

The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance



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ABSTRACT

Young adults typically display a processing advantage towards the left side of space (“pseudoneglect”), possibly as a result of right parietal dominance for spatial attention. This bias is ameliorated with age, with older adults displaying either no strongly lateralised bias, or a slight bias towards the right. This may represent an age-related reduction of right hemispheric dominance and/or increased left hemispheric involvement. Here, we applied anodal transcranial direct current stimulation (atDCS) to the right posterior parietal cortex (PPC; R-atDCS), the left PPC (L-atDCS) and a Sham protocol in young and older adults during a titrated lateralised visual detection task. We aimed to facilitate visual detection sensitivity in the contralateral visual field with both R-atDCS and L-atDCS relative to Sham. We found no differences in the effects of stimulation between young and older adults. Instead the effects of atDCS were state-dependent (i.e. related to task performance at baseline). Relative to Sham, poor task performers were impaired in both visual fields by anodal stimulation of the left posterior parietal cortex (PPC). Conversely, good performers maintained sensitivity in both visual fields in response to R-atDCS, although this effect was small. We highlight the importance of considering baseline task ability when designing tDCS experiments, particularly in older adults.

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1. Introduction

The global population is aging rapidly, with the proportion of adults aged over 60 predicted to double by 2050 to more than 2 billion individuals (United Nations, 2013). As a result of this demographic shift, age-related cognitive decline is now considered one of the most pressing issues to be addressed if independence and quality of life are to be maintained throughout our later years (Depp and Jeste, 2006). Leaving aside the impact that pathological aging (e.g. dementia) enacts at both an individual and societal level, healthy non-pathological aging is also accompanied by neural changes that result in decreased performance across a wide range of cognitive abilities. Whilst there are large individual differences in the speed and extent of cognitive aging, linguistic and numerical performance seem relatively spared into older adulthood, (Hedden and Gabrieli, 2004; Schaie, 1996) whereas domains such as working memory (Craik, 1994; Park et al., 2002; Wingfield et al., 1988), executive control (Dempster, 1992; Hasher et al., 1999; Lamar et al., 2002) and processing speed (Deary et al., 2010;

Salthouse, 1991, 1996) are more vulnerable to decline.

Aging brains differ from younger brains both structurally (e.g. reduced brain volume and enlarged ventricles; see Fjell and Walhovd, 2010 for review) and in their functional organisation (Raz et al., 2005). In functional imaging studies, young adults generally display brain activity patterns that are highly lateralised to one cerebral hemisphere, as typified in the classic dichotomy of left-hemispheric dominance for language and right-sided superiority for spatial attention. This strong lateralisation diminishes with age, with activity becoming more bilaterally distributed in older adults in response to tasks involving memory (Bäckman et al., 1997; Cabeza et al., 1997, 2004; Grady et al., 2002; Madden et al., 1999; Morcom et al., 2003; Reuter-Lorenz et al., 2000), inhibitory control (Nielson et al., 2002), problem solving (Esposito et al., 1999), lexical decisions (Collins and Mohr, 2013) and face perception (Collins and Mohr, 2013; Grady et al., 1994).

These findings support the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model (Cabeza, 2002). This model describes a compensatory strategy whereby a functional decline within the (previously) dominant hemisphere for a particular task is bolstered by the recruitment of neurons within the opposite hemisphere. Indeed, functional reorganisation has been positively correlated with task performance, with high-performing older adults demonstrating a greater degree of bilateral activation in

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working memory tasks compared to low-performing adults of the same age (Cabeza, 2002; Cabeza et al., 1997, 2002; Reuter-Lorenz et al., 2000). In corroboration Huang et al. (2012) report superior performance on numerical and size judgement tasks in older adults with increased bilateral involvement of the posterior parietal cortex (PPC). Secondly, an age-related functional reorganisation from posterior to anterior regions has also been described. Analogous with the HAROLD model, a larger posterior–anterior shift appears to be positively correlated with task performance (Davis et al., 2008, Grady et al., 1994; Spreng et al., 2010). Thus, it seems plausible that the large individual differences in cognitive performance observed in older adults may, to some degree, be related to the extent of functional reorganisation that has taken place.

Asymmetric patterns of activity between the two cerebral hemispheres may also represent the neural underpinning of “pseudoneglect”, a phenomenon described within the visuospatial attention literature which mirrors the left inattention resulting from right parietal lobe damage in patients with hemispatial neglect (Bowers and Heilman, 1980). Young adults typically display a processing advantage within the left visual field (LVF)/space, which is considered a consequence of predominant right parietal involvement for spatial attention (Heilman and Van Den Abell, 1980; Kinsbourne, 1970; Malhotra et al., 2009; Thiebaut de Schotten et al., 2011; Weintraub and Mesulam, 1987). Although the magnitude of this pseudoneglect bias is small, relative to the often debilitating effects of left-sided inattention in hemispatial neglect, both phenomena highlight the crucial role of the right hemisphere for spatial attention. Moreover, this leftward preference is consistently found in a variety of lateralised visual perception tasks, such as the landmark task (Benwell et al., 2013a, 2013b; Milner et al., 1992), line bisection (Bradshaw et al., 1986; Varnava et al., 2002), greyscales (Mattingley et al., 1994, 2004), grating scales (Chen and Niemeier, 2014; Niemeier et al., 2007, 2008; Singh et al., 2011) and lateralised visual detection tasks (Hilgetag et al., 2001; Sparing et al., 2009; Thut et al., 2006). Pseudoneglect has also been reported in non-human animals such as pigeons and domestic chicks (Chiandetti et al., 2013, 2014; Diekamp et al., 2005; Regolin, 2006), hinting that there may be some evolutionary advantage gained by hemispheric processing asymmetries.

Although, as described above, this leftward preference is a well observed phenomenon in young adults, older people do not consistently display a preference towards either side of space, or indeed show a slight rightward bias in line bisection (Failla et al., 2003; Fujii et al., 1995; Fukatsu et al., 1990; Stam and Bakker, 1990), landmark (Benwell et al., 2014; Schmitz and Peigneux, 2011) and lateralised visual detection tasks (Nagamatsu et al., 2009, 2011, 2013). Interestingly, there is empirical evidence that older adults have a specific deficit in left visual field processing and that the extent of this decrement is positively correlated with an increased incidence of falls (Nagamatsu et al., 2009, 2011, 2013). This behaviour may be incorporated within the HAROLD model: a decrease in processing efficiency of the right parietal lobe that is compensated for by a recruitment of the left hemisphere, resulting in a rightward shift or elimination of the attentional bias. Alternatively, the findings are also compatible with the “accelerated aging” model in which the right hemisphere is more susceptible to the effects of age relative to the left hemisphere (Brown and Jaffe, 1975; Dolcos et al., 2002; Goldstein and Shelly, 1981). The two models differ in the extent of left hemisphere involvement and are therefore not mutually exclusive. However, functional imaging has provided mixed evidence of both increased (Grady et al., 2010; Huang et al., 2012; Madden et al., 2007; Townsend et al., 2006) and decreased activity (Milham et al., 2002; Rosano et al., 2005) in the parietal lobes with age, which is likely to be highly task-specific (see Spreng et al., 2010 for review). Given the likelihood of a

functional advantage gained by improving spatial attention in older adults, and within the left visual field specifically, we aimed to boost parietal lobe activity using non-invasive brain stimulation, in this case transcranial direct current stimulation (tDCS).

Transcranial direct current stimulation (tDCS) is a safe and well-tolerated method of altering cortical activity which enables the relationship between brain activity and behaviour to be examined (Nitsche and Paulus, 2000). The application of a small current to a neuronal population is thought to alter their membrane potential in a polarity-specific manner, thus rendering the neurons more (under the anode) or less (under the cathode) likely to fire (Stagg and Nitsche, 2011). Effects last within the order of a few minutes in typical experimental designs, although longer lasting effects of up to 6 months have also been reported with repeated stimulation over multiple sessions (Cohen Kadosh et al., 2010).

tDCS has proved effective in altering behaviour in young adults, as well as offering rehabilitative hope for some clinical populations (e.g. Fregni et al., 2005; Hummel and Cohen 2006). The application of anodal tDCS (atDCS) in healthy older adults is attracting interest as a potentially promising method of alleviating age-related cognitive decline (Fertonani et al., 2014; Flöel et al., 2012; Holland and Crinion, 2011; Meinzer et al., 2013; Zimmerman and Hummel, 2010). When applied to the left ventral inferior frontal gyrus, atDCS reinstated a more “youth-like” (i.e. uni-hemispheric rather than bilateral) pattern of activation in older adults during a word generation task that could be visualised on functional magnetic resonance imaging (fMRI) (Meinzer et al., 2013). However, the efficacy of atDCS may be partly dependent on baseline factors that differ across the population. Berryhill and Jones (2012) aimed to improve working memory in older adults using 1.5 mA atDCS to either the left or right prefrontal cortex for 10 min, just prior to participants performing verbal and visual 2-back tasks. Performance was facilitated on both tasks, independent of stimulation site, but only for individuals with a high level of education. Conversely, seniors with fewer completed years of education either did not benefit, or were in fact impaired, on the task post-tDCS.

In the present study, we presented a lateralised visual detection task (titrated to each individual's peri-threshold ability) to both young and older participants. The task was based on a protocol of Hilgetag et al. (2001) who reduced activity within the parietal cortices of young adults using 1 Hz repetitive transcranial magnetic stimulation (rTMS). Detection rates improved for stimuli presented ipsilateral to the rTMS, which was indicative of each hemisphere exerting a regulatory effect on the other within the attention network. Suppression of one parietal lobe thus effectively released the contralateral hemisphere from inhibition, resulting in an improvement in detection accuracy. In later work Sparing et al. (2009) incorporated this titrated lateralised visual detection task within a tDCS protocol, using 1 mA anodal or cathodal stimulation over either the left or right parietal lobes (P3 or P4 of the 10–20 EEG system; return electrode Cz). tDCS-induced changes were elicited in young, healthy adults, with 10 min of atDCS vs cathodal tDCS (ctDCS), facilitating vs reducing accuracy in the contralateral visual field.

We aimed to extend this protocol in the present study, by using atDCS to reinstate an adaptive, “youth-like” pattern of right-hemispheric dominance for spatial attention in older adults. We applied 1 mA atDCS in a uni-hemispheric montage over either the right or left hemisphere (P3 or P4; return over contralateral supraorbital), plus a sham protocol, to both healthy young and older adults. The P4-Left supraorbital montage has previously been successful in reducing pathological left-sided inattention in patients with hemispatial neglect (Ko et al., 2008; Sunwoo et al., 2013) and here we extend the protocol by introducing the

mirrored P3-Right supraorbital condition. We predicted that both R-atDCS and L-atDCS would facilitate detection accuracy in the contralateral visual field, relative to Sham, replicating the findings of Sparing et al. (2009). Regarding the older age group, as outlined above, there is currently conflicting evidence as to whether aging is associated with an increase or decrease in parietal activity, and this is also likely to be task-dependent. However, the finding that older people do not exhibit lateralised spatial attention biases indicates that the right hemisphere may be reduced in activity and/or the left hemisphere over-recruited. Thus, we expected that older adults might show a different response profile to tDCS than young controls and we expected particular improvements within the left visual field as a result of R-atDCS, which would generate a unilateral pattern of activity similar to young adults.

2. Methods

2.1. Participants

20 young adults (11 females, mean age=20.9 years; SD=1.97, range=18–24) and 20 older adults (10 females, mean age=66.6 years; SD=5.11, range=60–77) were recruited. All participants were right-handed, had normal or corrected-to-normal vision and were screened for contraindications to tDCS. Written, informed consent was obtained from each participant. The study was approved by the University of Glasgow College of Science and Engineering ethics committee.

2.2. Procedure

At the beginning and end of each day, participants indicated their subjective alertness on a linear scale (0=almost asleep, 100=fully alert). They were seated in front of a computer screen with their midsagittal plane aligned with the screen. The stimulus titration phase was completed at the start of Day 1, followed by an extended rest period when the tDCS electrodes were placed.

A direct current was delivered to the head using a battery-driven constant current stimulator (NeuroConn GmbH, Germany). Three experimental conditions were applied in a within-subject design: (i) Left anodal (L-atDCS), (ii) Right anodal (R-atDCS), (iii) Sham (counterbalanced L-atDCS or R-atDCS montage) stimulation (Fig. 1). Each condition was applied on a different day (a minimum of 24 h between sessions) and the order was counterbalanced across participants. The anode was placed over either the left or right posterior parietal cortex (PPC) (centred on P3 or P4 of the 10–20 International EEG system) with the cathode (return electrode) placed on the contralateral supraorbital region. All 3 protocols began and ended with a 30 s ramp-up period. The current was then maintained at 1 mA for 15 min in the two active tDCS sessions, followed by a 30 s ramp-down period. The current was maintained at 1 mA for 30 s in the Sham protocol before being ramped-down again, which has previously been reported as perceptually indistinguishable from “active” tDCS (Gandiga et al., 2006). The anode measured $5 \times 5 \text{ cm}^2$ (current density=0.04 mA/cm²), the cathode $5 \times 7 \text{ cm}^2$ (0.03 mA/cm²) and each rubber electrode was inserted into 0.09% NaCl saline-dampened sponges.

One block of a landmark task was completed (not reported here), then a pre-tDCS baseline block (Block 1) of the lateralised visual detection task. At the end of Block 1, the stimulator was turned on and allowed to ramp up to 1 mA, at which point Block 2 began. The stimulation was maintained at 1 mA during Blocks 2 and 3 (online), then ramped down to 0 mA. Blocks 4 and 5 were undertaken post-tDCS (offline). A final landmark block was then completed (not reported here). After the electrodes were removed, a questionnaire documented the presence and severity of 5 sensory experiences during the session (headache, tingling, itching, burning, pain). Score 1=“Not experienced at all”, 5=“Experienced very strongly” (modified from Brunoni et al., 2011). Days 2 and 3 began with the tDCS electrode application but subsequently proceeded in an identical manner. Participants were invited to guess which of the 3 days had involved Sham tDCS at the close of their final session.

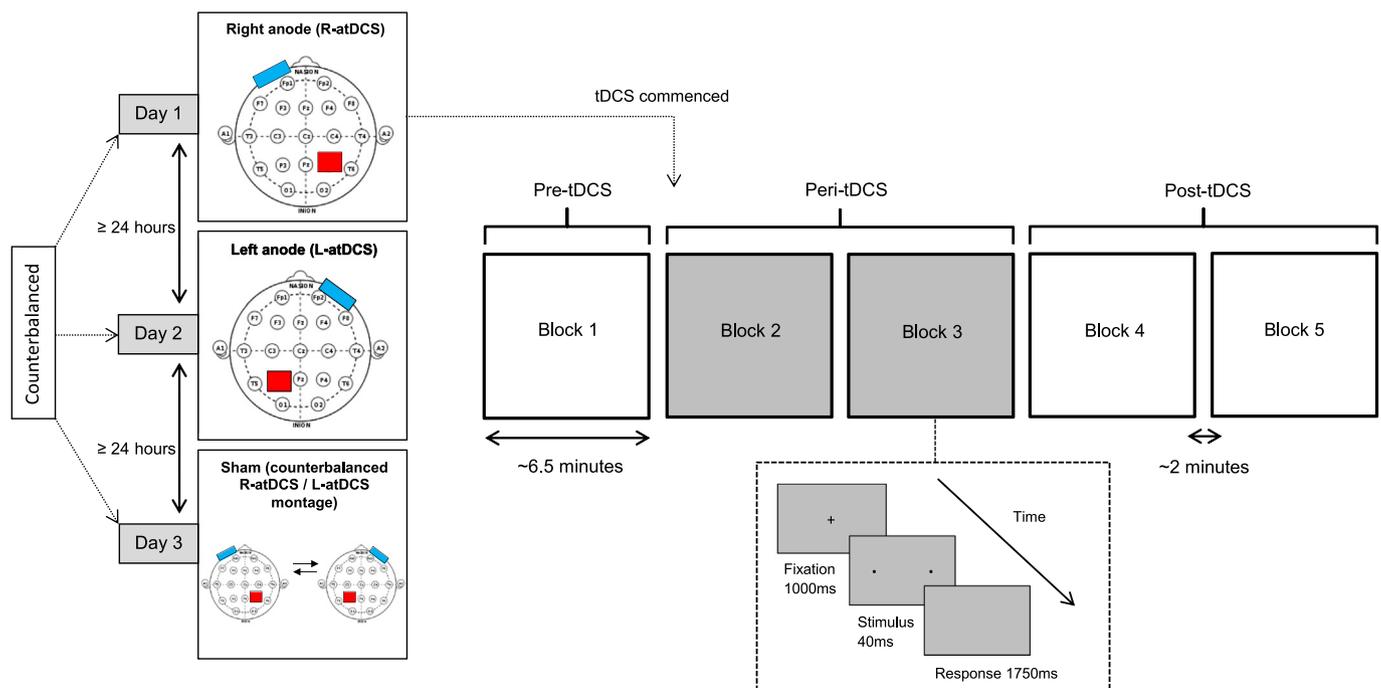


Fig. 1. Schematic of the experimental procedure and the lateralised visual detection task. Three tDCS conditions (R-atDCS/L-atDCS/Sham) counterbalanced across testing days (≥ 24 h between sessions). 1 block of lateralised visual detection pre-tDCS. Sham tDCS applied online for 30 s at the start of Block 2. R-atDCS and L-atDCS applied online for 15 min throughout Blocks 2 and 3. Blocks 4 and 5 post-tDCS.

2.3. Stimuli

Stimuli were presented using E-Prime 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) using a Dell Precision 380 PC and a 19" Dell 1908FP UltraSharp LCD Flat Panel monitor with a 1280 × 1024 pixel resolution. The viewing distance was fixed with a chin rest at 0.5 m.

2.4. Lateralised visual detection task

The task was adapted from Hilgetag et al. (2001). Stimuli consisted of small black squares or rectangles (with the longer edge along the horizontal axis) presented against a grey screen (hue=179, saturation=0, luminance=160). Stimuli were presented either to the left of fixation (−145 mm; −16.5° visual angle (VA)), to the right (+145 mm; +16.5° VA), or were presented bilaterally (subtending 290 mm; 32.34° VA). Blank “catch” trials were randomly interspersed throughout each block.

Each trial started with a centred fixation cross (15 × 15 pixels; 0.58° visual angle) which remained on the screen for 1000 ms, followed by a stimulus for 40 ms then a blank response screen for 1750 ms (see Fig. 1). Participants used their dominant right hand to indicate on a keyboard whether the dot appeared on the left (index finger), right (ring finger) or bilaterally (middle finger). Participants were instructed to withhold their response when no stimulus was detected.

In order to equate the difficulty of the experiment across individuals, each participant completed a *stimulus titration phase* to identify their peri-threshold stimulus sizes at the start of their first session. A total of 270 trials were randomly presented across 3 short blocks (75 left-presented stimuli, 75 right, 75 bilateral and 45 catch trials). Each titration phase involved the random presentation of five different stimulus sizes. Based on pilot data, young adults were shown stimuli of 1 × 2, 2 × 2, 2 × 3, 3 × 3, 3 × 4 pixels and older adults stimuli of 3 × 3, 3 × 4, 4 × 4, 4 × 5, 5 × 5 pixels. One pixel measured approximately 0.29 mm × 0.29 mm. Similar to the titration phase of Hilgetag et al. (2001), Sparing et al., 2009 and Thut et al. (2006) percentage accuracy was averaged across the left and right visual fields for each of the 5 pixel sizes. The 2 adjacent peri-threshold pixel sizes, just above (supra-threshold) and just below (sub-threshold) 50% accuracy, were selected as the stimuli to be presented in the main experiment. If participants did not achieve approximately 50% accuracy in this phase (i.e. they performed at floor or ceiling levels), the pixel size was successively titrated upwards or downwards until 50% accuracy was achieved in one further block of testing. The main experimental task was identical to the titration phase, however only the 2 individually-titrated stimulus sizes were presented. This comprised 5 blocks (1 block pre-, 2 blocks peri- and 2 blocks post-stimulation) lasting ~6.5 min each (see Fig. 1). Each block contained 140 randomly-presented trials (40 left-presented stimuli, 40 right, 40 bilateral, and 20 catch trials). Participants were instructed that they could take a 1–2 min break at the end of each block if desired.

2.5. Analysis

2.5.1. Visual detection titration

The distribution of the pixel sizes that elicited just above or below 50% accuracy across the left and right visual fields is shown in Fig. 2. As expected, threshold accuracy was achieved at smaller pixel sizes in the young adults with most titrated to 2 × 2/2 × 3 pixels. A wider range of larger pixels were required for older adults with the majority performing at comparable levels with 3 × 3/3 × 4 or 3 × 4/4 × 4 pixels. Group-level mean accuracy across left- and right-presented stimuli was 35.37% for the smaller (sub-

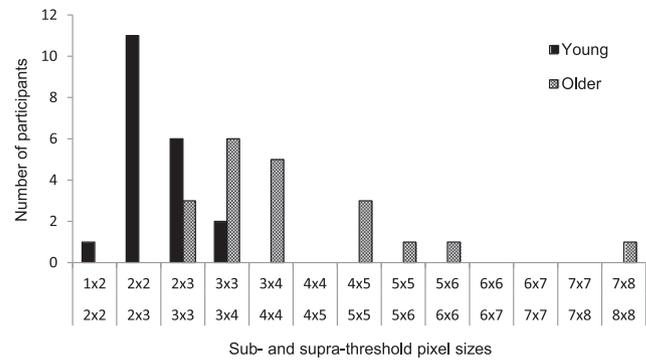


Fig. 2. Distribution of peri-threshold pixel sizes determined in the titration phase.

threshold) and 65.79% for larger (supra-threshold) dots. Accuracy was similar across age groups (Young 32.5% and 68.83%; Older 38.96% and 62.41%).

2.5.2. *d*-Prime (*d'*)

Lateralised visual detection task sensitivity was calculated by computing *d*-prime (*d'*) scores for each visual field separately within each block of trials. In signal detection theory, *d'* is a method of assessing task sensitivity which takes into account both accuracy (when stimuli are present) and false positives (in response to catch trials) (Green and Swets, 1966; Macmillan and Creelman, 2005). *d'* was calculated in Matlab using the function:

$$d' = z(\text{Hits}) - z(\text{False Alarms})$$

(Borgo et al., 2012) where *z* represents the *z*-score for each visual field within a block. Larger *d'* scores represent a greater sensitivity to detecting stimuli relative to false positives.

3. Results

3.1. Subjective alertness

A 3 (STIMULATION: *R-atDCS*, *L-atDCS*, *Sham*) × 2 (TIME: *pre* vs *post* experiment) × 2 (AGE: *young* vs *older*) factor mixed-design analysis of variance (ANOVA_{MD}) confirmed that subjective alertness reduced over the course of the experiment [TIME: $F(1,38) = 90.9$, $p < 0.001$] (Mean score *pre* = 80.3 (SD = 12.3); *post* = 61.73 (SD = 17.5)). Older adults reported higher levels of alertness overall [AGE: $F(1,38) = 12.1$, $p = 0.001$] (Mean score *Young* = 65.4 (SD = 17.3); *Older* = 76.7 (SD = 16.4)). TIME did not differentially affect alertness levels between groups [TIME × AGE: $F(1,38) = 0.282$, $p = 0.589$] and there was no effect of STIMULATION on subjective alertness.

3.2. Side-effects questionnaire

Sensory side-effects were reported as ≤ 3 out of 5 in the majority of sessions (93.67%) mostly due to moderate scores on tingling or itching sensations (but low scores on burning or pain) indicating that the tDCS was generally well tolerated. A Friedman's test found differences between STIMULATION sessions for reports of slight burning sensation ($\chi^2 = 6.031$, $p = 0.049$), but Wilcoxon's Signed Rank post hoc comparisons with a Bonferroni adjusted alpha of 0.017 did not survive correction. Of the 40 participants, only 16 correctly guessed which of the 3 sessions involved Sham tDCS and this did not differ between AGE groups (Pearson $\chi^2 = 0.417$, $p = 0.519$).

3.3. Age group split

3.3.1. Baseline sensitivity (d'): age groups

A total of 84,000 trials were analysed. As predicted, young adults were more sensitive to detecting stimuli in the left VF than the right VF at baseline (Block 1) [$t(19)=2.516$, $p=0.021$], reflecting a leftward bias in visuospatial attention (pseudoneglect) which was not present in the older group [$t(19)=0.408$, $p=0.688$]. A one-sample t -test against zero using lateralised d' index (Left VF d' subtracted from Right VF d') confirmed that older adults lacked an attentional bias [R-atDCS: $t(19)=-0.601$, $p=0.555$; L-atDCS: $t(19)=1.65$, $p=0.871$; Sham: $t(19)=-0.521$, $p=0.608$] whereas young adults were more sensitive to the left VF at baseline in the R-atDCS [$t(19)=-2.114$, $p=0.048$] and Sham sessions [$t(19)=-2.326$, $p=0.031$] with a trend towards a leftward preference in L-atDCS [$t(19)=-2.007$, $p=0.059$]. Baseline lateralised d' scores were compared across the 3 days by correlating performance in Block 1 and were found to be stable in the young adults [R-atDCS/L-atDCS: Spearman $r=0.636$, $p=0.03$; R-atDCS/Sham: $r=0.567$, $p=0.009$; L-atDCS/Sham: $r=0.594$, $p=0.006$], but in only 1 of 3 comparisons in the older adults [R-atDCS/L-atDCS: Spearman $r=0.456$, $p=0.043$; R-atDCS/Sham: $r=0.776$, $p<0.001$; L-atDCS/Sham: $r=0.304$, $p=0.193$, adjusted $\alpha=0.017$] (Fig. 3). There were no reaction time (RT) differences between the two visual fields for either age group at baseline.

3.3.2. d' Sensitivity: age groups

A full-factorial ANOVA_{MD} (3 STIMULATION \times 5 BLOCK \times 2 VF \times 2 AGE) revealed lower d' sensitivity in older adults compared to young [AGE: $F(1,38)=7.286$, $p=0.01$, $\eta^2=0.161$] and a general reduction in sensitivity across the 5 experimental blocks [BLOCK: $F(4,152)=4.274$, $p=0.003$, $\eta^2=0.101$] (Fig. 4). There were no main effects of VF or STIMULATION and no significant interactions were

found. Specifically, there was no STIMULATION \times BLOCK \times AGE interaction [$F(8,304)=1.564$, $p=0.135$, $\eta^2=0.04$]. The order in which the STIMULATION sessions were undertaken had no effect on d' scores.

3.3.3. Bilateral errors: age groups

Accuracy for the bilaterally-presented stimuli was analysed separately from those presented to the left and right VFs. Block error rates were obtained by calculating the number of responses made to the Left or the Right when the bilateral trial was answered incorrectly. ANOVA_{MD} (3 STIMULATION \times 5 BLOCK \times 2 VF \times 2 AGE) confirmed only an effect of AGE [$F(1,38)=11.88$, $p=0.001$, $\eta^2=0.238$] with young adults erring on 6.36 bilateral trials per block on average (SD=2.11) and older adults 9.27 times (SD=3.13).

3.3.4. Reaction times (RTs): age groups

Reaction times for correct left- and right-presented trials (excluding those where RT was > 2 standard deviations above the mean for each participant) were subjected to a full-factorial ANOVA (Fig. 5), revealing that response times became faster overall across the experiment [BLOCK: $F(4,152)=4.717$, $p=0.001$, $\eta^2=0.11$] but were generally slower in older participants [AGE: $F(1,38)=21.4$, $p<0.001$, $\eta^2=0.36$] (Mean RT Young: 477.2 ms, SD=46.55; Older: 581.8 ms, SD=92.65). Paired comparisons for an AGE \times BLOCK interaction [$F(4, 152)=7.311$, $p<0.001$, $\eta^2=0.161$] found that young adults became faster relative to baseline in Blocks 2, 4 and 5 (all p -values < 0.01), whereas older adults slowed in Block 3 [$t(19)=-4.138$, $p=0.001$, adjusted $\alpha=0.0125$]. There was no effect of VF or STIMULATION on reaction times nor were there any significant interactions with these factors.

3.3.5. Interim discussion: no clear effects of tDCS in aging

In line with the previous spatial attention literature, young

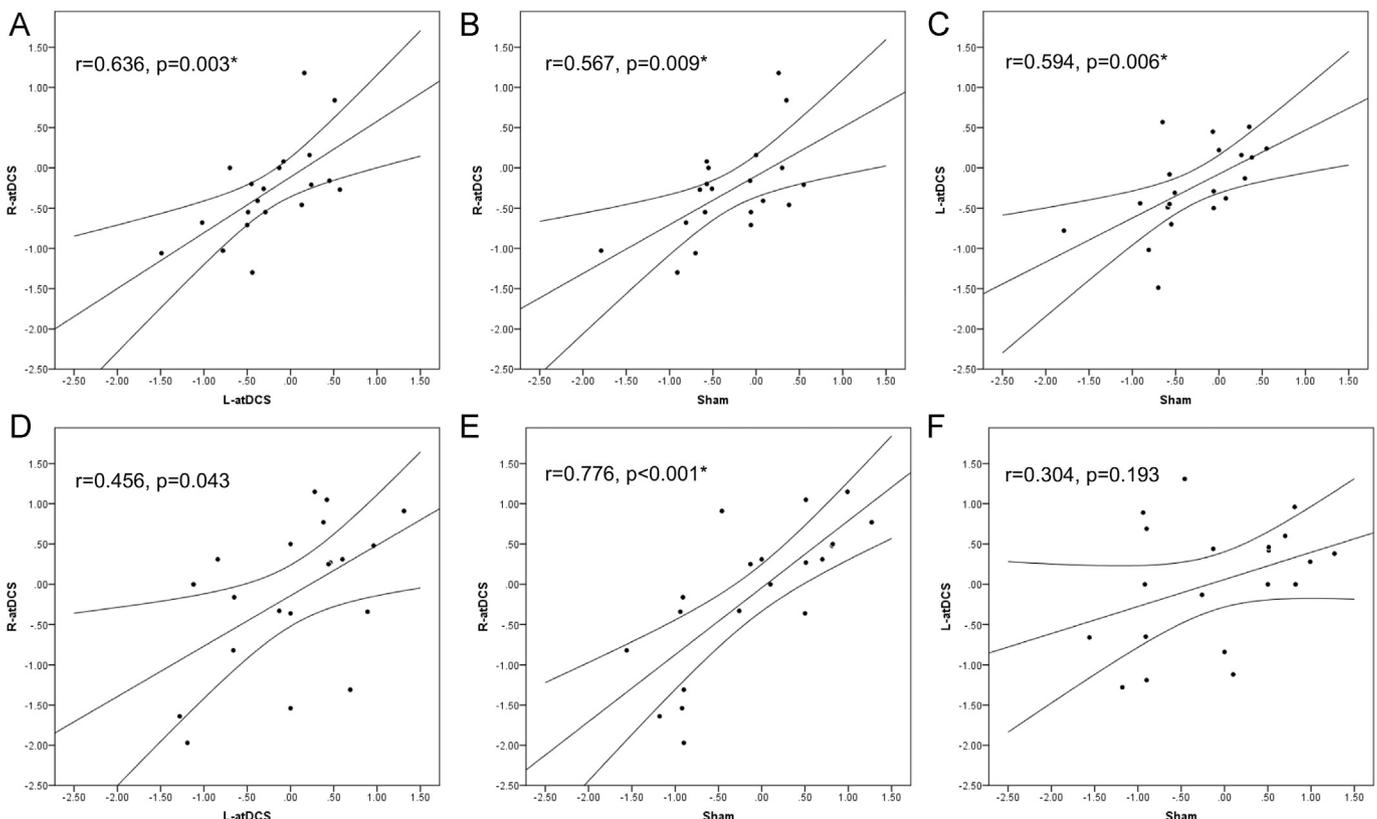


Fig. 3. Correlation plots of lateralised d' index (Left VF d' subtracted from Right VF d') at baseline (Block 1) over the 3 testing days. A–C: Young adults. D–F: Older adults. Young adults exhibit a stable bias across days, whereas the older group are less consistent. * Significant at $\alpha < 0.017$.

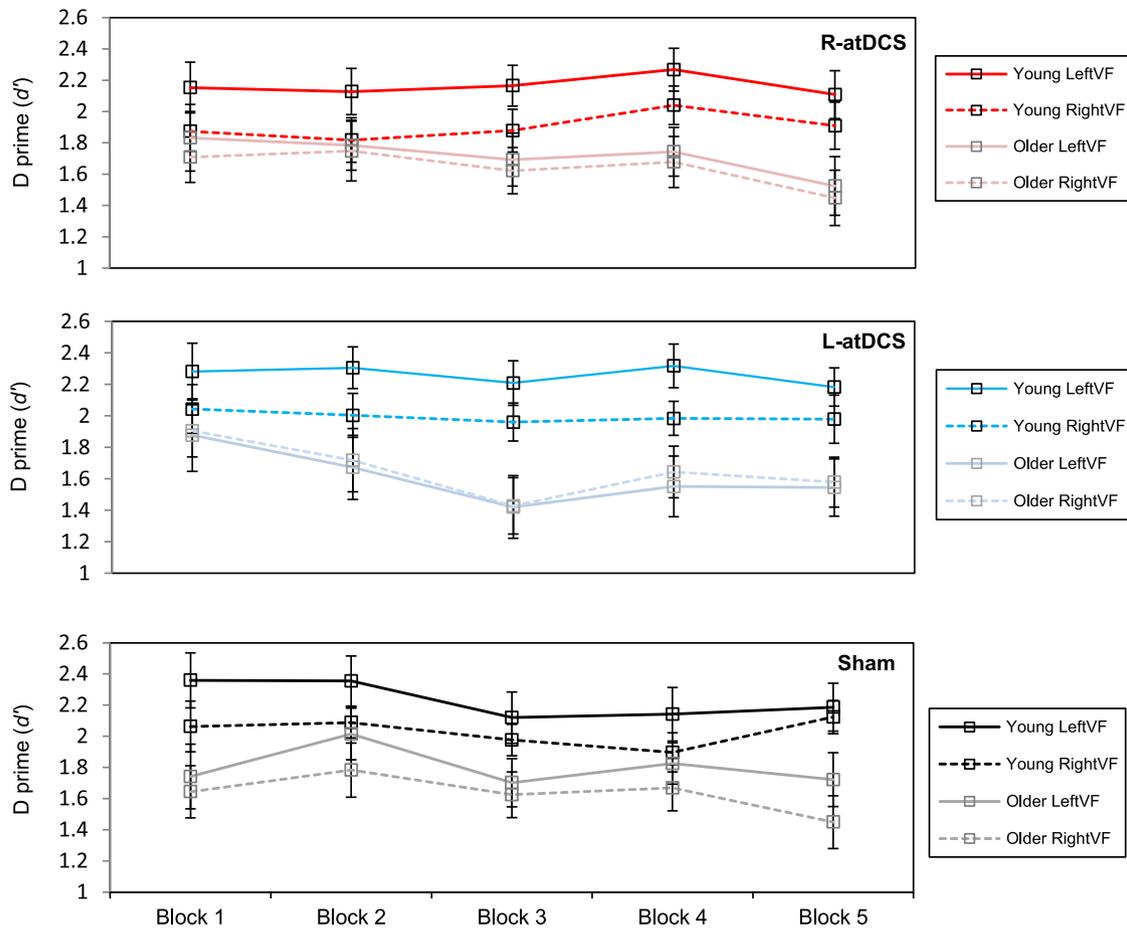


Fig. 4. d' Sensitivity scores for both visual fields (VFs) (left and right), across both AGE groups (Young and Older) and 3 STIMULATION conditions (R-atDCS, L-atDCS and Sham) (\pm standard error of the mean (SEM)).

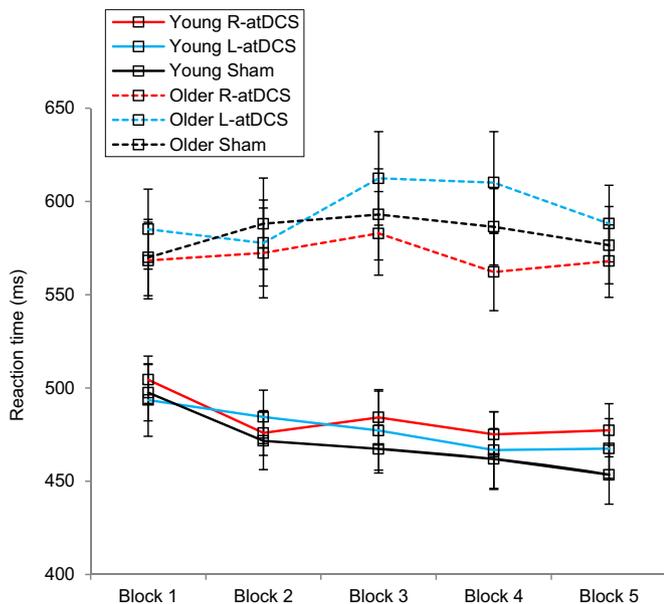


Fig. 5. Reaction times for correct trials (excluding RTs > 2 SD above the mean for each subject), averaged across both VFs (left and right), for both AGE groups (young and older) and 3 STIMULATION conditions (R-atDCS, L-atDCS and Sham) (\pm SEM).

adults displayed a significant leftward spatial attention bias at baseline (i.e. pseudoneglect) that was consistent across testing sessions. Older adults showed no bias towards either side and their lateralised sensitivity scores also showed inconsistency

across baseline blocks. Contrary to our predictions, there were no main effects of STIMULATION in either group on any of the measures (d' or RT) and also no interactions between STIMULATION and AGE or VF.

However, recently there has been increasing evidence that the 'traditional' anode-excitation/cathode-inhibition dichotomy may be an oversimplification of the mechanisms underpinning non-invasive brain stimulation. There exists a high variability of response to tDCS both between individuals and across multiple testing sessions (Horvath et al., 2014, 2015a, 2015b; Fricke et al., 2011; López-Alonso et al., 2014; Krause and Cohen Kadosh, 2014; Wiethoff et al., 2014). Multiple factors have been reported to influence the response to tDCS, for example task type (i.e. motor vs cognitive) (Jacobson et al., 2012; Vallar and Bolognini, 2011), task difficulty (Jones and Berryhill, 2012; Wu et al., 2014), motivation (Jones et al., 2014) and baseline activity within the targeted neural network (Antal et al., 2007; Benwell et al., (submitted for publication); Berryhill and Jones, 2012; Dockery et al., 2009). Importantly, distinct differences in response to tDCS have been reported that are dependent on task performance. Tseng et al. (2012) found that young adults who performed poorly at a visual short term memory task at baseline benefitted from 1.5 mA atDCS to the right PPC (P4) whereas good performers did not, and this may be linked to changes in pre-stimulus alpha activity (Hsu et al., 2014). This performance effect is supported in the aging literature (although in the opposite direction) by the finding that older adults with a high level of education improved on working memory tasks whereas those with lower educational attainment were impaired as a result of 1.5 mA atDCS (Berryhill and Jones, 2012). In the

present study, participants were therefore (rather than by age group) divided into 2 groups based on their peri-threshold pixel sizes (determined during the stimulus titration phase).

3.4. Baseline performance split

Twenty-one participants were relatively 'good' at the later-alised visual detection task reaching a 50% accuracy threshold at small pixel sizes (between $1 \times 2/2 \times 2$ and $2 \times 3/3 \times 3$ pixels) whereas the remaining 19 required larger pixels to meet the same level of accuracy ($3 \times 3/3 \times 4$ to $7 \times 8/8 \times 8$ pixels). Eighteen of the 'good' performers were young and 17 older adults comprised the 'poor' performance group. Thus, 3 older adults performed within the typical range for young adults whereas 2 young individuals performed relatively poorly.

3.4.1. Subjective alertness questionnaire: performance groups

The questionnaire data was re-analysed for differences in alertness and sensory experience between PERFORMANCE groups. Subjective alertness reduced throughout the experiment [TIME: $F(1,38)=90.4$, $p < 0.001$] and Poor performers reported higher levels of alertness overall [PERFORMANCE: $F(1,38)=5.047$, $p=0.031$] (Mean score *Good*=67.29 (SD=10.18); *Poor*=75.16 (SD=11.97)). No interactions were found.

3.4.2. Side-effects questionnaire: performance groups

Mann–Whitney U test found that side-effects were not experienced more strongly in either PERFORMANCE group (all p -values > 0.015 , adjusted $\alpha=0.003$). The groups did not differ in their ability to guess which session involved Sham tDCS (Pearson $\chi^2=0.819$, $p=0.366$).

3.4.3. Baseline sensitivity (d'): performance groups

There were no sensitivity differences between the two PERFORMANCE groups at baseline (3 STIMULATION \times 1 BLOCK \times 2 VF \times 2 PERFORMANCE). One-sample t -tests against zero using lateralised d' scores (Left VF d' subtracted from Right VF d') revealed that there were no group-level visuospatial attention biases towards either visual field in either of the 3 testing days. One of the 3 baseline lateralised d' score comparisons were correlated in *Good* performers [R-atDCS/L-atDCS: Spearman $r=0.342$, $p=0.129$; R-atDCS/Sham: $r=0.658$, $p=0.001$; L-atDCS/Sham: $r=0.282$, $p=0.216$] and 2 of 3 in the *Poor* performance group [R-atDCS/L-atDCS: Spearman $r=0.622$, $p=0.004$; R-atDCS/Sham: $r=0.785$, $p < 0.001$; L-atDCS/Sham: $r=0.473$, $p=0.041$, adjusted $\alpha=0.017$].

3.4.4. d' Sensitivity: performance groups

The full-factorial ANOVA_{MD} was repeated for d' and RTs, but including PERFORMANCE rather than AGE as a factor (3 STIMULATION \times 5 BLOCK \times 2 VF \times 2 PERFORMANCE). As in the previous analysis, detection sensitivity reduced across the 5 experimental BLOCKS [$F(4,152)=4.335$, $p=0.002$, $\eta^2=0.102$] but due to the titration phase which equated the task difficulty for each participant, there was no sensitivity difference between PERFORMANCE groups. Interestingly, a significant 3-way interaction involving STIMULATION \times BLOCK \times PERFORMANCE was revealed [$F(8,304)=2.316$, $p=0.02$, $\eta^2=0.057$] (Fig. 6).

Planned comparisons for the *Poor* performance group highlighted a sensitivity difference between L-atDCS (reduced sensitivity) and Sham as a function of block [STIMULATION (L-atDCS vs Sham) \times BLOCK: $F(4,72)=4.836$, $p=0.002$, $\eta^2=0.212$]. Further paired samples t -tests found that the sensitivity difference emerged between L-atDCS and Sham at the end of the stimulation period (Block 3) [$t(18)=-2.568$, $p=0.019$]. There was no difference between R-atDCS and Sham in the *Poor* performance group. The same comparisons for the *Good* performers highlighted a

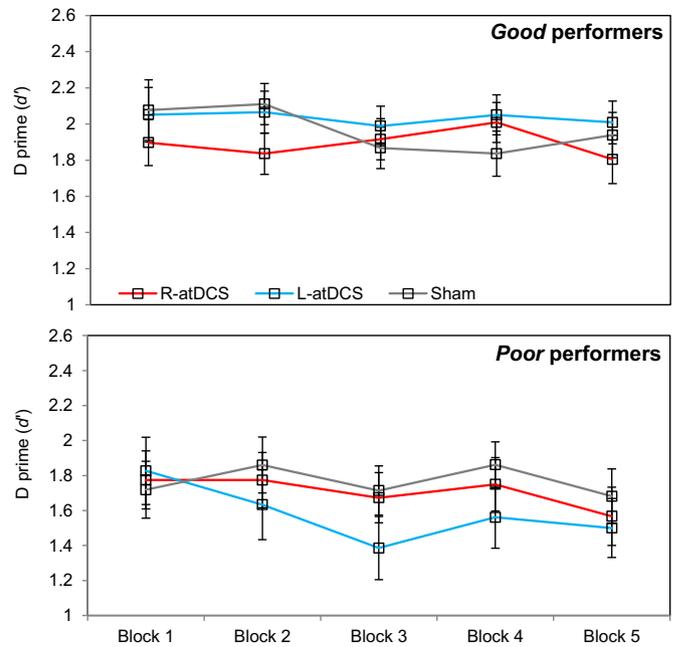


Fig. 6. d' Sensitivity scores averaged across both VFs (left and right), for both PERFORMANCE groups (*Good* and *Poor*) and 3 STIMULATION conditions (R-atDCS, L-atDCS and Sham) (\pm SEM).

difference between R-atDCS (enhanced sensitivity) and Sham as a function of block [STIMULATION (R-atDCS vs Sham) \times BLOCK [$F(4,80)=4.635$, $p=0.002$, $\eta^2=0.188$] but further paired samples tests did not reveal any specific significant differences between STIMULATION conditions in any of the 5 BLOCKS. L-atDCS did not elicit any differences compared to Sham in the *Good* performance group. Finally, comparing the L- and R-atDCS groups directly [STIMULATION (L-atDCS vs R-atDCS) \times BLOCK [$F(4, 152)=2.623$, $p=0.037$, $\eta^2=0.065$] showed again that the largest between-group difference appeared during Block 3 [$t(38)=2.273$, $p=0.029$]. In summary, whereas L-atDCS reduced sensitivity in *Poor* performers, R-atDCS seemed to maintain sensitivity in *Good* performers. These effects were most apparent during the end of the stimulation block (Block 3).

3.4.5. Reaction times (RTs): performance groups

Poor performers were generally slower than *Good* [PERFORMANCE: $F(1,38)=16.653$, $p < 0.001$, $\eta^2=0.305$] (Fig. 7) but mean response times decreased across the duration of the experiment [BLOCK: $F(4,152)=4.153$, $p=0.003$, $\eta^2=0.099$]. However these effects were modified by a significant interaction between PERFORMANCE \times BLOCK [$F(4,152)=4.506$, $p=0.002$, $\eta^2=0.106$]. Post hoc comparisons revealed that *Good* performers responded faster in Blocks 2, 4 and 5 relative to baseline (Block 1) (all p -values < 0.011 , adjusted $\alpha=0.0125$) whereas *Poor* performers maintained their baseline reaction time throughout the experiment. Finally, there was an interaction between STIMULATION and PERFORMANCE [$F(2,76)=3.968$, $p=0.023$, $\eta^2=0.095$] with *Poor* performers slower in response to L-atDCS compared to R-atDCS however this did not survive Bonferroni correction (paired comparisons R-atDCS vs L-atDCS: $t(18)=-2.343$, $p=0.031$; Sham vs L-atDCS: $t(18)=-2.043$, $p=0.056$, adjusted $\alpha=0.017$).

3.4.6. Bilateral errors: performance groups

Overall, *Poor* performers made more errors in response to bilateral trials than *Good* performers [PERFORMANCE: $F(1,38)=13.85$, $p=0.01$, $\eta^2=0.267$] (Mean *Poor*: 6.35, SD=1.89; *Good*: 9.43, SD=3.24) and there was an interaction between PERFORMANCE \times BLOCK group [F

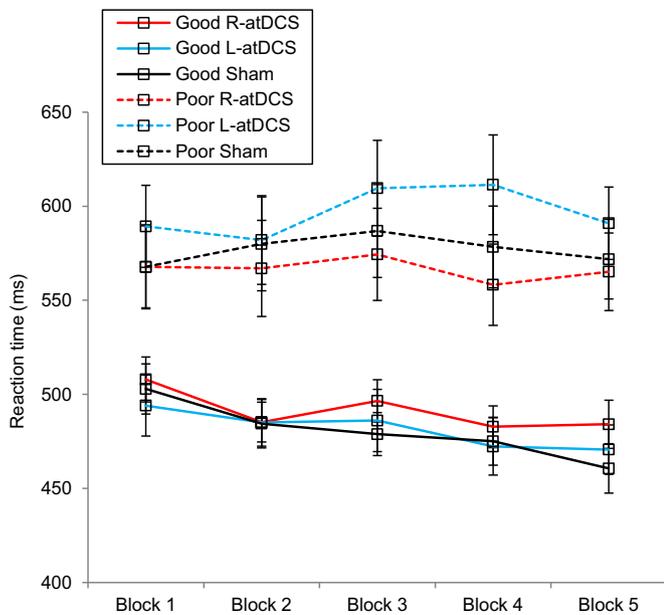


Fig. 7. Reaction times for correct trials (excluding RTs > 2 SD above the mean for each subject), averaged across both VFs (*left* and *right*), for both PERFORMANCE groups (*Good* and *Poor*) and 3 STIMULATION conditions (*R-atDCS*, *L-atDCS* and *Sham*) (\pm SEM).

(4,152) = 3.347, $p = 0.012$, $\eta^2 = 0.081$]: although *Poor* performers made more errors overall, they did not deteriorate over the course of the experiment. Conversely, *Good* performers made more errors by the end of the experiment (Block 5) when compared to the baseline (Block 1) [$t(20) = 3.41$, $p = 0.003$]. Bilateral error rates were not affected by STIMULATION condition.

4. General discussion

We predicted that left and right posterior parietal anodal tDCS would elicit sensitivity improvements in the visual field contralateral to the site of stimulation and that spatial attention might be differentially enhanced in young and older adults. However we did not succeed in improving either detection sensitivity or reaction time in either age group. Instead we describe a (subtle) state-dependent effect of tDCS that is consistent with previous findings (Antal et al., 2007; Benwell et al., (submitted for publication); Berryhill and Jones, 2012; Dockery et al., 2009). Only when participants were divided into *Good* and *Poor* task performers did we find significant differences between groups in response to tDCS. Sensitivity gradually deteriorated over time in both *Good* and *Poor* performers during the Sham condition, probably due to fatigue. *Poor* performers were further impaired when atDCS was applied to the left PPC. In contrast, *Good* performers maintained sensitivity in both visual fields as a result of anodal stimulation of the right PPC, highlighting the importance of considering baseline task performance when designing non-invasive brain stimulation protocols.

4.1. No effect of age in response to atDCS

Our prediction that atDCS would elicit distinct outcomes depending on the participant's age was founded on the premise that different neural populations may be recruited to execute spatial attention tasks in young vs older adults. In line with previous studies, we found a group-level, consistent leftward bias in young adults at baseline (pseudoneglect; Bowers and Heilman, 1980; see also Benwell et al., 2013b) whilst older adults showed no consistent preference towards either visual field. This behavioural

pattern reflects previous findings (Benwell et al., 2014; Failla et al., 2003; Fujii et al., 1995; Fukatsu et al., 1990; Jewell and McCourt, 2000; Nagamatsu et al., 2009, 2011, 2013; Schmitz and Peigneux, 2011; Stam and Bakker, 1990) and could indicate an age-related reduction of lateral asymmetry (i.e. the HAROLD model or the *accelerated aging* model). However, in the absence of strong functional imaging evidence with which to map age-related cortical reorganisation in the spatial attention domain, this premise remains speculative. It is also conceivable that a more extensive functional reorganisation had taken place in the older adults. The posterior–anterior shift in aging (PASA) model predicts that posterior regions become less active in older adults in favour of more frontal regions of the visuospatial attention network (Davis et al., 2008). If so, our choice of electrode placement over the posterior parietal cortex, on one side only, may have proved sub-optimal in targeting the more distributed brain regions that support lateralised spatial attention in the older group. Such a shift would not be observable in our lateralised detection task data and would therefore represent a potential focus of enquiry in future functional imaging studies.

4.2. State-dependent (performance) effects of tDCS

We must stress that the effects found here were small. We found sustained performance relative to Sham in the *Good* performers for the R-atDCS condition and reduced performance in the *Poor* task performers in response to L-atDCS compared to Sham. Reaction times also decreased over time but this variable did not interact with STIMULATION condition in the *Good* performers. The principal finding of this study—that baseline task performance determined the response to tDCS rather than age per se—is congruent with a growing body of research revealing state-dependent effects of non-invasive brain stimulation. Rather than exerting a homogeneous effect on each neuron underneath the electrodes and across individuals, it is likely that tDCS instead interacts with endogenous activity levels within target neuronal populations. This results in individualised effects of tDCS that are dependent on the pre-existing activation state of the targeted neurons (Antal et al., 2007; Dockery et al., 2009; Fertonani et al., 2014; Hsu et al., 2014; Tseng et al., 2012). We found that relative to the Sham protocol, the application of anodal stimulation to the right parietal cortex maintained stimulus detection sensitivity in the *Good* performance group. Given that there were no differences in the severity of sensory side-effects reported between the 'active' and Sham tDCS conditions, this sustained performance is unlikely to have been caused by a non-specific (i.e. sensory) effect of tDCS. Our results are compatible with the finding of Berryhill and Jones (2012) who elicited an improvement in working memory but only in older adults with high educational attainment, whereas those with a low educational background deteriorated. In both studies, it is plausible that the 'good' performers (i.e. the highly-educated, or individuals reaching threshold accuracy at small pixel sizes) shared a similar baseline state that determined whether neurons responded to non-invasive stimulation.

4.3. Left anodal tDCS impairs accuracy and RTs in Poor performers

Our principal finding was that for the left anode condition (atDCS applied to the left posterior parietal cortex) visual detection sensitivity was reduced in *Poor* performers across both visual fields. Reaction times were also increased, although this effect did not survive multiple comparison correction. Our initial aim was to achieve specific sensitivity improvements within each contralateral visual field, similar to the protocol of Sparing et al. (2009) (i.e. increased left VF sensitivity with R-atDCS and vice versa), but we did not successfully replicate these findings. In

direct contrast, anodal stimulation of the left parietal cortex resulted in an inhibitory rather than facilitatory effect across both sides of space for individuals with lower baseline performance. This decrement was most pronounced near the end of the stimulation period, when the effects of tDCS have been shown to be strongest (Nitsche and Paulus, 2000, 2001; Sparing et al., 2009; Stagg and Nitsche, 2011). These results can be explained most effectively by an interhemispheric competition account of visuospatial attention. Whilst the left cerebral hemisphere directs attention exclusively towards the right side of space, the dominant right hemisphere directs attention to both the left and right sides (Bisiach and Vallar, 2000; Kinsbourne, 1977, 1994; Mesulam, 2002; Szczepanski et al., 2010). In this case, the *Poor* performers may have been disproportionately affected by a disruption to the balance of activity between the left and right hemispheres. Whereas the *Good* performers (who were likely to have utilised the right hemisphere more optimally, given their superior performance), were somewhat resistant to this increase in the left PPC, this may have impacted negatively on individuals who were already less efficient at the task.

4.4. R-atDCS maintains sensitivity across both VFs in good performers.

The model of competing interhemispheric attention mechanisms may also explain the subtle finding of maintained task sensitivity in *Good* performers. If, as predicted, the *Good* task performers exhibited a more optimal engagement of the dominant right PPC at baseline, then the right hemisphere may have been more amenable to the effects of tDCS than the less dominant left PPC, thus resulting in the observed maintenance of performance after right but not left anodal tDCS. In line with this, previous research has indicated that tDCS elicits greater effects when the underlying target neuronal populations are actively engaged in a task (Antal et al., 2007; Dockery et al., 2009; Miniussi et al., 2013) which may have been the case for right-hemisphere neurons for this task.

However, like the effects found in the *Poor* performance group, the behavioural pattern in the *Good* performers is still different from the findings of Sparing et al. (2009): neither visual field was unilaterally improved (nor inhibited) by atDCS. However, rather than placing the return electrode on the vertex (Cz) to constrain the current flow around the parietal region as in the protocol of Sparing et al. (2009) we chose instead to place the cathode on the forehead contralateral to the site of anodal stimulation. This montage has been used successfully to modulate neural activity in patients with hemispatial neglect (Ko et al., 2008; Sunwoo et al., 2013) and is similar to standard electrode placements used within the motor domain (e.g. Antal et al., 2007; Nitsche and Paulus, 2001; Priori, 2003). This PPC-contralateral supraorbital placement may have diffused the current into more distant frontal regions within the opposite hemisphere. As a result, a less focal effect of tDCS may have been generated, which could have resulted in a general maintenance of alertness, rather than targeting neurons that are specifically responsible for the lateral orientation of attention.

4.5. Limitations of our study

Our interpretation may still represent a rather simplistic view of tDCS mechanisms, since the application of non-invasive brain stimulation in older populations must also take into account age-related differences in the plasticity of the neural system. It has recently been reported that compared to young adults, older people exhibit a delayed response to anodal tDCS within the motor domain. Peak neural excitability was reported to occur immediately post-tDCS in young adults but was delayed until 30 min

after stimulation in older adults (Fujiyama et al., 2014). We may therefore have ended the testing session too soon after tDCS to identify any improvements in the older group and could also potentially derive greater and more lasting improvements with multiple stimulation sessions.

Finally, it is possible that in addition to state-dependent performance effects, anodal tDCS did indeed exert a differential effect in young and older adults yet this may have been somewhat diluted by within-group heterogeneity. As described above, the *Poor* performance group we report here consisted predominantly of older adults and *Good* performers were mostly young. Three older adults performed well enough to be reassigned into the *Good* performance group and 2 young adults performed at a *Poor* level. We acknowledge that the sensitivity effects reported here are small and that this reflects a wider debate surrounding the efficacy of transcranial electrical stimulation (e.g. Horvath et al., 2014, 2015a, 2015b; Walsh, 2013). Nevertheless, these considerations give rise to questions that would be of interest to the spatial attention and brain stimulation communities: do highly-performing older adults display different patterns of cortical activity compared to poorly-performing age-matched individuals in attention tasks? Likewise, are there distinct patterns of activity in young adults with good task performance compared to less able young people? Further neuroimaging studies would assist in answering these questions and, importantly, would map the extent and role of functional reorganisation for visuospatial attention in older adults. In turn, this is likely to foster a more targeted (and thus more successful) approach to improving spatial attention in the elderly using non-invasive brain stimulation.

5. Conclusions

Here we provide further evidence that the 'standard' anode-excitation/cathode-inhibition effects of tDCS do not apply uniformly across the population. The response to tDCS in this study was state-dependent: influenced by an individual's baseline task performance, whereas age did not differentially affect response to tDCS per se. *Good* task performers benefitted from anodal stimulation of the right PPC, perhaps by interacting with an already optimally-functioning attention network. Most importantly, *Poor* task performers were actively impaired by atDCS to the left PPC. This suggests the need for caution in applying tDCS in an undifferentiated manner across individuals. Indeed, we have found reversed effects in the group who would clearly benefit most from an improvement in their visuospatial attention function (i.e. those who performed worse at baseline). This highlights the importance of considering baseline performance in the application of non-invasive stimulation, particularly when aiming to improve performance in older adults. This caution may also apply more generally to tDCS stimulation in the older population, as the *Poor* performers consisted largely (if not exclusively) of this age group.

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