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Impact of transcranial direct current stimulation on sustained attention in breast cancer survivors: Evidence for feasibility, tolerability, and initial efficacy

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ABSTRACT

Background: A significant subset of breast cancer survivors experience cognitive difficulties in attention and memory, which persist for years following treatment. Transcranial direct current stimulation (tDCS) has been shown to be effective in improving working memory, attention, processing speed, and other cognitive functions in both healthy and clinical populations. To date, no studies have examined tDCS for rehabilitation of cancer-related cognitive dysfunction.
Objective/hypothesis: We aimed to provide preliminary evidence for feasibility, tolerability, acceptability, and efficacy of tDCS in improving performance on a measure of sustained attention.
Methods: In a within-subjects design, 16 breast cancer survivors underwent 2 consecutive days of active tDCS over the prefrontal cortex, and 2 days of sham tDCS, counterbalanced for order of stimulation condition, while performing a continuous performance test.
Results: Stimulation was feasible and tolerable, with 89% of participants completing all sessions, and none reporting more than mild to moderate discomfort. Analyses of efficacy showed that during active stimulation, participants had significantly lower standard errors of reaction times overall, indicating better sustained attention ability, as compared to sham stimulation ($p < 0.05$). Furthermore, the effect of stimulation on standard errors of reaction times differed by inter-stimulus interval (ISI): for 1 and 2 s ISIs, there was no significant difference in performance between sham and active tDCS conditions, but for 4 s ISIs, stimulation improved variability in response times relative to sham ($p < 0.05$).
Conclusions: Results suggest that tDCS is feasible, tolerable, and may be an effective intervention to improve sustained attention difficulties in survivors with cancer-related cognitive dysfunction.

Introduction

Among the most distressing and intractable symptoms for breast cancer survivors is cognitive dysfunction following treatment [1,2]. Neuropsychological studies have documented approximately 25–40% of chemotherapy-treated survivors exhibit dysfunction in two or more cognitive domains [3–6]. Cancer-related cognitive dysfunction (CRCD) interferes with the ability to return to their normal lives, disrupting family, career and social responsibilities [2,7–12]. As a result, leading breast cancer survivorship guidelines highlight the critical need to provide treatment for cognitive dysfunction [13].

There have been limitations in previous interventions for cognitive dysfunction among cancer survivors. These interventions include cognitive rehabilitation strategies [14–18] and those targeting factors associated with cognitive function, such as fatigue [19–22], stress [23,24], or physical activity [25–28]. Overall, cognitive rehabilitation strategies were successful in improving some subjective and objective aspects of cognitive performance, but required significant time commitments ranging from four [17,18] to 12 weeks [29]. Studies aimed at improving cognition by reducing fatigue showed no changes to objective performance,

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whether administering D-methylphenidate [20,22] or delivering cognitive behavioral therapy [19]. There were also no changes in objective cognitive performance by reducing stress with meditation [30], and concomitantly increasing physical activity with yoga [27,28] or medical qigong [25].

Identifying targets for intervention can be guided by previously observed structural and functional brain changes associated with CRCD, which appear to generally center on prefrontal areas. Chemotherapy-treated survivors show more pronounced reductions in brain volume in prefrontal regions [31–35]; reduced brain activity during functional tasks in anterior and dorsolateral prefrontal regions of the brain [35–39]; and reduced white matter connectivity in tracts connecting prefrontal areas [40–42], and animal studies using common chemotherapies produce deficits in electrophysiological measures of brain function [43] and reductions in neurogenesis [44]. This research suggests specific anatomical targets for intervention to alter underlying brain activity, specifically in prefrontal areas, as can be achieved with transcranial direct current stimulation (tDCS).

tDCS can manipulate brain activity underlying cognition [45,46], and meta-analyses have shown prefrontal stimulation can alter aspects of behavioral performance [47], although only one case report has described specific application in cancer survivorship. Authors applied five sessions of tDCS to the prefrontal cortex in a breast cancer survivor and found improved outcomes in a computerized neuropsychological battery of executive function [48]. Meanwhile, targeting prefrontal regions that are largely implicated in supporting attention [49] with tDCS may be beneficial given converging evidence of the susceptibility of attentional processes, in particular, following cancer treatment. Chemotherapy-treated breast cancer survivors show worse attentional performance on neuropsychological tests [41,50,51], and greater intra-individual variability in reaction time on attention tasks [52]. This pattern is associated with variable and lapsing attention, consistent with attention deficit disorder and brain injury [53]. Moreover, attention can modulate memory performance [54], an important consideration given that 58%–68% of chemotherapy-treated survivors report subjective memory dysfunction [38,55–59]. Replicated results from our lab identify a memory deficit selective to the initial learning trial of five repeated recall trials, suggesting that initial attention [60,61] for to-be-learned information may be a specific deficiency in survivors following treatment [62,63]. This interaction between memory and attention is also suggested by our previous work that finds stronger association between attention/working memory deficits and self-reported memory complaints than memory performance [64].

Despite accumulating evidence that cancer survivors exhibit attention and working memory deficits, none of these findings have made their way into diagnostic use or treatment development for survivors. This research is the first to test the feasibility, acceptability, tolerability, and preliminary efficacy of tDCS for cancer-related cognitive dysfunction in breast cancer survivors. A large group of breast cancer survivors who report cognitive problems will have been treated with chemotherapy and are on endocrine therapy: therefore, this was the target population for this research. To establish feasibility and acceptability, a short course of 2 active sessions and 2 sham sessions of prefrontal tDCS, counterbalanced, was administered over four consecutive days. To evaluate preliminary efficacy of tDCS to improve attentional performance, we conducted active and sham stimulation while survivors completed the Conners' Continuous Performance Test (https://www.mhs.com/), a computerized assessment of sustained attention, attentional consistency and inhibition of response. We focused on sustained attention given our own and other previous research that finds attentional dysfunction, prefrontal volume reduction, and prefrontal reduction in functional activation during attentional tasks, as well as the association of initial attention/working memory deficits with survivor reported memory difficulties [64–67].

Methods

Participants

Eighteen breast cancer survivors were recruited by screening clinic appointment schedules at the MSKCC Department of Psychiatry Counseling Center and reviewing Electronic Medical Records of identified breast cancer survivors to further verify their eligibility based on disease and treatment. We selected breast cancer survivors who were more than six months post-completion of cancer treatment in order to capture the subset of survivors who experience lasting cognitive deficits as opposed to those whose acute treatment-related cognitive difficulties resolve within a few months following completion of treatment [68]. Inclusion criteria: 1) Breast cancer survivors treated with chemotherapy between 40 and 65 years of age with no evidence of disease, with treatment completed at least six months prior to study participation with or without current ongoing endocrine therapy; 2) Self-reported new-onset presence of cognitive dysfunction since treatment determined by telephone screen using the brief (3 questions) assessment established by Ercoli et al. [16]. Exclusion criteria: 1) History of seizure disorder, a dementing condition, or other neurological illness (multiple sclerosis, history of cerebrovascular accident, etc.) as assessed by self-report and review of medical history; 2) Untreated depression or anxiety as assessed by self-report and review of medical history; 3) History of treated or untreated schizophrenia or bipolar disorder as assessed by self-report and review of medical history; 4) current pregnancy; or 5) pacemakers, intracranial electrodes, implanted defibrillators, or any other prosthesis. All participants were fluent in English and underwent informed consent. All methods were approved by the MSKCC IRB. Participants were compensated $70 for their participation upon completion of all four sessions. Two consented participants failed to return for all four required sessions due to scheduling conflicts, resulting in a total sample size of 16 participants.

Materials

tDCS: Starstim wireless hybrid EEG/tES multichannel transcranial current stimulator (http://www.neuroelectrics.com) was used to administer tDCS stimulation. Two Ag/AgCl electrodes with a 1 cm radius were used to administer stimulation over the left dorsolateral prefrontal cortex (dlPFC): the anode (stimulating electrode) was placed over the F3 position, and cathode (return electrode) was placed over F4 based on the 10–20 EEG system (Fig. 1).

Cognitive task: Attention performance was measured using the Conners' Continuous Performance Test (CPT-II), a computer-based task that requires the subject to monitor single letters presented on a computer screen in succession, and to respond to target letters while withholding response to a non-target letter. The task consisted of 360 total trials divided into 18 blocks of 20 trials each. Ninety percent of trials were targets, i.e. letters other than 'X' that required the participant to press the space bar as soon as seeing the stimulus, and 10% consisted of the non-target 'X' for which subjects were instructed to withhold a response. Inter-stimulus intervals (ISIs) varied across blocks, with 6 blocks each of 1-s, 2-s and 4-s ISIs. Given that this is a go/no go task, there is no requirement that participants hold in mind previous trial information; the only requirement is to respond as quickly as possible to each letter and to withhold response to the letter X. Blocks with longer ISIs are

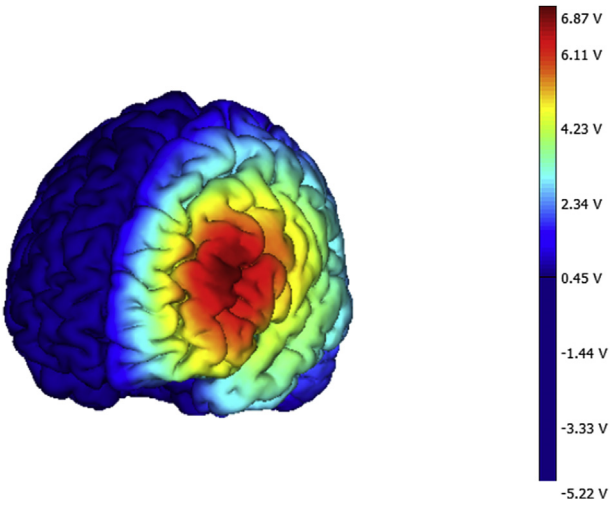

Fig. 1. tDCS montage with modeled current density for left dlPFC stimulation.

considered to place a greater load on sustained attention processes, as participants must maintain engagement with the task over a longer delay in order to respond as quickly as possible to the next stimulus. Therefore, while the task is thought to engage several subprocesses of attention such as vigilance and impulsivity, changes in response speed and changes in variability of response speed as a function of ISI are specifically reflective of sustained attention processes.

Questionnaires: Sociodemographic questionnaire, including information about patient age, race, ethnicity, years of education, marital status; Memorial Symptom Assessment Scale Short Form (MSAS-SF), a measure of patient-reported physical, psychological, and global distress symptoms; Patient Assessment of Own Functioning Inventory (PAOFI), a self-report measure of difficulty with memory, attention, concentration, language, and thinking abilities; Sensory Gating Inventory (SGI), a measure of difficulties with attention and concentration related to difficulty filtering irrelevant sensory information; tDCS Patient Experience Questionnaire, which assesses patients' experience with the device and any noticeable changes in thinking; and Brunoni Adverse Events Questionnaire, which assesses presence and severity of any discomfort or adverse events related to tDCS. Table 1 indicates sessions at which each questionnaire was completed.

Procedure

Participants completed four study visits over four consecutive days, at the same time each day. Visits 2–4 were approximately 60 min in duration, including tDCS setup, stimulation, completion of attention task, and post-stimulation questionnaires; visit 1 lasted approximately 90 min, with the additional ~30 min allocated for the consent process. During each session, the tDCS device was adjusted over the participant's scalp and impedance of electrodes was assessed by the Starstim software interface. Participants performed a brief practice CPT task to ensure that task instructions were understood, as is the procedure in standardized administration. The tDCS device delivered a 30-s ramp-up and the experimental run of the computerized CPT task was initiated. Once the ramp-up was complete, a steady state current of 1 mA was administered for the duration of the behavioral task (15 min) for active sessions; during sham sessions, stimulation was ramped up over 30 s and then down over 30 s at both the start and end of the task, with no active current delivered through the duration of the task. The current of 1 mA was chosen to reduce sensititvity to the higher current density under the 1 cm electrodes used, which reduces ability to detect differences between sham and active conditions within subjects, and has been shown to enhance cortical excitability to an equal or greater extent than higher intensities [69]. Reaction time and accuracy were measured throughout task performance. At completion of active sessions, the tDCS device delivered a ramp-down stimulation over 30 s. The device was then removed, and participants completed self-report questionnaires. Order of sham and active stimulation sessions were counterbalanced between subjects, such that half of participants (N = 8) received two consecutive days of active stimulation followed by two consecutive days of sham stimulation, and half of participants received two sham followed by two active stimulation sessions.

Table 1
Questionnaires completed at each session.

Questionnaire	Session			
	1	*2*	*3*	*4*
Sociodemographic	X			
MSAS-SF	X			
PAOFI	X			X
SGI	X			X
Patient Experience	X	X	X	X
Brunoni Adverse Events	X	X	X	X

Data analyses

Changes in self-reported cognitive function from before the start of the study to after the final session were analyzed using repeated measures ANOVAs. The relationship between stimulation condition (sham vs. active) and performance on the CPT was analyzed using mixed linear models and post hoc t-tests in SPSS. Six individual mixed linear models were used to analyze the effects of tDCS on primary outcome measures of attentional variability and response speed (Table 2), and a further six models were constructed to analyze the effects of stimulation on variability and response speed within each of the three inter-stimulus interval blocks. Another two models were constructed to analyze response accuracy.

Previous research has suggested the effects of tDCS may vary based on a number of individual differences, including age [70], and internal psychological states, such as transient changes in mood [71,72], alertness [73], motivation [74], and expectations about tDCS effectiveness [75] that can alter baseline neural activity, likely mediating the effects of tDCS on behavior. Thus, to control for the effects of individual differences in response to tDCS, we included covariates reflecting participants' age, mood, alertness, and sensitivity to stimulation (self-reported headache, scalp pain, tingling, itching, burning) with participant ID entered as a random effect. All predictors were mean-centered to allow for interpretation of the intercept and avoid multicollinearity when assessing interactions. Measures of reaction time and standard errors were log transformed to account for non-normal distributions. To account for the number of fixed-effects parameters being estimated, all models used a restricted maximum likelihood procedure (SPSS Version 23.0) to yield unbiased parameter estimates.

Results

Feasibility

Between May 2017 and July 2019, potentially eligible participants for the current study were identified by screening MSKCC's institutional database for women currently aged 40–65 years,

Table 2
CPT outcome measures.

Outcome measure	Description
Overall Standard Error (Hit RT SE)	Response speed consistency
Standard Error by Inter-Stimulus Interval (Hit SE ISI Change)	Change in the standard error of reaction times at different ISIs
Standard Error by Block (Hit SE Block Change)	Change in response consistency across duration of test
Overall Hit Reaction Time (Hit RT)	Average speed of correct responses
Reaction Time by Inter-Stimulus Interval (Hit RT ISI Change)	Change in reaction times at different ISIs
Hit Reaction Time by Block (Hit RT Block Change)	Change in reaction time across duration of test
Commissions	Responses given to non-targets
Omissions	Failure to respond to target letters

previously treated with chemotherapy, and who had or were scheduled to have an appointment with one of the attending neuropsychologists in the MSKCC Counseling Center. Of the 235 individuals who met these criteria, 154 were ineligible, most often due to history of psychiatric or neurological disorders, a diagnosis of cancer other than or in addition to breast cancer, or no history of treatment with chemotherapy.

Of the remaining 81 eligible potential participants, 34 were not interested in participating, primarily due to the time commitment required, and 29 were unable to be reached by phone after three attempts, and thus were considered to have silently declined. We speculate that lack of interest may have resulted from this being a feasibility study, in which participants may not expect to see improvements in cognition, as opposed to a clinical trial in which subjects might expect a therapeutic benefit from participating. The remaining 18 subjects who were eligible and interested were enrolled. One subject was unable to return for one session due to inclement weather, and another missed a session due to a scheduling error, resulting in a total of 16 participants who completed the study protocol.

Tolerability and acceptability

Tolerability and acceptability of four consecutive sessions of tDCS were assessed using the Brunoni Adverse Events questionnaire and the tDCS Patient Experience Questionnaire, which were completed following each tDCS session. Stimulation was generally well tolerated: the most commonly experienced side-effects were itching and burning on the scalp, which the majority of participants rated as mild (2) to moderate (3) on a 1 to 4 scale (Table 3). No sessions needed to be aborted due to side effects. On the Patient Experience Questionnaire, participants were asked to rate how comfortable the device was overall, from 1 (very comfortable) to 4 (very uncomfortable). During nearly all 64 sessions, participants reported the device was very or somewhat comfortable (Mean rating = 1.64, SD = 0.72). On nine of the sessions, participants gave ratings of 3 indicating tDCS was “somewhat uncomfortable”. However, all participants at all sessions indicated they would be ‘very likely’ or ‘somewhat likely’ to participate in tDCS treatment to improve cognitive performance if it were recommended, suggesting tDCS is tolerable and acceptable in breast cancer survivors with cancer-related cognitive dysfunction.

Participant blinding

To assess whether participants were blinded to the stimulation condition (i.e., active vs. sham), we asked participants if they could determine whether they received stimulation or not: 61% of participants reported they could not determine whether they received stimulation or not. Of those who felt they could determine stimulation condition, 76% of sham stimulation sessions were identified as active, and 91% of active stimulation sessions were identified as active. Therefore, it appears that sham was successful in blinding participants to whether they were receiving active stimulation: most participants were unable to differentiate between sham and active, and of those who did feel they could detect a difference, the majority incorrectly believed they were receiving active stimulation during sham.

Changes in self-reported cognitive difficulties

There was no significant difference in mean PAOFI scores before and after the tDCS sessions ($F[1,13] = 2.28$, $p = 0.155$). However, there was a nominal decrease in self-reported cognitive problems in the anticipated direction: mean PAOFI score prior to the start of the first stimulation session was 97.71 (SD = 25.54), and this score reduced to a mean of 93.93 (SD = 21.90) by the end of the last session. There was a marginally significant change in SGI scores from pre-stimulation (M = 62.14, SD = 30.49) to the last session after stimulation (M = 56.43, SD = 29.22; $F[1,13] = 3.17$, $p = 0.098$). Taken together, it appears that participants experienced a subtle improvement in subjective experience of cognitive function following tDCS, and this suggests the sensory-gating inventory, that focuses more specifically on attentional focus and distractibility, may be more sensitive to stimulation-associated changes in self-reported cognition as compared to the PAOFI.

Effects of stimulation on CPT performance

Attentional variability

Stimulation condition was a significant predictor of overall Hit RT SE ($F[1,38.887] = 4.948$; $p < 0.05$): predicted Hit RT SE during active stimulation (M = 1.546, SE = 0.063) was significantly lower than predicted Hit RT SE during sham (M = 1.648, SE = 0.063), suggesting tDCS improved participants’ response speed consistency. Stimulation condition was a marginally significant predictor of Hit SE ISI Change ($F[1,40.16] = 3.92$, $p = 0.055$), with predicted mean Hit SE ISI Change during active stimulation (M = 0.01, SE = 0.02) lower than during sham (M = 0.047, SE = 0.02),

Table 3
Ratings of stimulation side-effects.

	Maximum	Mean	SD
Headache	2	1.078	0.27
Neck Pain	3	1.078	0.37
Scalp Pain	3	1.156	0.444
Tingling	3	1.812	0.639
Itching	4	1.156	0.712
Burning	4	1.625	0.845
Redness	1	1.00	0.00
Sleepiness	4	1.594	0.886
Trouble Concentrating	4	1.39	0.657
Acute Mood Change	3	1.078	0.37

suggesting tDCS decreased the degree to which standard error of reaction times changed with different ISIs, a reflection of vigilance.

In order to examine in which ISI blocks stimulation affected Hit RT SE to produce differences in Hit SE ISI Change, we then analyzed the effects of tDCS on standard errors of reaction times within each of the three different ISI blocks (1-s, 2-s, and 4-s ISIs) to determine whether stimulation affected variability in the typical slowing of response times that is expected to occur with increased ISI due to greater demand on the ability to sustain vigilance. Results showed a significant difference specifically for the 4-s ISI ($F[1,39.025] = 5.544$; $p < 0.05$), but not for the 1-s ISI ($F[1,39.00] = 0.325$; $p = 0.572$), or 2-s ISI ($F[1,40.405] = 0.805$; $p = 0.375$). For the 4-s ISI, subjects had lower SE under active stimulation ($M = 2.023$, $SE = 0.083$) as compared to under sham ($M = 2.161$; $SE = 0.083$) (Fig. 2). These results suggest tDCS decreased the degree to which reaction times became more variable at longer ISIs, when participants' sustained attention is expected to be most challenged. Stimulation was not significantly associated with Hit SE Block Change ($F[1,40.49) = 0.13$, $p = 0.73$).

Response speed

To determine whether stimulation affected response speed, we used mixed linear models to analyze the effects of tDCS on overall reaction times, and change in reaction times across ISI blocks. There was no significant effect of stimulation on mean predicted overall reaction time ($F[1,39.623] = 1.032$, $p = 0.316$). Stimulation condition significantly predicted Hit RT ISI Change ($F[1,38.92] = 9.14$, $p < 0.01$), with predicted mean Hit RT ISI Change during active stimulation ($M = 0.044$, $SE = 0.01$) significantly lower than during sham stimulation ($M = 0.057$, $SE = 0.01$), indicating tDCS decreased the change in average reaction times at different ISIs. Stimulation was not significantly associated with Hit RT Block Change ($F[1,42.54] = 0.31$, $p = 0.58$).

To examine how the effects of stimulation differed based on ISI block, we constructed models to assess the effects of tDCS on Hit RT ISI within each of the three different ISI blocks. Results showed a marginally significant difference specifically for the 4-s ISI ($F[1,40.053] = 3.954$; $p = 0.054$), but not for the 1-s ISI ($F[1,38.887] = 0.254$; $p = 0.617$), or 2-s ISI ($F[1,39.726] = 0.484$; $p = 0.491$). For the 4-s ISI, predicted reaction times were faster under active stimulation ($M = 6.132$, $SE = 0.022$) as compared to sham ($M = 6.166$, $SE = 0.022$) (Fig. 3). Therefore, in addition to decreasing variability in response speed, stimulation also decreased mean reaction times during longer ISIs, when maintaining sustained attention is most challenging.

Response accuracy

Turning to the effects of tDCS on response accuracy, we found that stimulation condition was a significant predictor of mean commissions ($F[1,39.06] = 4.21$; $p < 0.05$), with mean predicted commissions during active stimulation ($M = 10.23$, $SE = 1.80$) significantly higher than during sham ($M = 8.77$, $SE = 1.80$). This may suggest that under the condition in which reaction times were faster and less variable, indicating greater sustained attention, participants were also less able to withhold responses, suggesting poorer inhibition/greater impulsivity. Stimulation condition did not significantly predict mean omissions ($F[1,41.27] = 0.07$; $p = 0.79$).

Discussion

This is the first study to test the feasibility, tolerability, acceptability, and efficacy of using tDCS to improve attention performance in breast cancer survivors with cancer-related cognitive dysfunction. We successfully recruited 18 breast cancer survivors, 16 of whom completed four consecutive daily sessions of active and sham stimulation, with the largest obstacle to recruitment being scheduling difficulties due to this population being largely composed of middle-aged women in the workforce with children. Of the majority who completed the study, most reported very minimal or no side effects related to stimulation, and none reported adverse effects that led to termination of the study protocol. Lastly, all participants reported they would receive tDCS in the future if offered as a treatment. Together, our data support the hypothesis that tDCS is tolerable, feasible, and acceptable in breast cancer

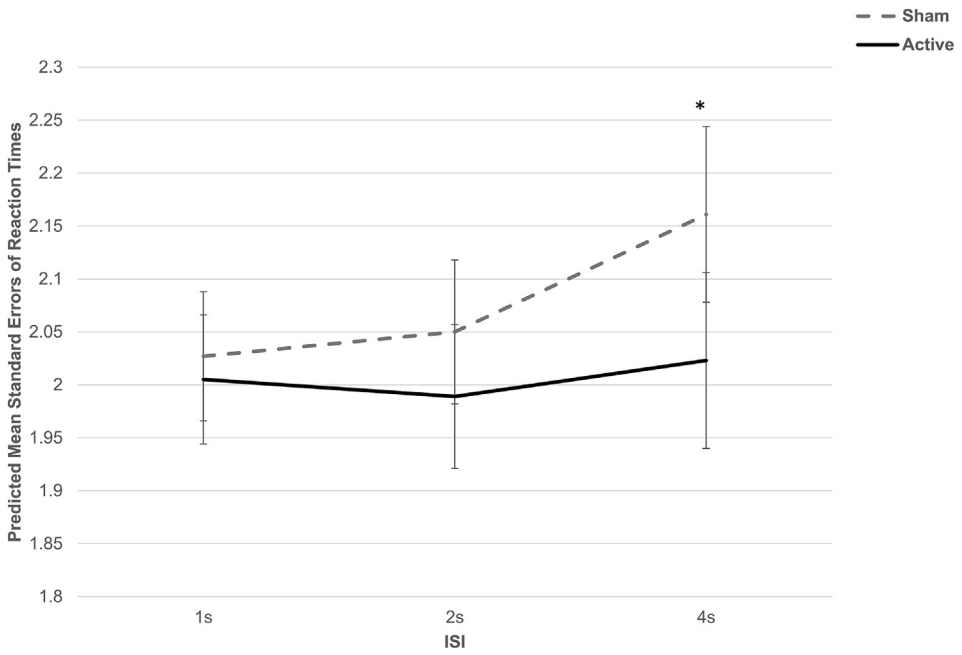

Fig. 2. Stimulation did not have a significant effect on predicted mean standard errors of reaction times for 1s and 2s ISIs, but active stimulation significantly decreased variability in reaction times at 4s ISIs relative to sham. *$p < 0.05$. Error bars represent standard errors of the means.

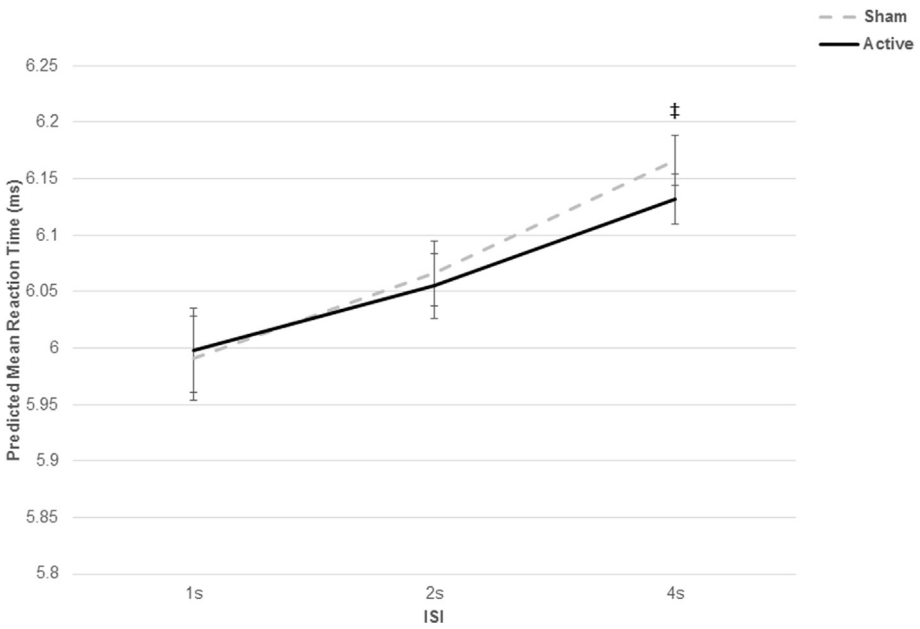

Fig. 3. Stimulation did not have a significant effect on predicted mean reaction times for 1s and 2s ISIs, but active stimulation marginally decreased reaction times 4s ISIs relative to sham. ‡p = 0.0565. Error bars represent standard errors of the means.

survivors, and warrant the development of further clinical trials to support its use as a treatment for cancer-related cognitive dysfunction.

We found evidence of preliminary efficacy in that tDCS over the prefrontal cortex improved performance on a computerized continuous performance task. Under conditions of active stimulation, participants had less variability in reaction times, and this effect was most notable during task blocks with the longest and most challenging inter-stimulus intervals, a condition during which increased variability is expected due to higher condition demand and resulting challenges to vigilance. There is a growing body of research showing that cancer patients and survivors demonstrate difficulties with attention that may be reflected by increased variability in reaction times. Yao et al. [76] found that breast cancer patients had greater reaction time variability with increased task difficulty on a Stroop task as compared to healthy controls, and others have demonstrated that breast cancer survivors have abnormal intraindividual variability (IIV) in response times on continuous performance tasks [52; Ryan, Ahles, and Root, in preparation]. Greater IIV has also been associated with greater prefrontal activity, likely due to increased demand on executive control processes [52,77]. The impact of cancer and its treatments on frontal executive networks has been demonstrated using converging evidence from functional [37] and structural [40,41] MRI, diffusion tensor imaging [38,78], and electrophysiological recording methods [79,80]. Therefore, our findings suggest that non-invasive brain stimulation to the prefrontal cortex, a region which is known to be impacted by cancer and cancer treatments, may be an effective means by which to improve frontally-mediated attentional processes that are disrupted in survivors. The finding of higher rates of commission errors was unexpected. While interpretation of this result is qualified in our limited sample size, increased commission errors, faster reaction time, and decreased variability are suggestive of a "speed over accuracy" approach. This finding may suggest that stimulation acted primarily to improve sustained attention, with faster and more consistent speed of response to the predominant task demand, i.e., button presses on "go" trials that are the majority of trials (90% of trials), but also generalized to the "no-go" trials, which are infrequent by contrast (10% of trials). It is also possible that stimulation acted to weaken inhibitory processes leading to increased impulsivity. The finding that improvement in speed and variability of responses came at a cost of response accuracy has implications for the use of tDCS as an intervention for attentional dysfunction in CRCD, and future research should examine whether improvements in sustained attention are seen in the context of changes in performance on attention-related inhibitory processes.

One limitation to the design of the current experiment is that for participants who received two days of active stimulation followed by two days of sham, there is a potential for after-effects of active stimulation to persist into the sham days. Given that repeated administration of tDCS over the course of several days is thought to increase the likelihood of changes in plasticity that can persist after stimulation is ceased [94], we recognize that this is a potential confound of the current study design, although we note that stimulation after-effects would only act to decrease the observed effect on our reported primary outcome variables reported above. Although we did not find any differences in performance during sham for those who received active tDCS for the first two days as compared to sham for the first two days, we had a very limited sample size per group (N = 8), and a future randomized controlled trial could separately examine differences in consecutive days of active tDCS compared to sham sessions, as well as include follow up to determine if behavioral effects are sustained.

Another potential limitation to the current experiment relates to the possibility that the position of the cathodal electrode induced inhibition of the right DLPFC. Although past literature often distinguishes between anodal electrodes as being excitatory while cathodal electrodes are inhibitory, these polarity effects are less clear in tDCS studies of cognitive function as compared to motor function. The effects of polarity on neural excitability and performance in cognitive tasks has been shown to be variable, and some studies have demonstrated that cathodal stimulation can improve cognitive performance similarly to anodal stimulation [81], while others have shown no changes in cortical excitability during and after cathodal tDCS as compared to pre-stimulation [82]. Therefore,

it remains unclear whether the changes in sustained attention demonstrated in the current study resulted from excitation of the left DLPFC, inhibition of the right DLPFC, or both. Future research aimed at testing the precise role of the left DLPFC in sustained attention should utilize a unilateral montage with an extracephalic cathode, or an HD-tDCS montage, in which a single anode is surrounded by several cathodes, such that cathodal current is distributed among multiple return electrodes, decreasing the functional efficacy of the cathodes and the potential for inhibitory effects on underlying cortical regions.

Related to the above limitation, it is worth noting that some past research has suggested the left DLPFC contributes to sustained attention [83,84], whereas right DLPFC has been shown to contribute to response inhibition but not sustained attention [85]. Therefore, although our chosen montage does not allow us to distinguish between the roles of the right and left DLPFC, it is possible that the increased commissions under the active stimulation condition was due in part to impairment of response inhibition caused by cathodal inhibition of the right DLPFC. Further research is needed to examine the effects of right vs. left DLPFC stimulation on subprocesses of attention, but future studies aiming to selectively improve sustained attention using tDCS may benefit from the use of a unilateral montage over the left DLPFC only.

Conclusions and future directions

As the first feasibility study to examine tDCS among a cohort of breast cancer survivors, our results provide promising evidence for the clinical utility of tDCS to improve cancer-related cognitive dysfunction. Future work aiming to bring tDCS from research into clinical practice should consider what individual differences may mediate the effects of stimulation on behavior, in order to better identify under what circumstances tDCS is most effective in improving performance. For instance, the effects of tDCS have been shown to vary based on age, mood, alertness, task difficulty, and motivation levels [74,86,87], and understanding the relationships between these factors and stimulation-related improvements in cognitive performance will allow researchers and clinicians to better tailor stimulation parameters to increase therapeutic benefits for each survivor. Moreover, repeated sessions of tDCS may be beneficial in producing long-lasting changes in performance by facilitating plasticity and stabilizing the strength of neural connections over time [46,94] and have resulted in cognitive improvement for various clinical populations [88–91]. Remotely-supervised tDCS (rs-tDCS) has demonstrated feasibility and efficacy in improving cognitive function in other clinical populations [92,93], and the ability to administer stimulation at home would not only allow for repeated daily sessions that could produce long-lasting benefits to performance, but also avoid obstacles to feasibility related to multiple clinic visits. Future research is needed to test the optimal means of administration of tDCS, but our preliminary results indicate that stimulation to the prefrontal cortex may be a promising method by which to improve attentional deficits in breast cancer survivors with cancer-related cognitive impairment.

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Declaration of competing interestCOI

All authors have confirmed that they have no conflict of interest to disclose.

CRediT authorship contribution statement

Alexandra M. Gaynor: Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Denise Pergolizzi:** Conceptualization, Methodology, Software, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Yesne Alici:** Conceptualization, Methodology, Funding acquisition, Writing - review & editing. **Elizabeth Ryan:** Resources, Writing - review & editing. **Katrazyna McNeal:** Investigation, Data curation, Writing - review & editing. **Tim A. Ahles:** Conceptualization, Project administration, Funding acquisition. **James C. Root:** Conceptualization, Methodology, Software, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Appendix A. Supplementary data

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References

[1] Lobiondo-Wood G, Brown CG, Knobf MT, Lyon D, Mallory G, Mitchell SA, et al. Priorities for oncology nursing: the 2013 national survey. Oncol Nurs Forum 2014;42:67–76.
[2] Lauver DR, Connolly-Nelson K, Vang P. Stressors and coping strategies among female cancer survivors after treatments. Canc Nurs 2007;30:101–11. https://doi.org/10.1097/01.NCC.0000265003.56817.2c.
[3] Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol Off J Am Soc Clin Oncol 2002;20:485–93. https://doi.org/10.1200/JCO.2002.20.2.485.
[4] Hurria A, Rosen C, Hudis C, Zuckerman E, Panageas KS, Lachs MS, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. J Am Geriatr Soc 2006;54:925–31. https://doi.org/10.1111/j.1532-5415.2006.00732.x.
[5] Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 1999;85:640–50.
[6] Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FSAM. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. J Natl Cancer Inst 2006;98:1742–5. https://doi.org/10.1093/jnci/djj470.
[7] Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. J Cancer Surviv Res Pract 2009;3:223–32. https://doi.org/10.1007/s11764-009-0098-x.
[8] Munir F, Burrows J, Yarker J, Kalawsky K, Bains M. Women's perceptions of chemotherapy-induced cognitive side affects on work ability: a focus group study. J Clin Nurs 2010;19:1362–70. https://doi.org/10.1111/j.1365-2702.2009.03006.x.
[9] Calvio L, Peugeot M, Bruns GL, Todd BL, Feuerstein M. Measures of cognitive function and work in occupationally active breast cancer survivors. J Occup Environ Med 2010;52:219–27. https://doi.org/10.1097/JOM.0b013e3181d0bef7.
[10] Ottati A, Feuerstein M. Brief self-report measure of work-related cognitive limitations in breast cancer survivors. J Canc Surviv 2013;7:262–73. https://doi.org/10.1007/s11764-013-0275-9.
[11] Myers JS. Chemotherapy-related cognitive impairment: the breast cancer experience. Oncol Nurs Forum 2012;39:E31–40. https://doi.org/10.1188/12.ONF.E31-E40.
[12] Von Ah D, Habermann B, Carpenter JS, Schneider BL. Impact of perceived cognitive impairment in breast cancer survivors. Eur J Oncol Nurs 2013;17:236–41. https://doi.org/10.1016/j.ejon.2012.06.002.
[13] Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American cancer society/American society of clinical oncology breast cancer survivorship care guideline. J Clin Oncol 2016;34:611–35. https://doi.org/10.1200/JCO.2015.64.3809.
[14] Bray VJ, Dhillon HM, Bell ML, Kabourakis M, Fiero MH, Yip D, et al. Evaluation of a web-based cognitive rehabilitation program in cancer survivors reporting cognitive symptoms after chemotherapy. J Clin Oncol 2017;35:217–25. https://doi.org/10.1200/JCO.2016.67.8201.
[15] Cherrier MM, Anderson K, David D, Higano CS, Gray H, Church A, et al. A randomized trial of cognitive rehabilitation in cancer survivors. Life Sci 2013;93:617–22. https://doi.org/10.1016/j.lfs.2013.08.011.
[16] Ercoli LM, Castellon SA, Hunter AM, Kwan L, Kahn-Mills BA, Cernin PA, et al. Assessment of the feasibility of a rehabilitation intervention program for

breast cancer survivors with cognitive complaints. Brain Imag Behav 2013;7:543–53. https://doi.org/10.1007/s11682-013-9237-0.
[17] Ferguson RJ, Ahles TA, Saykin AJ, McDonald BC, Furstenberg CT, Cole BF, et al. Cognitive-behavioral management of chemotherapy-related cognitive change. Psycho Oncol 2007;16:772–7. https://doi.org/10.1002/pon.1133.
[18] Schuurs A, Green HJ. A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. Psycho Oncol 2013;22:1043–9. https://doi.org/10.1002/pon.3102.
[19] Goedendorp MM, Knoop H, Gielissen MF, Verhagen CA, Bleijenberg G. The effects of cognitive behavioral therapy for postcancer fatigue on perceived cognitive disabilities and neuropsychological test performance. J Pain Symptom Manag 2014;47:35–44. https://doi.org/10.1016/j.jpainsymman.2013.02.014.
[20] Lower EE, Fleishman S, Cooper A, Zeldis J, Faleck H, Yu Z, et al. Efficacy of dexmethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. J Pain Symptom Manag 2009;38:650–62. https://doi.org/10.1016/j.jpainsymman.2009.03.011.
[21] Kohli S, Fisher SG, Tra Y, Adams MJ, Mapstone ME, Wesnes KA, et al. The effect of modafinil on cognitive function in breast cancer survivors. Cancer 2009;115:2605–16. https://doi.org/10.1002/cncr.24287.
[22] Mar Fan HG, Clemons M, Xu W, Chemerynsky I, Breunis H, Braganza S, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. Support Care Canc 2008;16:577–83. https://doi.org/10.1007/s00520-007-0341-9.
[23] Johns SA, Von Ah D, Brown LF, Beck-Coon K, Talib TL, Alyea JM, et al. Randomized controlled pilot trial of mindfulness-based stress reduction for breast and colorectal cancer survivors: effects on cancer-related cognitive impairment. J Canc Surviv 2016;10:437–48. https://doi.org/10.1007/s11764-015-0494-3.
[24] Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to III breast cancer: a randomized, controlled trial. J Clin Oncol Off J Am Soc Clin Oncol 2012;30:1335–42. https://doi.org/10.1200/JCO.2010.34.0331.
[25] Oh B, Butow PN, Mullan BA, Clarke SJ, Beale PJ, Pavlakis N, et al. Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. Support Care Canc 2012;20:1235–42. https://doi.org/10.1007/s00520-011-1209-6.
[26] Hartman SJ, Natarajan L, Palmer BW, Parker B, Patterson RE, Sears DD. Impact of increasing physical activity on cognitive functioning in breast cancer survivors: rationale and study design of Memory & Motion. Contemp Clin Trials 2015;45:371–6. https://doi.org/10.1016/j.cct.2015.09.021.
[27] Derry HM, Jaremka LM, Bennett JM, Peng J, Andridge R, Shapiro C, et al. Yoga and self-reported cognitive problems in breast cancer survivors: a randomized controlled trial. Psycho Oncol 2015;24:958–66. https://doi.org/10.1002/pon.3707.
[28] Culos-Reed SN, Carlson LE, Daroux LM, Hately-Aldous S. A pilot study of yoga for breast cancer survivors: physical and psychological benefits. Psycho Oncol 2006;15:891–7. https://doi.org/10.1002/pon.1021.
[29] Kesler S, Hadi Hosseini SM, Heckler C, Janelsins M, Palesh O, Mustian K, et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Canc 2013;13:299–306. https://doi.org/10.1016/j.clbc.2013.02.004.
[30] Milbury K, Chaoul A, Biegler K, Wangyal T, Spelman A, Meyers CA, et al. Tibetan sound meditation for cognitive dysfunction: results of a randomized controlled pilot trial. Psycho Oncol 2013;22:2354–63. https://doi.org/10.1002/pon.3296.
[31] McDonald BC, Conroy SK, Smith DJ, West JD, Saykin AJ. Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. Brain Behav Immun 2013;30:S117–25. https://doi.org/10.1016/j.bbi.2012.05.007.
[32] McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Canc Res Treat 2010;123:819–28. https://doi.org/10.1007/s10549-010-1088-4.
[33] Conroy SK, McDonald BC, Smith DJ, Moser LR, West JD, Kamendulis LM, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Canc Res Treat 2013;137:493–502. https://doi.org/10.1007/s10549-012-2385-x.
[34] Inagaki M, Yoshikawa E, Matsuoka Y, Sugawara Y, Nakano T, Akechi T, et al. Smaller regional volumes of brain gray and white matter demonstrated in breat cancer survivors exposed to adjuvant chemotherapy. Cancer 2007;109:146–56. https://doi.org/10.1002/cncr.22368.
[35] Ferguson RJ, Mcdonald BC, Saykin AJ, Ahles TA. Brain structure and function differences in monozygotic twins: possible effects of breast cancer therapy. J Clin Oncol 2007;25:3866–70. https://doi.org/10.1200/JCO.2007.10.8639.Brain.
[36] Kesler SR, Bennett FC, Mahaffey ML, Spiegel D. Regional brain activation during verbal declarative memory in metastatic breast cancer. Clin Canc Res 2009;15:6665–73. https://doi.org/10.1158/1078-0432.CCR-09-1227.
[37] McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Alterations in brain activation during working memory processing associated with breast cancer and treatment: a prospective functional magnetic resonance imaging study. J Clin Oncol Off J Am Soc Clin Oncol 2012;30:2500–8. https://doi.org/10.1200/JCO.2011.38.5674.
[38] de Ruiter MB, Reneman L, Boogerd W, Veltman DJ, van Dam FSAM, Nederveen AJ, et al. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. Hum Brain Mapp 2011;32:1206–19. https://doi.org/10.1002/hbm.21102.
[39] Kesler SR, Kent JS, O'Hara R. Prefrontal cortex and executive function impairments in primary breast cancer. Arch Neurol 2011;68:1447–53. https://doi.org/10.1001/archneurol.2011.245.
[40] Deprez S, Amant F, Smeets A, Peeters R, Leemans A, Van Hecke W, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. J Clin Oncol 2012;30:274–81. https://doi.org/10.1200/JCO.2011.36.8571.
[41] Deprez S, Amant F, Yigit R, Porke K, Verhoeven J, Van den Stock J, et al. Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. Hum Brain Mapp 2011;32:480–93. https://doi.org/10.1002/hbm.21033.
[42] Deprez S, Vandenbulcke M, Peeters R, Emsell L, Smeets A, Christiaens MR, et al. Longitudinal assessment of chemotherapy-induced alterations in brain activation during multitasking and its relation with cognitive complaints. J Clin Oncol 2014;32:2031–8. https://doi.org/10.1200/JCO.2013.53.6219.
[43] Gandal MJ, Ehrlichman RS, Rudnick ND, Siegel SJ. A novel electrophysiological model of chemotherapy-induced cognitive impairments in mice. Neuroscience 2008;157:95–104. https://doi.org/10.1016/j.neuroscience.2008.08.060.
[44] Rendeiro C, Sheriff A, Bhattacharya TK, Gogola JV, Baxter JH, Chen H, et al. Long-lasting impairments in adult neurogenesis, spatial learning and memory from a standard chemotherapy regimen used to treat breast cancer. Behav Brain Res 2016;315:10–22. https://doi.org/10.1016/j.bbr.2016.07.043.
[45] Santarnecchi E, Brem AK, Levenbaum E, Thompson T, Kadosh RC, Pascual-Leone A. Enhancing cognition using transcranial electrical stimulation. Curr Opin Behav Sci 2015;4:127–78. https://doi.org/10.1016/j.cobeha.2015.06.003.
[46] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17:37–53. https://doi.org/10.1177/1073858410386614.
[47] Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimulat 2016;9:501–17. https://doi.org/10.1016/j.brs.2016.04.006.
[48] Knotkova H, Malamud SC, Cruciani RA. Transcranial direct current stimulation (TDCS) improved cognitive outcomes in a cancer survivor with chemotherapy-induced cognitive difficulties. Brain Stimulat 2014;7:767–8. https://doi.org/10.1016/j.brs.2014.05.007.
[49] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–15. https://doi.org/10.1038/nrn755.
[50] Hermelink K, Untch M, Lux MP, Kreienberg R, Beck T, Bauerfeind I, et al. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer 2007;109:1905–13. https://doi.org/10.1002/cncr.22610.
[51] Weis J, Poppelreuter M, Bartsch HH. Cognitive deficits as long-term side-effects of adjuvant therapy in breast cancer patients: 'subjective' complaints and 'objective' neuropsychological test results. Psycho Oncol 2009;18:775–82. https://doi.org/10.1002/pon.1472.
[52] Bernstein LJ, Catton PA, Tannock IF. Intra-individual variability in women with breast cancer. J Int Neuropsychol Soc 2014;20:380–90. https://doi.org/10.1017/S1355617714000125.
[53] MacDonald SWS, Nyberg L, Bäckman L. Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. Trends Neurosci 2006;29:474–80. https://doi.org/10.1016/j.tins.2006.06.011.
[54] Wais PE, Gazzaley A. Distractibility during retrieval of long-term memory: domain-general interference, neural networks and increased susceptibility in normal aging. Front Psychol 2014;5:1–12. https://doi.org/10.3389/fpsyg.2014.00280.
[55] Downie FP, Mar Fan HG, Houédé-Tchen N, Yi Q, Tannock IF. Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: evaluation with patient interview after formal assessment. Psycho Oncol 2006;15:921–30. https://doi.org/10.1002/pon.1035.
[56] Hurria A, Goldfarb S, Rosen C, Holland J, Zuckerman E, Lachs MS, et al. Effect of adjuvant breast cancer chemotherapy on cognitive function from the older patient's perspective. Breast Canc Res Treat 2006;98:343–8. https://doi.org/10.1007/s10549-006-9171-6.
[57] Jenkins V, Shilling V, Deutsch G, Bloomfield D, Morris R, Allan S, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Canc 2006;94:828–34. https://doi.org/10.1038/sj.bjc.6603029.
[58] Shilling V, Jenkins V. Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. Eur J Oncol Nurs Off J Eur Oncol Nurs Soc 2007;11:6–15. https://doi.org/10.1016/j.ejon.2006.02.005.
[59] Kohli S, Griggs JJ, Roscoe Ja, Jean-Pierre P, Bole C, Mustian KM, et al. Self-reported cognitive impairment in patients with cancer. J Oncol Pract 2007;3:54–9. https://doi.org/10.1200/JOP.0722001.

[60] Donders J. A confirmatory factor Analysis of the California verbal learning test—second edition (CVLT-II) in the standardization sample. Assessment 2008;15:123–31. https://doi.org/10.1177/1073191107310926.
[61] Donders J. Subtypes of learning and memory on the California verbal learning test–second edition (CVLT–II) in the standardization sample. J Clin Exp Neuropsychol 2008;30:741–8. https://doi.org/10.1080/13803390701689595.
[62] Root JC, Ryan E, Barnett G, Andreotti C, Bolutayo K, Ahles TA. Learning and memory performance in a cohort of clinically referred breast cancer survivors: the role of attention versus forgetting in patient-reported memory complaints: memory performance in breast cancer survivors. Psycho Oncol 2015;24:548–55. https://doi.org/10.1002/pon.3615.
[63] Root JC, Andreotti C, Tsu L, Ellmore TM, Ahles TA. Learning and memory performance in breast cancer survivors 2 to 6 years post-treatment: the role of encoding versus forgetting. J Canc Surviv 2016;10:593–9. https://doi.org/10.1007/s11764-015-0505-4.
[64] Li Y, Root JC, Atkinson TM, Ahles TA. Examining the association between patient-reported symptoms of attention and memory dysfunction with objective cognitive performance: a latent regression rasch model approach. Arch Clin Neuropsychol 2016;31:365–77. https://doi.org/10.1093/arclin/acw017.
[65] Apple AC, Schroeder MP, Ryals AJ, Wagner LI, Cella D, Shih P-A, et al. Hippocampal functional connectivity is related to self-reported cognitive concerns in breast cancer patients undergoing adjuvant therapy. NeuroImage Clin 2018;20:110–8. https://doi.org/10.1016/j.nicl.2018.07.010.
[66] Holohan KN, Von Ah D, McDonald BC, Saykin AJ. Neuroimaging, cancer, and cognition: state of the knowledge. Semin Oncol Nurs 2013;29:280–7. https://doi.org/10.1016/j.soncn.2013.08.008.
[67] Menning S, de Ruiter MB, Veltman DJ, Koppelmans V, Kirschbaum C, Boogerd W, et al. Multimodal MRI and cognitive function in patients with breast cancer prior to adjuvant treatment — the role of fatigue. NeuroImage Clin 2015;7:547–54. https://doi.org/10.1016/j.nicl.2015.02.005.
[68] Ahles TA, Root JC. Cognitive effects of cancer and cancer treatments. Annu Rev Clin Psychol 2018;14:425–51. https://doi.org/10.1146/annurev-clinpsy-050817-084903.
[69] Jamil A, Batsikadze G, Kuo H-I, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation: effects of DC intensity on cortical excitability. J Physiol 2017;595:1273–88. https://doi.org/10.1113/JP272738.
[70] Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. Front Psychiatr 2012;3. https://doi.org/10.3389/fpsyt.2012.00091.
[71] Harrison BJ, Pujol J, Ortiz H, Fornito A, Pantelis C, Yücel M. Modulation of brain resting-state networks by sad mood induction. PloS One 2008;3:e1794. https://doi.org/10.1371/journal.pone.0001794.
[72] Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatr 1999;156:675–82. https://doi.org/10.1176/ajp.156.5.675.
[73] Braboszcz C, Delorme A. Lost in thoughts: neural markers of low alertness during mind wandering. Neuroimage 2011;54:3040–7. https://doi.org/10.1016/j.neuroimage.2010.10.008.
[74] Berryhill ME, Peterson DJ, Jones KT, Stephens JA. Hits and misses: leveraging tDCS to advance cognitive research. Front Psychol 2014;5. https://doi.org/10.3389/fpsyg.2014.00800.
[75] Rabipour S, Wu AD, Davidson PSR, Iacoboni M. Expectations may influence the effects of transcranial direct current stimulation. Neuropsychologia 2018;119:524–34. https://doi.org/10.1016/j.neuropsychologia.2018.09.005.
[76] Yao C, Rich JB, Tannock IF, Seruga B, Tirona K, Bernstein LJ. Pretreatment differences in intraindividual variability in reaction time between women diagnosed with breast cancer and healthy controls. J Int Neuropsychol Soc 2016;22:530–9. https://doi.org/10.1017/S1355617716000126.
[77] Bellgrove MA, Hester R, Garavan H. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia 2004;42:1910–6. https://doi.org/10.1016/j.neuropsychologia.2004.05.007.
[78] Koppelmans V, Groot M de, Ruiter MB de, Boogerd W, Seynaeve C, Vernooij MW, et al. Global and focal white matter integrity in breast cancer survivors 20 years after adjuvant chemotherapy. Hum Brain Mapp 2014;35:889–99. https://doi.org/10.1002/hbm.22221.
[79] Kreukels BPC, Hamburger HL, de Ruiter MB, van Dam FSAM, Ridderinkhof KR, Boogerd W, et al. ERP amplitude and latency in breast cancer survivors treated with adjuvant chemotherapy. Clin Neurophysiol 2008;119:533–41. https://doi.org/10.1016/j.clinph.2007.11.011.
[80] Kreukels BPC, Schagen SB, Ridderinkhof KR, Boogerd W, Hamburger HL, Van Dam FS. Electrophysiological correlates of information processing in breast-cancer patients treated with adjuvant chemotherapy. Breast Canc Res Treat 2005;94:53–61. https://doi.org/10.1007/s10549-005-7093-3.
[81] Brückner S, Kammer T. Both anodal and cathodal transcranial direct current stimulation improves semantic processing. Neuroscience 2017;343:269–75. https://doi.org/10.1016/j.neuroscience.2016.12.015.
[82] Varoli E, Pisoni A, Mattavelli GC, Vergallito A, Gallucci A, Mauro LD, et al. Tracking the effect of cathodal transcranial direct current stimulation on cortical excitability and connectivity by means of TMS-EEG. Front Neurosci 2018;12. https://doi.org/10.3389/fnins.2018.00319.
[83] Rubia K, Smith AB, Halari R, Matsukura F, Mohammad M, Taylor E, et al. Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. Am J Psychiatr 2009;166:83–94. https://doi.org/10.1176/appi.ajp.2008.08020212.
[84] Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 2012;48:194–215. https://doi.org/10.1016/j.cortex.2011.04.007.
[85] Christakou A, Murphy CM, Chantiluke K, Cubillo AI, Smith AB, Giampietro V, et al. Disorder-specific functional abnormalities during sustained attention in youth with attention deficit hyperactivity disorder (ADHD) and with autism. Mol Psychiatr 2013;18:236–44. https://doi.org/10.1038/mp.2011.185.
[86] Krause B, Cohen Kadosh R. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. Front Syst Neurosci 2014;8. https://doi.org/10.3389/fnsys.2014.00025.
[87] Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front Cell Neurosci 2015;9. https://doi.org/10.3389/fncel.2015.00181.
[88] Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, et al. Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimulat 2012;5:223–30. https://doi.org/10.1016/j.brs.2011.06.006.
[89] Fregni F, Gimenez R, Valle AC, Ferreira MJL, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum 2006;54:3988–98. https://doi.org/10.1002/art.22195.
[90] Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety 2006;23:482–4. https://doi.org/10.1002/da.20201.
[91] Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr Res 2015;168:260–6. https://doi.org/10.1016/j.schres.2015.06.011.
[92] Agarwal S, Pawlak N, Cucca A, Sharma K, Dobbs B, Shaw M, et al. Remotely-supervised transcranial direct current stimulation paired with cognitive training in Parkinson's disease: an open-label study. J Clin Neurosci 2018;57:51–7. https://doi.org/10.1016/j.jocn.2018.08.037.
[93] Kasschau M, Reisner J, Sherman K, Bikson M, Datta A, Charvet LE. Transcranial direct current stimulation is feasible for remotely supervised home delivery in multiple sclerosis. Neuromodulation Technol Neural Interface 2016;19:824–31. https://doi.org/10.1111/ner.12430.
[94] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimulaion 2013;6(3):424–32. https://doi.org/10.1016/j.brs.2012.04.011.