Research report

Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias

Christopher S.Y. Benwell [a,b,*], Gemma Learmonth [a,b], Carlo Miniussi [c,d], Monika Harvey [b] and Gregor Thut [a,*]

[a] Centre for Cognitive Neuroimaging, Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK
[b] School of Psychology, University of Glasgow, Glasgow, UK
[c] Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[d] Cognitive Neuroscience Section, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a well-established technique for non-invasive brain stimulation (NIBS). However, the technique suffers from a high variability in outcome, some of which is likely explained by the state of the brain at tDCS-delivery but for which explanatory, mechanistic models are lacking. Here, we tested the effects of bi-parietal tDCS on perceptual line bisection as a function of tDCS current strength (1 mA vs 2 mA) and individual baseline discrimination sensitivity (a measure associated with intrinsic uncertainty/signal-to-noise balance). Our main findings were threefold. We replicated a previous finding (Giglia et al., 2011) of a rightward shift in subjective midpoint after Left anode/Right cathode tDCS over parietal cortex (sham-controlled). We found this effect to be weak over our entire sample ($n = 38$), but to be substantial in a subset of participants when they were split according to tDCS-intensity and baseline performance. This was due to a complex, nonlinear interaction between these two factors. Our data lend further support to the notion of state-dependency in NIBS which suggests outcome to depend on the endogenous balance between task-informative 'signal' and task-uninformative 'noise' at baseline. The results highlight the strong influence of individual differences and variations in experimental parameters on tDCS outcome, and the importance of fostering knowledge on the factors influencing tDCS outcome across cognitive domains.

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* *Corresponding authors.* Institute of Neuroscience & Psychology, 58 Hillhead Street, Glasgow G12 8QB, UK.
E-mail addresses: chrisb@psy.gla.ac.uk (C.S.Y. Benwell), Gregor.Thut@glasgow.ac.uk (G. Thut).

1.   Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive tool for research into healthy brain function and is also being increasingly investigated for its therapeutic and neuro-enhancing potential in various cognitive domains (Brunoni et al., 2012; Oliveri, 2011). It involves the application of a weak electrical current to the scalp which shifts the resting membrane potential of the underlying cortical neurons, thereby allowing for an up-versus down-regulation of the neuronal firing rate depending on the polarity of stimulation (anodal vs cathodal), as shown in animals (Bindman, Lippold, & Redfearn, 1964; Creutzfeldt, Fromm, & Kapp, 1962) with an analogous effect on motor cortex excitability in humans (Nitsche & Paulus, 2000; Pellicciari, Brignani, & Miniussi, 2013; Stagg & Nitsche, 2011). In cognitive studies using tDCS, a similar a priori assumption is often made, whereby behavioural effects are directly mapped onto these physiological effects. However, the classic anodal-facilitation/cathodal-inhibition distinction does not always hold for cognitive functions (Jacobson, Koslowsky, & Lavidor, 2012; Vallar & Bolognini, 2011) and recent meta-analyses cast doubt on the reliability of tDCS effects on neurophysiological and cognitive outcome measures in healthy participants (Horvath, Forte, & Carter, 2015a, 2015b). An explanation for this may lie in the trait- and/or state-dependent nature of tDCS effects. Previous studies have shown that tDCS outcome is not always uniform, but instead can be dependent on factors such as differences in individual trait levels (Berryhill & Jones, 2012; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Hsu, Tseng, Liang, Cheng, & Juan, 2014; Learmonth, Thut, Benwell, & Harvey, in press; Sarkar, Dowker, & Cohen Kadosh, 2014; Tseng et al., 2012), the initial activation state of the stimulated network (Antal, Terney, Poreisz, & Paulus, 2007) and the administered current strength (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Hoy et al., 2013; Teo, Hoy, Daskalakis, & Fitzgerald, 2011). Failure to account for potentially subtle differences in sample characteristics and/or experimental design may hence explain the large variability in tDCS-outcome across participants and studies (Horvath et al., 2015a, 2015b; Krause & Cohen Kadosh, 2014; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014; Wiethoff, Hamada, & Rothwell, 2014). For a better understanding of tDCS effects, it is therefore of importance to map those factors, and the relationships between them, that may determine tDCS outcome across different cognitive domains.

Here, we tested the contribution of two factors in influencing tDCS outcome. Previous studies have independently suggested tDCS intensity (Batsikadze et al., 2013; Hoy et al., 2013; Teo et al., 2011) and baseline task ability (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al., in press; Tseng et al., 2012;) to be important contributing factors. In the present study, we manipulated tDCS intensity while at the same time accounting for individual differences in baseline performance. Recent papers have highlighted the dependence of non-invasive brain stimulation (NIBS) outcome on endogenous neural activity at the moment of stimulation, i.e., on baseline activity (e.g., Miniussi, Harris, & Ruzzoli, 2013; Miniussi, Ruzzoli, & Walsh, 2010; Ruzzoli, Marzi, & Miniussi, 2010). One framework in particular distinguishes between task-informative and task-uninformative neurons in the stimulated cortex at baseline (Bienenstock, Cooper, & Munro, 1982; Cattaneo, Rota, Vecchi, & Silvanto, 2008; Cattaneo, Sandrini, & Schwarzbach, 2010; Silvanto, Muggleton, Cowey, & Walsh, 2007; Silvanto, Muggleton, & Walsh, 2008), or the related concepts of signal and noise (Abrahamyan, Clifford, Arabzadeh, & Harris, 2011; Miniussi et al., 2010; 2013; Ruzzoli et al., 2010; Schwarzkopf, Silvanto, & Rees, 2011), and highlights that it is the relative activity of task-informative versus uninformative neurons (or signal-to-noise ratio) at baseline that will shape NIBS-induced perceptual/behavioural effects (for examples see Silvanto et al., 2007; or Abrahamyan et al., 2011). Accordingly, it is of interest to test measures that index the balance between these types of neuronal activities at baseline as to their explanatory potential for tDCS outcome, alongside other potentially determining factors (e.g., tDCS-intensity). One such measure is the slope of the psychometric function (PF). In PFs derived from two-alternative forced choice (2-AFC) tasks, changes in slope have been linked to changes in intrinsic uncertainty, or the ability to distinguish information from task-relevant and task-irrelevant "channels", in guiding perceptual decisions (Gold & Ding, 2013; Kontsevich & Tyler, 1999; Pelli, 1985, 1987; Tyler & Chen, 2000) (see also Aihara, Kitajo, Nozaki, & Yamamoto, 2008; 2010 for use of the slope/width of the PF as a measure of internal noise). This intrinsic uncertainty reflected in the slope has been proposed to arise at a late readout stage of sensory information processing, and Gold, Law, Connolly, and Bennur (2010) have identified selective neuronal pooling mechanisms in the parietal cortex that may reduce this intrinsic uncertainty and hence increase the PF slope. Based on this interpretation of the slope of the PF and the NIBS/tDCS-literature reviewed above, we predicted that tDCS effects may differ depending on the administered current intensity and the psychophysical measure of intrinsic task uncertainty at baseline, and tested for the first time for an interaction between the two. To this end, we applied tDCS at 1 mA and 2 mA (between participants) and split our participant into groups according to the slope of the fitted PF (discrimination sensitivity).

We tested this within the cognitive domain of visuospatial attention, known to be governed by a bilateral frontoparietal network (Benwell, Harvey, & Thut, 2014; Blankenburg et al., 2010; Kinsbourne, 1977; Szczepanski & Kastner, 2013). Stimulation of this network by tDCS has been shown to influence both spatial (Giglia et al., 2011; Loftus & Nicholls, 2012; Sparing et al., 2009; Wright & Krekelberg, 2014) and non-spatial aspects of visual attention in healthy participants (Ball, Lane, Smith, & Ellison, 2013; Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010; Bolognini, Olgiati, Rossetti, & Maravita, 2010; Jacobson, Goren, Lavidor, & Levy, 2012; Moos, Vossel, Weidner, Sparing, & Fink, 2012), although with more consistent results across studies for the spatial aspects of performance. Note that the parietal cortex is associated with higher-level readout/decision processes, rather than low level sensory representations (FitzGerald, Moran, Friston, & Dolan, 2015; Gold & Ding, 2013; Gold & Shadlen, 2007; Park, Meister, Huk, & Pillow, 2014), and hence provides an appropriate starting point to test our predictions. Here, we sought to investigate

the influence of the administered current strength and the psychophysical metric of intrinsic uncertainty at baseline on a previously observed effect of bi-parietal tDCS on subjective midpoint estimation during perceptual line bisection (Giglia et al., 2011). To do so, we employed a computerised 2-AFC version of the landmark task (Milner, Brechmann, & Pagliarini, 1992), a task which provides psychophysical metrics of discrimination sensitivity (i.e., slope) and lateralized spatial bias [i.e., point of subjective equality (PSE)]. Giglia et al., (2011) showed a rightward shift in subjective midpoint during landmark task performance when participants received 1 mA, bi-parietal (Left anode/Right cathode) stimulation. Here, in a larger sample of participants, across two current strengths (1 mA and 2 mA) and accounting for baseline intrinsic task uncertainty, we sought to replicate this bi-parietal effect and also tested whether the opposite polarity (Left cathode/Right anode) may drive an opposite leftward shift in spatial bias, in line with the interhemispheric competition model of visuospatial attention (Kinsbourne, 1977; Sparing et al., 2009; Szczepanski & Kastner, 2013).

2. Materials and methods

2.1. Participants

Forty right-handed participants took part in the experiment. One participant had to be excluded due to task performance not being above chance level (non-adherence to task) and another one dropped out (not returning for sessions 2–3). This led to 38 participants whose data were entered into the final analysis (19 male, 19 female, mean age = 22.9 years; SD = 3.16). All participants were naive to the experimental hypothesis being tested, had normal or corrected-to-normal vision and reported no history of neurological disorder or any other contraindication for tDCS. Each participant gave written informed consent to participate in the study, which was approved by the local Ethics Committee of the College of Science and Engineering (University of Glasgow).

2.2. tDCS

Bilateral tDCS was delivered over parietal areas through a battery-driven, constant current stimulator (NeuroConn GmbH, Germany) using two 4 × 4 cm surface electrodes (placed in saline-dampened sponges). One electrode was positioned over the left and the other over the right parietal region (centred on P5 and P6 of the 10–20 International EEG system: adopted from Giglia et al., 2011). Here, we administered three different bi-parietal stimulation protocols to each participant on separate days: (i) Left anode/right cathode (LA/RC) (replicating Giglia et al.'s design); (ii) Left cathode/right anode (LC/RA) (extending Giglia et al.'s design by introducing an opposite electrode polarity) and (iii) sham stimulation (in which electrode polarity was counter-balanced across participants). Stimulation duration was 20 min (with 30-sec ramping up/down), but stimulation was discontinued after 30-sec in sham. Half of the participants (n = 19) received 1 mA stimulation (current density = .0625 mA/cm^2) for each stimulation protocol, while the other half (n = 19) received 2 mA

stimulation (current density = .125 mA/cm^2). The tDCS sessions were separated by at least 24 h for each participant with counter-balanced ordering of the tDCS protocols across participants to control for learning and carry-over effects.

2.3. Stimuli and task

To assess discrimination sensitivity during perceptual performance at baseline as well as changes in lateralized spatial bias with parietal tDCS, we employed a computerized version of the landmark task (Benwell, Learmonth, Thut, & Harvey, 2013; Milner et al., 1992) in which pre-transected black and white lines of 100% Michelson contrast were presented on a grey background (luminance = 179, hue = 160) and participants were asked to judge which end of the line (left or right) appeared to be shorter (2-AFC task). Lines measured 24.3 cm in length by .5 cm in height and, at a viewing distance of 70 cm, subtended 19.67° (width) by .40° (height) of visual angle. Lines were transected at 1 of 17 points ranging symmetrically from ±4% of absolute line length relative to (and including) veridical centre (see Fig. 1A for an example of a line stimulus). This represented a range of −.8° (−24 pixels) to .8° (24 pixels) of visual angle relative to veridical centre.

Fig. 1A depicts a schematic representation of the trial procedure. Each trial began with presentation of a fixation cross [.40° (height) × .40° (width) of visual angle] for 1 sec followed by presentation of a transected line for 150 msec. The transection mark was always aligned with the fixation cross (i.e., the eccentricity of the line endpoints varied across trials while the transection point always appeared at the same central position), therefore preventing use of the fixation cross as a reference point for bisection judgments. The fixation cross then reappeared for the duration of the response period, during which participants indicated which end of the line the transection mark had appeared closest to, by pressing either the left or right response key. Participants always responded using their dominant right hand (right index and middle finger respectively) and were instructed to keep their gaze on the fixation cross throughout each trial. The subsequent trial began as soon as the response was made. Trials lasted approximately 2 sec with each block lasting 3–4 min. Trial type (location of transector in line) was selected at random.

2.4. Procedure (see Fig. 1B)

At the beginning and end of each experimental session, all participants completed the Stanford Sleepiness Scale (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973), a subjective measure of alertness ranging from 1 (fully alert) to 7 (asleep). Participants were then seated and their midsagittal plane aligned with the display monitor. Viewing distance was kept constant using a chin rest. The electrodes were then attached to the participants scalp by the experimenters and held in place by a rubber band. After tDCS set-up was complete, the task was explained to the participant and a block of 9 practice trials was performed immediately prior to the beginning of the experimental blocks. During the practice block, only the most lateral transector locations to both the left and right of veridical centre were presented (i.e., ± 4% of absolute line length). Accordingly, participants were able to
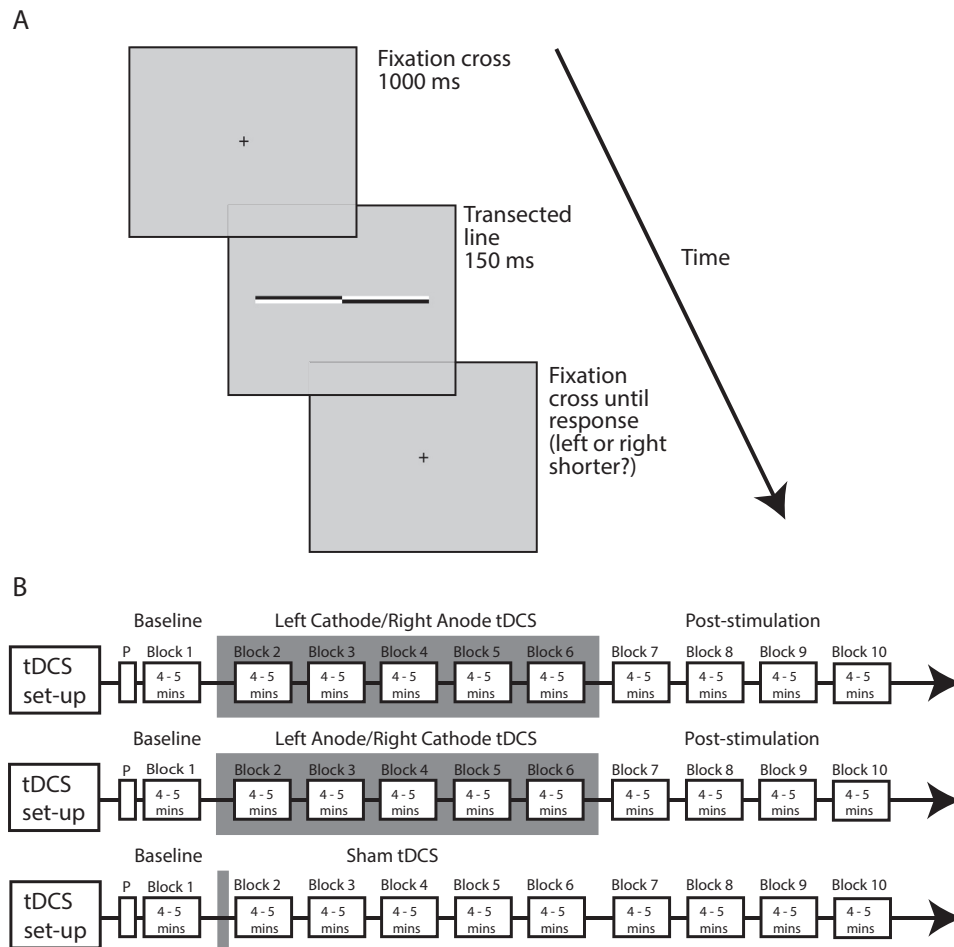
Fig. 1 — (A) A schematic representation of the trial procedure. Following 1000 msec presentation of a fixation cross, transected lines were presented for 150 msec before reappearance of the fixation cross on the screen until the subject responded, by pressing either the left or right (shorter) response key. The subsequent trial began as soon as the response was made. **(B)** A schematic representation of the session procedure. 'P' represents a set of 9 practice trials preceding each baseline block. Each participant completed all three session procedures on separate days, with the order counter-balanced across participants.

perform the task without difficulty. Upon completion of the practice block, all participants indicated that they understood the task and were ready to begin the experiment (that no further practice was required). In each of the three days testing LA/RC-, LC/RA- and sham-tDCS respectively, each participant completed 10 experimental blocks of the landmark task. Each experimental block consisted of 136 trials (8 judgments at each of the 17 transector locations). The first block was performed with no tDCS and served as a baseline against which performance in the subsequent 9 blocks (#2–10) was compared. After performance of the first block, participants were instructed to wait while tDCS was turned on by the experimenter. Once the stimulation was initiated, participants were instructed to begin the second block and continue at their own pace with the rest of the experiment. Participants were allowed to take short breaks between blocks. During active tDCS sessions, stimulation ended for the majority of participants between blocks 6 and 7. The entire experiment lasted approximately 40–50 min. At the end of every session, each participant completed a questionnaire assessing their

subjective experience of possible side effects associated with tDCS (Kessler, Turkeltaub, Benson, & Hamilton, 2012). The side-effects assessed were headache, tingling, itching, burning and pain, on a scale of 1 (not experienced at all) to 5 (experienced very strongly). In addition, at the end of their final session, each participant was asked to guess in which of the three experimental sessions they had received sham stimulation. Both the side-effect questionnaire and the sham identification question were used to investigate any potentially confounding differences in the experience of tDCS between our four experimental groups (see O'Connell et al., 2012; Russo, Wallace, Fitzgerald, & Cooper, 2013).

2.5. Analysis

2.5.1. Psychometric function (PF) measures
In order to obtain an objective measure of discrimination sensitivity and perceived line midpoint for each block in each participant, PFs were derived using the method of constant stimuli. The dependent measure was the proportion of trials

on which the participant indicated that the transector had appeared closer to the left end of the line. Non-linear least-squares regression was used to fit a cumulative logistic function to the data. The cumulative logistic function is described by the equation:

$$f(\mu, x, s) = 1/(1 + \exp((x - \mu)/-w))$$

where x are the tested transector locations, μ corresponds to the x-axis location with a 50% 'left' and 50% 'right' response rate and w is the estimated width (measured in pixels on the x-axis) spanning the distance between the lower and upper asymptotes of the sigmoid curve (hereafter referred to as curve width, which is inversely related to slope). The 50% location is known as the point of subjective equality (PSE) and represents an objective measure of perceived line midpoint. The width of the fitted PF provides a measure of the precision of the participants' line midpoint judgments (visual discrimination sensitivity) and hence was adopted here as an index of baseline intrinsic uncertainty (curve width in block 1 without tDCS: High width values indicate high intrinsic uncertainty, low width values indicate low intrinsic uncertainty). PF measures were obtained for all ten blocks of each of the three sessions in every participant. However, since we were interested in replicating (and extending) the previously observed effects of tDCS on subjective midpoint estimation (Giglia et al., 2011), PSE was our tDCS outcome measure of interest whilst curve width was primarily employed as a measure by which to split participants according to intrinsic performance level at baseline (see section 2.5.2 below).

2.5.2.   Experimental group assignment

In order to investigate whether participants' baseline discrimination sensitivity would influence the effects of tDCS, participants were split into 4 groups. Group assignment was based on the participants' PF curve width estimates in block 1 (averaged over the baseline data from all three sessions). Separately for each current intensity (1 mA, 2 mA), participants displaying baseline PF curve width above the group average were assigned to the 'high discrimination sensitivity' ('HDS') groups and those displaying widths below the average were assigned to the 'low discrimination sensitivity' ('LDS') groups. The group demographics were as follows: (i) 1 mA 'HDS' group (5 male, 5 female, mean age = 23 yrs, range: 20–29) (ii) 1 mA 'LDS' group (5 male, 4 female, mean age = 24.2 yrs, range: 18–35), (iii) 2 mA 'HDS' group (5 male, 6 female, mean age = 22.27 yrs, range: 17–26), (iv) 2 mA 'LDS' group (4 male, 4 female, mean age = 22.28 yrs, range: 20–25).

2.5.3.   Baseline data (block 1, no tDCS): Test-retest reliability of PF curve width and PSE between sessions

In order to assess the consistency of the measures (width and PSE) within participants, robust correlation analyses were performed between the values obtained during the baseline blocks of the three testing sessions. This analysis was performed separately for width and PSE values respectively using Spearman's rho and Shepherd's pi. Shepherd's pi is a robust test of statistical association between two variables. Outliers are detected by first bootstrapping the Mahalanobis distance of each data point from the bivariate mean and then excluding all observations whose distance is ≥ 6. Shepherd's pi is equivalent to Spearman's rho after outlier removal. The p-value is doubled because the removal of outliers can inflate false positive rates (Schwarzkopf, De Haas, & Rees, 2012).

2.5.4.   TDCS effects

TDCS-effects on PSE values between the baseline block (#1) and the subsequent 9 blocks (#2–10) were analysed using repeated measure analysis of variance (ANOVA). Shifts across the course of each experimental session were isolated by subtracting the PSE of baseline block 1 from each of blocks 2–10 within each participant. In order to isolate tDCS induced behavioural effects during the active sessions, the raw shift values obtained for each block of the sham session were then subtracted from each corresponding block of the active sessions (LC/RA and LA/RC respectively). This allowed us to subtract out and hence control for the potentially confounding influence of the time-on-task effect previously observed during landmark task performance, which manifests in a progressive rightward shift in attentional bias with prolonged performance (see Benwell, Harvey, Gardner, & Thut, 2013; Benwell, Learmonth et al., 2013; Manly, Dobler, Dodds, & George, 2005). The ANOVA then comprised the between-subjects factors tDCS-intensity [2 levels: 1 mA vs 2 mA] and Baseline performance level [2 levels: high vs low discrimination sensitivity] and the within-subject factors tDCS-polarity [2 levels: LC/RA vs LA/RC] and Block-rank [9 levels: blocks 2:10]. The dependent variable was the PSE.

3.   Results

3.1.   Baseline performance and sham data across groups

Fig. 2A illustrates group-averaged PFs fitted to baseline data (block 1 collapsed across all three experimental sessions) for all four groups of participants (resulting from the 2 × 2 between-subject aspect of our design), consisting of either participants with steep slope/narrow curve width of the individually fitted PFs ("high discrimination sensitivity") or shallow slope/large curve width ("low discrimination sensitivity"), before undergoing either 1 mA- or 2 mA-tDCS. In line with previous studies, all four experimental groups displayed pseudoneglect at baseline; a tendency to overestimate the left side of the bisected lines corresponding to a left-skewed visuospatial attentional bias in healthy young participants (Benwell, Thut, Grant, & Harvey, 2014; Jewell & McCourt, 2000). This is illustrated in the left-biased subjective midpoint judgments (see dotted lines in Fig. 2A, corresponding to 50% left/right-responses, hence PSE), which are all significantly displaced to the left of veridical centre, as the 95% confidence intervals of the group-averaged PSEs do not overlap zero (veridical centre) for any of the groups [1 mA- 'high discrimination sensitivity' group: mean: −2.05 pixels/confidence interval (CI): −2.33 to −1.78; 1 mA-'low discrimination sensitivity' group: mean: −1.24 pixels/CI: −1.79 to −.60; 2 mA-'high discrimination sensitivity' group: mean: −2.13 pixels/CI: −2.44 to −1.81; 2 mA-'low discrimination sensitivity' group: mean:−3.43 pixels/CI: −3.96 to −2.90].
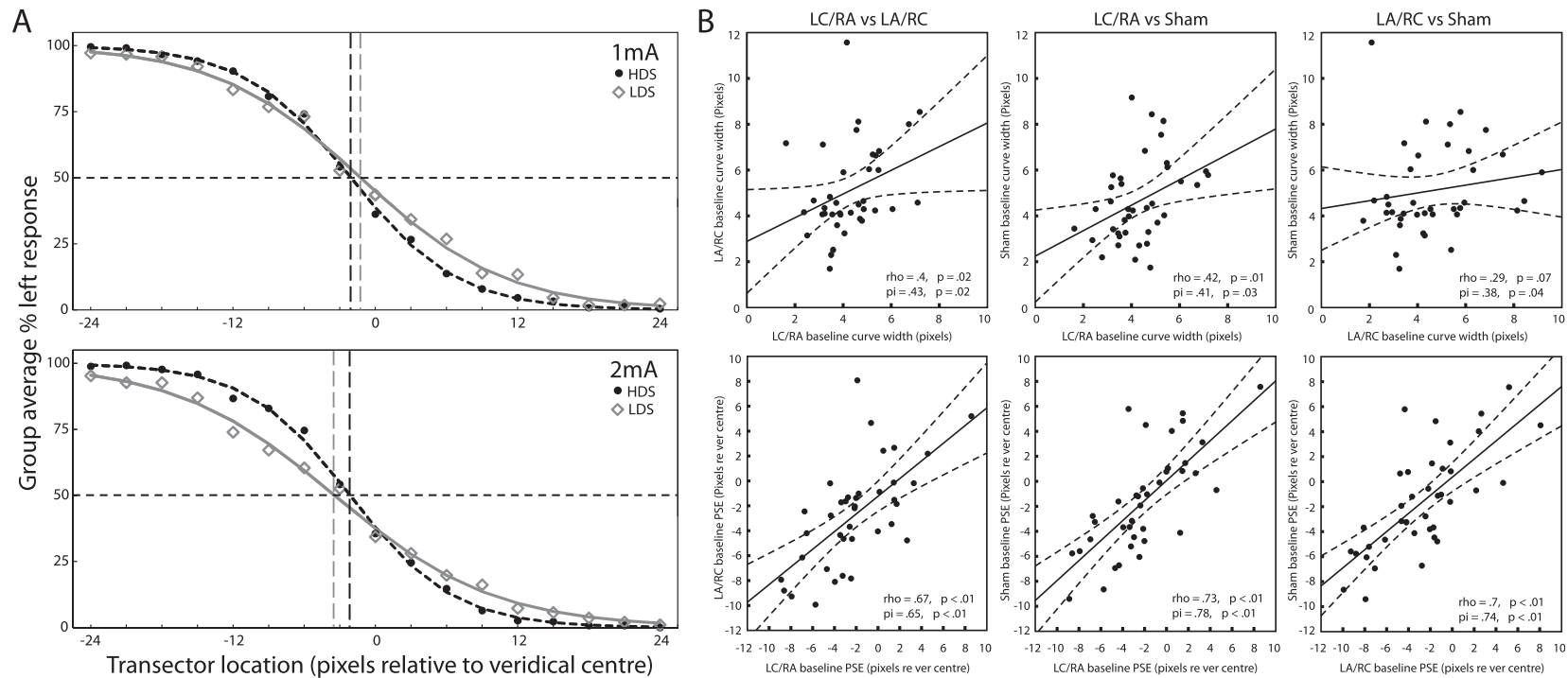
Fig. 2 – Baseline performance (block 1 before tDCS). **Fig. 2**A presents group averaged baseline psychometric functions (PFs) averaged over all three testing sessions (LA/RC, LC/RA, sham). Symbols plot mean percent left responses as a function of transector location per group ('high discrimination sensitivity' (HDS) *vs* 'low discrimination sensitivity' (LDS) performers: black *vs* grey symbols) and tDCS intensity (1 mA *vs* 2 mA: upper *vs* lower panel). The black (HDS performers) and grey (LDS performers) smooth curves represent the best fitting least-squares cumulative logistic PFs. The points at which the vertical dashed lines (black: HDS performers; grey: LDS performers) cross the black horizontal dashed line indicate the transector locations corresponding to the 50% left response rate (PSE's). **Fig. 2**B (upper panels) plots correlations between the individually fitted baseline PF widths from each of the three experimental sessions (dashed lines represent the upper and lower limits of the 95% confidence interval (CI) for the fitted slope (solid line)). **Fig. 2**B (lower panels) plots the correlations (slope = solid line, 95% CI = dashed lines) for individually fitted baseline PF PSE values from each of the sessions. Corresponding correlation analyses (Spearman's rho and Shepherd's pi) revealed all of the tested correlations to be significant, indicating high test-retest reliability of the employed measures.

Fig. 2B (upper panels) illustrates the consistency of baseline values within participants across the three sessions (i.e., for the repeated baseline measures before LC/RA-, LA/RC- and sham-tDCS) for visual discrimination sensitivity (curve width). Fig. 2B (lower panels) plots the same data but for visuospatial attentional bias (PSE values). To probe test-retest reliability across the three baseline sessions, consistency was estimated for both psychometric measures of line bisection performance between all session-combinations (LC/RA vs LA/RC; LC/RA vs sham, LA/RC vs sham) using correlation analysis (see Fig. 2B, bottom right hand corner of each scatterplot). The results replicate previous studies showing lateralized landmark task bias to be a stable, predictable trait within participants (Benwell, Learmonth et al., 2013; Tomer et al., 2013; Varnava, Dervinis, & Chambers, 2013), and extends this in the first instance also to visual discrimination sensitivity during landmark performance.

To exclude that any effects of tDCS may be driven by group differences at baseline, or across sham conditions (given the 2 × 2 between subject design), we first established that there were no baseline or sham differences across these groups. In terms of the individually fitted PSE values at baseline across the 2 × 2 groups (i.e., baseline performance level × tDCS-intensity), we did not find any significant difference. There were no effects of tDCS-intensity [$F(1,34) = .814$, $p = .373$], of baseline performance level [$F(1,34) = .015$, $p = .902$], and no interactions between these factors [$F(1,34) = .749$, $p = .393$]. In terms of curve width at baseline, there were likewise no effects of tDCS-intensity [$F(1,34) = .07$, $p = .793$] nor any interaction with baseline performance [$F(1,34) = 1.054$, $p = .312$], while the performance groups differed [as this was the splitting criterion; $F(1,34) = 110.244$, $p < .001$]. Additionally, there was no difference between groups in baseline sleepiness rating scales [Kruskal–Wallis test: $X2(3) = .639$, $p = .887$]. The absence of any difference at baseline on the dependent variable (PSE) between the 2 × 2 groups rules out that any effect of tDCS on PSE (baseline corrected) originates in a baseline difference. Similarly, analysis of sham PSE data (baseline corrected) did not reveal any effect of tDCS-intensity [$F(1, 34) = .06$, $p = .808$], baseline performance [$F(1, 34) = .932$, $p = .341$] nor any interaction between these factors [$F(1, 34) = .522$, $p = .475$], ruling out that any effect of tDCS on PSE (additionally sham corrected) originates in a sham difference between groups.

3.2. Questionnaire data: discriminability of tDCS protocols (1 mA vs 2 mA, active minus sham) based on subjective experience across groups

Active tDCS was well tolerated with low mean difference-ratings (active minus sham) of <.5 (out of 5) across all assessed side effects (headache, tingling, itching, burning, pain). No significant differences in tDCS associated side-effects were found between groups (Kruskal–Wallis tests performed for each side-effect separately, all p's > .05) indicating that protocols were similar in associated (low) discomfort. Overall, 50% of the participants correctly identified in which of the three sessions they had received sham tDCS. Broken down by intensity, correct guess rate was 47% versus 53% in the 1 mA versus 2 mA groups respectively. No

significant difference in the proportion of correct guesses was found between the four experimental groups (Pearson Chi-Square = 1.429, $p = .735$). Hence, the discriminability of the active protocols (compared to sham) based on subjective experience was not different between the experimental groups.
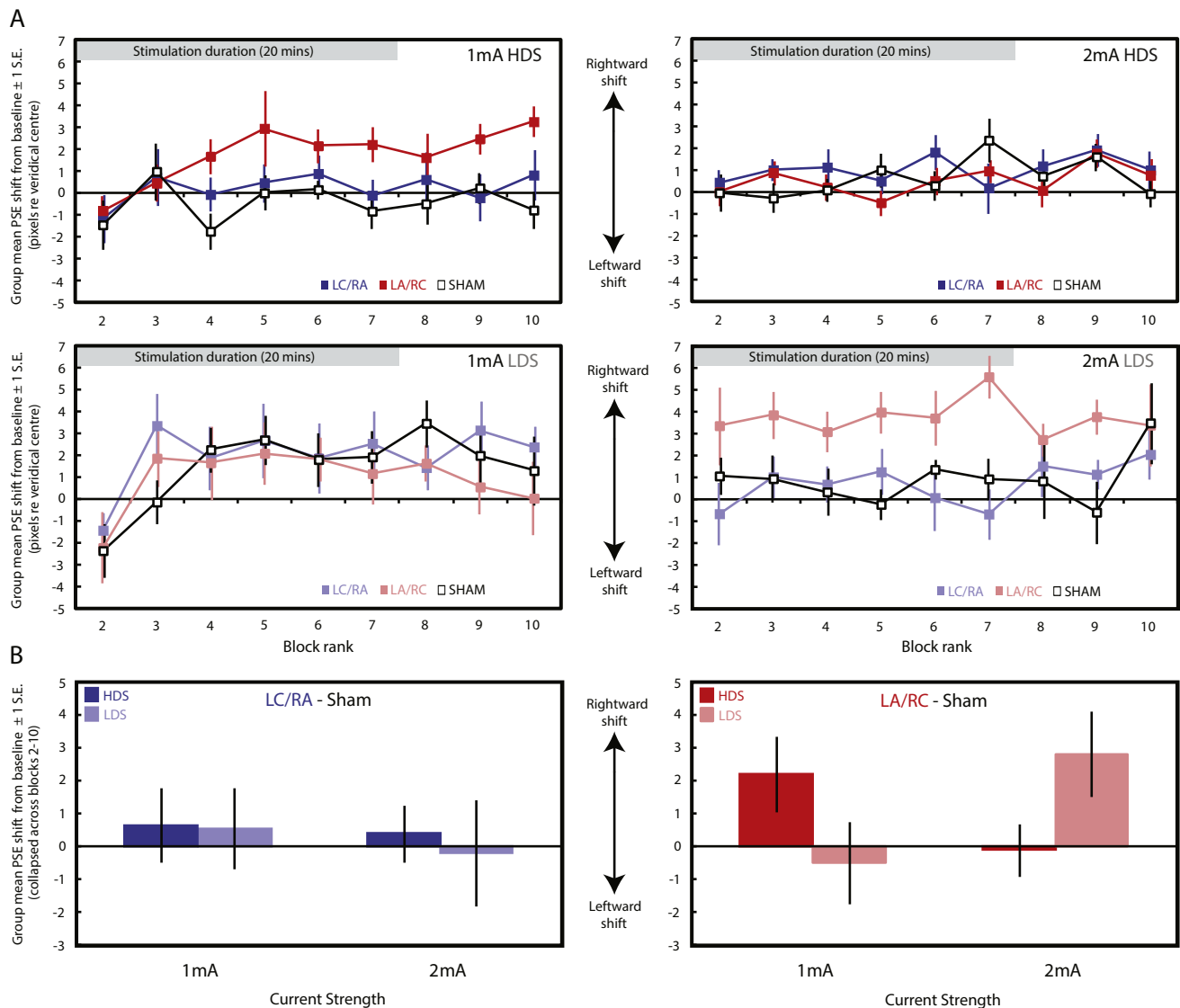
3.3. Effects of bi-parietal tDCS on lateralized visuospatial attentional bias

We then examined the effects of tDCS on lateralized visuospatial attention bias (indexed by the estimated PSE of the fitted PF). To this end, we used a 2 × 2 × 2 × 9 ANOVA on baseline and sham-corrected data (factors: tDCS-polarity, tDCS-intensity, Baseline performance level, Block-rank). See Fig. 3A for baseline corrected data across all blocks and conditions, and Fig. 3B for baseline/sham corrected data collapsed across blocks. We expected a polarity specific effect of tDCS on visuospatial bias (replicating Giglia et al., 2011), possibly as a function of the two contributors of tDCS outcome, i.e., tDCS intensity and baseline performance levels.

The ANOVA revealed no significant main effects of the two tDCS manipulations, i.e., tDCS-polarity [$F(1, 34) = 1.796$, $p = .189$, $\eta p^2 = .05$] and tDCS-intensity [$F(1,34) = .001$, $p = .993$, $\eta p^2 = .001$] as well as no main effects of baseline performance level [$F(1,34) = .016$, $p = .9$, $\eta p^2 = .001$] or block-rank [$F(8, 272) = .51$, $p = .848$, $\eta p^2 = .015$]. In addition, tDCS polarity did not show a two-way interaction with either of the two potential contributors to tDCS outcome investigated here (tDCS-intensity or baseline performance, both F's < .759, p's > .390, ηp^2's < .022), nor was there any interaction of this factor with block rank [$F (8,272) = .793$, $p = .609$, $\eta p^2 = .023$]. Hence, when considering tDCS-polarity independently of any other factor, or as a function of tDCS-intensity and baseline performance separately, there was no discernible effect of tDCS-polarity in our sample of 38 participants.

Crucially however, tDCS outcome (polarity-specific) depended on both tDCS-intensity and individual performance level at baseline, as revealed by a significant 3-way interaction between tDCS-polarity × tDCS-intensity × Baseline performance level [$F(1, 34) = 7.221$, $p = .011$, $\eta p^2 = .175$], that was independent of block-rank [no 4-way interaction with factor block: $F(8, 272) = .602$, $p = .776$, $\eta p^2 = .017$] (illustrated in Fig. 3B). Post hoc analysis revealed a significant tDCS-intensity × Baseline performance interaction for the LA/RC-montage [$F(1, 34) = 8.465$, $p = .006$, $\eta p^2 = .199$, Fig. 3B, right panel] not present for the other polarity-reversed (LC/RA) montage [$F(1, 34) = .041$, $p = .842$, $\eta p^2 = .001$, see Fig. 3B, left panel]. 1 mA LA/RC tDCS led to a larger rightward shift in PSE in the 'high discrimination sensitivity' group compared to the 'low discrimination sensitivity' group that almost reached significance [$t(17) = 1.757$, $p = .097$, Cohen's $d = .8$] whereas 2 mA-tDCS led to the opposite pattern: a larger rightward shift in PSE was observed in the 'low discrimination sensitivity' group than in the 'high discrimination sensitivity' group [$t(17) = -2.503$, $p = .023$, Cohen's $d = -1.08$].

To test whether the observed rightward shifts in midpoint judgment with LA/RC-tDCS differed significantly from what would be expected with extended time-on-task alone (whether differing significantly from sham), one-sample t-

Fig. 3 − Effects of bi-parietal tDCS on visuospatial attentional bias during line bisection. Negative values (plotted downwards) on the y-axis represent a leftward shift in subjective midpoint whereas positive values represent a rightward shift in subjective midpoint relative to baseline (Fig. 3A) and sham (Fig. 3B). Fig. 3A presents the mean shifts in pixels (±1 S E.) of landmark task PF point-of-subjective-equality (PSE) from baseline (block 1) across the subsequent 9 blocks of the experiment (x-axis) for the LC/RA condition (dark and light fill blue squares and lines), the LA/RC condition (dark and light fill red squares and lines) and the sham condition (white squares and black lines) in the 1 mA 'high discrimination sensitivity' (HDS) performers (top left panel), the 1 mA 'low discrimination sensitivity' (LDS) performers (middle left panel), the 2 mA 'HDS' performers (top right panel) and the 2 mA 'LDS' performers (middle right panel) respectively. The solid grey horizontal bars represent the stimulation duration (20 min). Fig. 3B presents the group average ('HDS' performers = dark fill/colour bars, 'LDS' performers = light fill/colour bars) shifts in PSE (baseline-corrected and sham-normalised) averaged over blocks 2−10 across both current strengths (x-axis) for the LC/RA condition (bottom left panel) and the LA/RC condition (bottom right panel) respectively. LA/RC-tDCS led to a rightward shift in visuospatial attention bias in the 1 mA 'HDS' group (high baseline signal/noise ratio) and in the 2 mA 'LDS' group (low baseline signal/noise ratio) whereas no shifts in spatial bias were observed in either the 1 mA 'LDS' group or in the 2 mA 'HDS' group.

tests (versus 0) were performed on the shift values for each group separately. 1 mA LA/RC tDCS led to a significant rightward shift in visuospatial attentional bias in the group with steep slope/narrow curve width ('high discrimination sensitivity') [$t(9) = 2.866$, $p = .019$, Cohen's $d = 1.91$] and 2 mA LA/RC tDCS led to a significant rightward shift in the group with

shallow slope/wide curve width ('low discrimination sensitivity') [$t(7) = 3.274$, $p = .014$, Cohen's $d = 2.47$]. No shift was observed in the other groups [1 mA LA/RC, 'low discrimination sensitivity': $t(8) = -.351$, $p = .735$, Cohen's $d = .25$; 2 mA LA/RC, 'high discrimination sensitivity': $t(10) = -.141$, $p = .891$, Cohen's $d = .09$]. Hence, when tDCS intensity and baseline

performance levels were considered, polarity specific effects with large effect sizes >>1 (consisting of a statistically significant rightward shift with LA/RC-tDCS) became evident even in small groups of 9–10 participants. In contrast, a t-test against zero on LA/RC data, not differentiating between tDCS intensity and baseline performance (i.e., considering the whole group of all 38 participants), only revealed a trend $[t(37) = 2.003, p = .052]$ with a medium effect size (Cohen's $d = .66$), despite the large number of participants. For the same comparison in the LC/RA condition, no shift was observed $[t(37) = .664, p = .511,$ Cohen's $d = .22]$.

3.4. Effects of bi-parietal tDCS on discrimination sensitivity

We also subjected visual discrimination sensitivity (indexed by the estimated width of the fitted PF) to the above $2 \times 2 \times 2 \times 9$ ANOVA on baseline- and sham-corrected data as well as to one sample t-tests against zero, but the data were inconclusive and therefore not further interpreted here.

In brief, the interaction of interest (tDCS-polarity × tDCS-intensity × Baseline performance level) was not significant $[F(1,34) = .05, p = .824, \eta p^2 = .001]$, but we found Baseline performance level and tDCS-intensity to interact $[F(1,34) = 13.36, p < .001, \eta p^2 = .282;$ see Supplemental Fig. for the corresponding data]. This may be suggestive of tDCS also affecting discrimination sensitivity (not only attentional bias) depending on the potential contributors to tDCS outcome (i.e., tDCS intensity and individual baseline performance level). However, these changes were inconclusive for two reasons. First, while there was a trend for active tDCS to show a Baseline performance × tDCS-intensity interaction [LA/RC: $F(1,34) = 3.871, p = .057, \eta p^2 = .102;$ LC/RA: $F(1,34) = 3.679, p = .064, \eta p^2 = .098]$, this interaction was also present (with inverted directionality) in the sham data $[F(1,34) = 4.793, p = .035, \eta p^2 = .124]$ (unlike for the attentional bias, see 3.1 above). Hence, the results may have been driven to some degree by the sham data and to a lesser extent by tDCS. Second, one sample t-tests did not provide clear evidence for changes during tDCS relative to sham [LA/RC: $t(1,37) = -.394, p = .696,$ Cohen's $d = .13;$ LC/RA: $t(1,37) = 1.337, p = .190,$ Cohen's $d = .44]$ (again unlike for the attentional bias, see 3.3 above). Potential tDCS-effects on visual discrimination sensitivity were hence clearly weaker (if present at all) than the effects on attentional bias, and are therefore not further discussed.

4. Discussion

We studied the effects of bi-parietal tDCS on subjective midpoint estimation during performance of a perceptual line bisection task. Our main findings were three-fold. First, we replicated the polarity specific effect of bi-parietal tDCS with a LA/RC electrode montage leading to a rightward shift in subjective midpoint (Giglia et al., 2011), but did not find the opposite effect with LC/RA-tDCS, i.e., this montage did not shift attention leftward. Second, we found only a weak overall effect in a group of 38 participants in line with recent meta-analyses of weak effects of tDCS on cognitive outcome measures (Horvath et al., 2015a; Jacobson, Koslowsky et al., 2012),

yet the effect was found to be strong in a subset of our participants when they were split according to individual baseline discrimination sensitivity; a measure associated with intrinsic uncertainty during perceptual decision making (Gold & Ding, 2013). Third, we found a non-linear interaction between this measure of intrinsic uncertainty at baseline and the administered tDCS current strength. This extends previous studies which have separately shown tDCS-effects to depend on the relative expertise/performance level of participants (Berryhill & Jones, 2012; Dockery et al., 2009; Hsu et al., 2014; Learmonth et al., in press; Tseng et al., 2012) and the administered tDCS-intensity (Batsikadze et al., 2013; Hoy et al., 2013; Teo et al., 2011). These three points are discussed in more detail below.

4.1. Polarity-specific effects of bilateral tDCS on lateralized visuospatial attention bias

In our data set, we found polarity specific effects expressed in a rightward shift of spatial attention after LA/RC tDCS, in accordance with the classical cathodal-inhibition and anodal-facilitation dichotomy of tDCS (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). Our findings are also in line with previously reported polarity-specific effects of parietal tDCS on lateralized visuospatial attention. Anodal tDCS has been found to bias attention towards the contralateral visual field and/or cathodal tDCS to bias attention away from the contralateral visual field, both in animals (Schweid, Rushmore, & Valero-Cabre, 2008) and humans (Giglia et al., 2011; Loftus & Nicholls, 2012; Sparing et al., 2009; Wright & Krekelberg, 2014). In the current study, only the LA/RC-montage shifted attention. Because right parietal dominance for visuospatial processing is thought to underlie the tendency for a behavioural bias in favour of stimuli appearing in the left visual field (a phenomenon termed pseudoneglect: Benwell, Harvey et al., 2014; Benwell, Thut et al., 2014; Jewell & McCourt, 2000), a rebalancing of lateralized parietal activity through LA/RC tDCS may have corrected here for the leftward spatial bias and hence driven a rightward shift in the distribution of visuospatial attention. Note that Giglia et al. (2011) directly compared bi-parietal LA/RC-tDCS (as applied here) with unilateral RC-tDCS and observed a rightward shift in bias in both conditions (relative to sham), albeit stronger for bilateral parietal tDCS, which appears to accord with the 'hemispheric rivalry' model of spatial attention (Kinsbourne, 1977; Szczepanski & Kastner, 2013). Interestingly, the reversed polarity we tested here for the first time during landmark task performance (LC/RA) induced no shift in subjective midpoint relative to sham. We speculate that tDCS cannot enhance the leftward bias further outside of an advantageous range for perception, in analogy to Goedert, LeBlanc, Tsai, and Barrett (2010) who observed a similar 'ceiling effect' during prism adaptation in healthy participants. In contrast to our results, Sparing et al., (2009) found polarity-specific bidirectional shifts in visuospatial attention bias displayed during a lateralized dot detection task, with unilateral parietal anodal versus cathodal tDCS enhancing versus impairing perception of stimuli in the contralateral visual field. Though both tasks (lateralized dot detection and the landmark task) putatively index lateralized visuospatial bias, the lack of an effect for the

LC/RA configuration in the current study may suggest differences in the neural networks subserving the respective tasks, or alternatively could be explained by differences in the effects induced by unilateral versus bilateral stimulation [see for instance Sehm, Kipping, Schäfer, Villringer, and Ragert (2013)].

4.2. tDCS outcome scales with a psychometric index of intrinsic uncertainty (related to signal-to-noise ratio), in interaction with tDCS current strength

While we could replicate the results of Giglia et al., (2011) for the LA/RC tDCS montage, this effect was weak (Cohen's $d = .66$) across our entire sample ($N = 38$). However, taking into consideration baseline discrimination sensitivity (i.e., the slope of the PF) and the administered current strength as factors in the analysis revealed that these two factors together strongly modulate tDCS-efficacy, with the response to tDCS differing between groups. 'High discrimination sensitivity' participants only responded to 1 mA-tDCS (Cohen's $d = 1.91$), whereas 'low discrimination sensitivity' participants responded only to 2 mA-tDCS (Cohen's $d = 2.47$). The potentially strong influence of subtle differences in sample characteristics and/or experimental protocols on tDCS outcome highlighted by our results may contribute to the large outcome variability observed across tDCS studies (Horvath et al., 2015a, 2015b; Jacobson, Koslowsky et al., 2012; Krause & Cohen Kadosh, 2014; Krause, Márquez-Ruiz, & Cohen Kadosh, 2013; López-Alonso et al., 2014; Vallar & Bolognini, 2011; Wiethoff et al., 2014). Conversely, research aimed at mapping the factors that influence tDCS outcome (and the relationships between them) across brain regions and cognitive domains may lead to the improvement of tDCS efficacy and specificity for both research and clinical purposes.

Our finding that tDCS outcome depends on discrimination sensitivity further highlights state/trait dependency of NIBS (e.g., in TMS, Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). Within this framework, it has been proposed that the relative balance between task-relevant and task-irrelevant neurons at baseline (e.g., Silvanto et al., 2007; Silvanto et al., 2008), or the related concept of signal and noise (e.g., Miniussi et al., 2010; 2013; Ruzzoli et al., 2010), is a determining factor of NIBS outcome. Note that the concept of the relative activity profile of subpopulations of neurons influencing NIBS outcome is primarily based on studies using transcranial magnetic stimulation (TMS, Abrahamyan et al., 2011; Cattaneo et al., 2008; Cattaneo et al., 2010; Schwarzkopf et al., 2011; Silvanto et al., 2007, 2008; see Miniussi et al., 2013), but is herein suggested to apply also to tDCS. We employed the slope of the PF as a measure of the degree of intrinsic uncertainty (Gold & Ding, 2013; Kontsevich & Tyler, 1999; Pelli, 1985, 1987; Tyler & Chen, 2000), which in turn has been related to the degree of pooling of task-relevant neurons during perceptual decisions (Gold et al., 2010). By extension, our data suggest that the level of intrinsic uncertainty/task relevant neuronal pooling modulates tDCS outcome (see Fig. 4 for a potential schematic of this relationship). On a cautionary note, the measures by which we split our participants into subgroups were behavioural. Hence we have not measured from task-relevant neurons ("signal") or task-irrelevant neurons ("noise") directly and can only speculate as to the mechanisms through
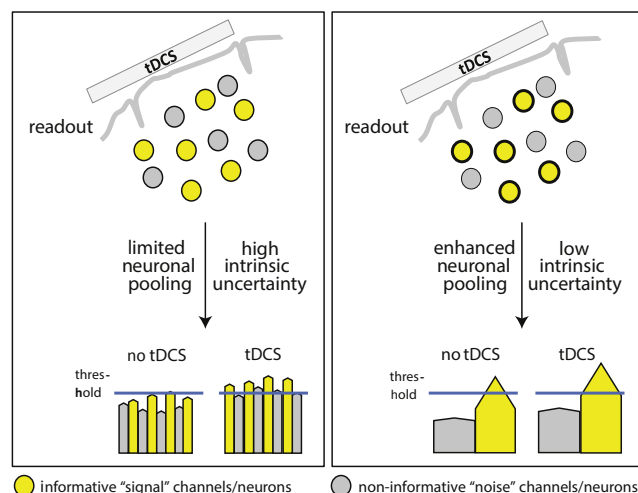
Fig. 4 — A schematic of the proposed state-dependency of tDCS outcome (as a function of uncertainty). tDCS effects are dependent on the overall endogenous balance between task-relevant (yellow dots/bars) and -irrelevant neurons (grey dots/bars) (or signal-to-noise ratio) which manifests behaviourally in the level of intrinsic task uncertainty (see left panel for a situation of low signal-to-noise/high intrinsic uncertainty and right panel for a situation of high signal-to-noise/low intrinsic uncertainty). Behaviourally relevant changes of neural activity will therefore depend on the preferential up or down-regulation of activity in either 'signal' or 'noise' neurons, depending on their respective activation state (depicted in the figure 'neurons' by the black outer rings: thicker outline = increased activation).

which tDCS may interact with baseline signal-to-noise ratio (see 4.3. below). In addition, this measure is indirect and can only provide an approximate estimate of neurophysiological makeup. To develop a mechanistic understanding of the relationship between tDCS and behavioural outcome, biophysical models tested through appropriate physiological and behavioural measures should be implemented (de Berker, Bikson, & Bestmann, 2013; Bestmann, de Berker, & Bonaiuto, 2015). Regardless of the mechanism underlying tDCS trait/ state dependency as observed in the current study, the results suggest that current theories of state-dependency of NIBS can be extended to tDCS and that tDCS specificity and efficacy may be improved by selecting dose as a function of a person's task performance level/endogenous signal-to-noise ratio.

4.3. Non-linear interactions between baseline performance groups and tDCS current strength: potential explanations

We found the polarity specific effects to be modulated by a complex interaction between tDCS-intensity and baseline task ability. We characterize the nature of this interaction as non-linear because one subset of participants responded to one dose whereas another subset responded to another dose. Accordingly, these effects are incompatible with floor or ceiling effects where 'high discrimination sensitivity'

participants simply show stronger effects than 'low discrimination sensitivity' participants (or vice versa), or with linear dose response accounts where effects should be stronger for 2 mA-than 1 mA-tDCS independent of group. How can the nonlinear dose-dependent effects of tDCS on behavioural performance then be explained?

One possible nonlinear mechanism that has been associated with NIBS outcome is stochastic resonance (Abrahamyan et al., 2011; Miniussi et al., 2010; 2013; Ruzzoli et al., 2010; Schwarzkopf et al., 2011). Stochastic resonance has been posited in various theoretical cognitive models and has also been observed empirically in experimental neuroscience (Faisal, Selen, & Wolpert, 2008; McDonnell & Ward, 2011; Moss, Ward, & Sannita, 2004; Simonotto et al., 1997). It denotes a phenomenon in which the relative modulation of signal-to-noise (either by the addition of a given level of input noise, or by the disproportional activation of "noise" channels) can paradoxically improve information processing. Stochastic resonance may fit our data because it is inherently non-linear and predicts NIBS outcome to depend on the endogenous signal-to-noise ratio of the participant for a given task. Yet, whether stochastic resonance could explain the present nonlinear effect remains elusive, and would require a better understanding of the degree to which tDCS can be considered a source of physiological noise, and a design more suited to test the specific predictions of the stochastic resonance model. Another mechanism associated with NIBS that shows nonlinearity and state-dependency is homeostatic metaplasticity (Ridding & Ziemann, 2010; Siebner, 2010; Siebner et al., 2004). However, homeostatic metaplasticity serves to maintain neuronal functions within predefined optimal ranges to avoid extreme dysfunctional levels of neural activity following prolonged periods of excitation/inhibition (Turrigiano & Nelson, 2004). Consequently, homeostatic metaplasticity pertains to compensatory mechanisms following plasticity-inducing protocols (Ziemann & Siebner, 2008) rather than the online effects of NIBS we observed. Hence, homeostatic metaplasticity can be excluded here, at least empirically, as an explanation for the observed non-linear effects.

We would like to emphasize that there are other possible non-linear mechanisms alongside stochastic resonance (and metaplasticity) which could underlie our findings. While our study contributes to support models of state-dependency of NIBS as well as to characterize the nature of the interaction with other tDCS factors (namely intensity), it cannot resolve which mechanisms are at play.

4.4.   Potential limitations of study

Despite there being no evidence of differences in the subjective somatosensory perceptions associated with stimulation between groups (as measured by a side-effects questionnaire), stimulation of peripheral nerves in the skin underlying the electrodes will vary systematically with stimulation intensity and even unconscious differences between the 1 mA and 2 mA groups may have affected behaviour. However, this could not explain the observed interaction between baseline discrimination sensitivity and current strength. Rather, a difference between current strength groups only would be expected under such a scenario, regardless of baseline performance level.

Additionally, the PSE measure of subjective midpoint adopted here is potentially confounded by response bias as participants always had to indicate which end of the line appeared 'shortest' of the two. This confound can be removed by alternating within participants trials in which they are requested to indicate the 'shortest' and 'longest' end of the line (Toraldo, McIntosh, Dijkerman, & Milner, 2004). Many previous studies employing either a single instruction (i.e., indicate the shortest) and/or separate instructions (i.e., alternating 'shortest' and 'longest' both within and across participants) have consistently shown baseline pseudoneglect in samples of healthy, young individuals (Benwell, Harvey et al., 2013; Benwell, Harvey et al., 2014; Benwell, Learmonth et al., 2013; Benwell, Thut et al., 2014; Jewell & McCourt, 2000; Schmitz, Deliens, Mary, Urbain, & Peigneux, 2011) so we do not believe that the baseline leftward bias is likely to be due to response bias. Additionally, any potential changes in response bias are unlikely to have contributed to the observed parietal-tDCS effects as the shifts in subjective midpoint were polarity-specific and modulated by performance group and current strength.

Finally, it is notable that stimulation intensity is not calibrated to individual cortical excitability in tDCS studies, including this study, while this is common in TMS studies. Therefore across participants potentially different stimulation intensities may be effectively delivered to the brain. Additionally, different current intensities potentially induce differential current distributions within the brain. Future studies may take into account these factors by incorporating models of current distribution based on individual physical differences (bone structure, tissue properties etc.) and the administered current density to titrate effective stimulation intensity and focality across participants.

5.   Conclusion

The current results show that bi-parietal left anodal/right cathodal tDCS can drive a rightward shift in subjective midpoint estimation during performance of the landmark task. However, this effect depends on the baseline task performance level of participants, in interaction with the administered tDCS-intensity. The opposite polarity (left cathodal/right anodal) resulted in no change in subjective midpoint estimation. The results highlight that individual differences and dose interact to influence tDCS outcome. We conclude that it is of importance to map and understand the factors that determine tDCS outcome across different cognitive domains, and the relationships between them, if tDCS is to be developed as a useful clinical and research tool in cognitive sciences.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2015.05.007.

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