range away from the top or bottom of the box) are plotted individually with a cross; circles (in magenta) represent individual scores.

\*Significant difference within or between groups based on 95% confidence intervals as described in the Results section.

intervention. The overall findings contradict our initial hypothesis stating that those with more intact baseline delayed recall would respond to HD-tDCS with more improvement.

Verbal fluency (both phonemic and category) is associated with function of the pre-SMA/dACC and the left inferior frontal gyrus [3,60,34,37]. Compared to phonemic fluency, category fluency relies on both cognitive control and semantic processing, dependent on both frontal and temporal regions according to volumetric and lesion studies [2,49,59]. Prior studies have shown that size of frontal brain lesions, frontal white matter integrity, and white matter tracts connecting frontal and temporal regions (e.g., uncinate fasciculus) predicted category fluency performance (in TBI, [64] and [23]; in multiple sclerosis, [4]). It is plausible that baseline delayed verbal recall is not only a sensitive measure for chronic TBI sequela but also an indicator for HD-tDCS response. We used RAVLT as our verbal learning test, which entails word list learning that introduces memory interference with an additional word list. Greater requirements for cognitive control as well as for semantic processing are likely required to encode and recall words only from the targeted list and to avoid recalling words from the interference list. Improvement in category fluency may be predicated on integrity of the frontal lobes and their connection (functional or structural) with the temporal regions, that could overlap with neural mechanisms for

delayed verbal recall [51,22]. This also suggests a ceiling effect in individuals with more intact delayed verbal recall and less room for improvement at least in the case of category fluency.

Both active groups with intact and impaired baseline delayed recall showed improvement in D-KEFS color-word inhibition/switch. Active HD-tDCS targeting the pre-SMA/ACC could facilitate cognitive control in selecting and inhibiting verbal information that depends on the prefrontal cortex [7,14], leading to better word retrieval during color-word inhibition and switch. However, in this more frontal lobe-focused test, it seems that baseline delayed verbal recall did not differentiate responses to HD-tDCS. This suggests that even though individuals with more intact delayed recall at baseline also had higher baseline performance in D-KEFS inhibition/switch, their performance still improved after active HD-tDCS. This supports possible differential benefits of HD-tDCS in individuals with different baseline cognitive profiles and argues against the contention that our data could be explained by regression toward the mean.

A neural circuit that includes pre-SMA, caudate, and thalamus has been proposed to facilitate verbal memory retrieval and verbal fluency [19,20,34], as well as cognitive control that involves inhibition and switching [7,14]. These interconnected regions are frequently affected by TBI, and intraregional/interregional disruption is correlated with the

degree of cognitive and verbal retrieval impairment [50]. Prior studies have further shown that fronto-cortical functional/structural connectivity and frontal white matter integrity predict executive function and task switching in TBI [27,30–32]. It is possible that the functional role of this circuit is tied not only to lexico-semantic retrieval but also in a more domain-general manner influencing speed of processing and cognitive control underlying response selection and inhibition, as can be demonstrated in verbal retrieval during category fluency and D-KEFS inhibition/switch.

Even though we found that delayed recall performance at baseline predicted responses in category fluency, we did not design our HD-tDCS montage to target its underlying neural mechanisms. As previously reported, no significant effect on delayed recall performance post-intervention was found based on a pilot study [39]. Hence delayed recall is a sensitive measure for TBI-related chronic change and potentially a predictor for HD-tDCS response but may not represent fully the electromodulatory effects, at least under the context of our current study design. Delayed recall may share some overlapping cognitive processes (semantic processing and cognitive control) as well as neural mechanisms (frontal and temporal systems) with verbal retrieval functions [26] (in mild cognitive impairment, [40]; in TBI, [5] and [55]). Indeed, we found positive correlations ( $R = 0.583$ ,  $p = 0.011$ ) between delayed recall and category fluency at baseline when we included participants who underwent active stimulation. However, these two measures are not equally responsive to pre-SMA/dACC HD-tDCS, as indicated by the significant post-intervention change for category fluency but not for delayed recall. On the other hand, delayed recall was also correlated with D-KEFS color-word inhibition/switch at baseline ( $R = -0.502$ ,  $p = 0.034$ ) but both intact and impaired groups showed significant improvement in the latter. Thus, the predictive power of baseline delayed recall on outcome measures could not simply be interpreted by correlations at baseline. Overall, baseline delayed verbal recall may be a potential predictor for those functions that require both the frontal and temporal lobe systems such as category fluency, but is less predictive of other functions that rely primarily on the frontal lobe system.

Pre-SMA/dACC HD-tDCS may modulate and resynchronize the underlying functional connectivity between regions that mediate behavioral changes [54], and appears to be more beneficial for those with greater interruption of fronto-temporal functional/structural connectivity as indirectly measured by their impaired baseline delayed verbal recall. Those with intact baseline delayed recall may have less underlying neural dysfunction that can be modulated. We presume, however, that if the severity of structural and functional damage exceeds a certain level (such as causing global cognitive deficits), the beneficial effects of HD-tDCS will be reduced, or nil. This has important implications for future application of HD-tDCS in selecting appropriate candidates for treatment.

We acknowledge some limitations of this study. First, the sample size is smaller. We are planning to collect a larger sample to confirm these findings. Second, the patient population in this study is strictly veterans who may have particular types of TBI and military experiences. Whether these findings are applicable to civilian TBI populations warrants future investigation.

In conclusion, our pilot results reveal a predictor of behavioral responses to electromodulatory intervention. More impaired delayed verbal recall in the setting of relatively intact global cognition predicts better response to anodal HD-tDCS targeting the pre-SMA/dACC as evidenced by improved category fluency.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Author contributions statement

H.-S. C. designed and implemented the data analysis and wrote the manuscript. J.H., Jr., M.M., and M.K. advised analysis framework. J.H., Jr., M.K., and S.V. designed the HD-tDCS protocol. R.O. recruited subjects, collected data, and participated in data analysis. All authors participated in editing.

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