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Original Article

ORIGINAL ARTICLE

Plasticity of the Right-Lateralized Cognitive Reserve Network in Ageing

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Abstract

Cognitive reserve (CR) is the phenomenon where older adults with more cognitively stimulating environments show less age-related cognitive decline. The right-lateralized fronto-parietal network has been proposed to significantly contribute to CR and visual attention in ageing. In this study we tested whether plasticity of this network may be harnessed in ageing.

We assessed CR and parameters of visual attention capacity in older adults. Transcranial direct current stimulation (tDCS) was employed to increase right fronto-parietal activity during a lateralized whole-report task. At baseline, older adults with greater CR showed a stronger hemifield asymmetry in processing speed towards the left visual-field, indicative of stronger involvement of the right hemisphere in these individuals. Correspondingly, processing speed improved during right prefrontal tDCS. Older adults with lower levels of CR showed tDCS-related improvements in processing speed in the left but not right hemifield: thus tDCS temporarily altered their processing speed asymmetry to resemble that of their high reserve peers.

The finding that stronger right hemisphere involvement is related to CR supports Robertson's theory. Furthermore, preserved plasticity within the right prefrontal cortex in older adults suggests this is a viable target area to improve visual processing speed, a hallmark of age-related decline.

Key words: ageing, cognitive reserve, plasticity, transcranial direct current stimulation, visual attention

Introduction

Many cognitive functions decline naturally as we age, and certain pathological ageing conditions, such as Alzheimer's Disease (AD), result in steeper declines and severe levels of cognitive impairment (2013). More cognitively stimulating environments, as measured for example via educational attainment, occupational complexity, or social engagement, are associated with less age-related cognitive decline and less clinical symptomology in a range of conditions including AD and Stroke, given the degree of neuropathology in the brain (Bowers and Heilman 1980; Nicholls et al. 1999; Voyer et al. 2012). This neuroprotective effect of an enriched environment was first termed cognitive reserve (CR) (Stern et al. 1992), and is an important variable to aid our understanding of the large inter-individual differences in rates of cognitive decline in ageing. Exploring the neural underpinnings of CR is central to understanding processes of plasticity in the ageing brain, these being of utmost importance for optimizing preventions against cognitive decline and interventions to improve cognitive performance in both healthy and pathological ageing.

In the first neuroscientific theory of CR, Robertson (2013) proposed that CR develops through repeated norepinephrine (noradrenaline) activation over a lifetime. Given norepinephrine's privileged relationship with right fronto-parietal networks (FPNs) underpinning arousal, novelty, sustained attention, working memory and self-monitoring processes, a pre-eminent role for these networks in CR is posited (Robertson 2014). Specifically, the continuous engagement of the core cognitive processes supported by the FPN is assumed to strengthen these networks, thereby cultivating greater levels of CR (Fig. 1).

It is well-established that hemisphere asymmetries observed in younger adults during many cognitive operations, including visual attention, become more balanced with age, particularly within the prefrontal cortex (PFC) (Reuter-Lorenz et al. 2000; Cabeza 2002a; Cabeza 2004). However, it is still unclear whether this pattern is due to a more bilateralized activation of the 2 hemispheres (Cabeza 2002b), or a more pronounced unilateral decline of the right hemisphere (Brown and Jaffe 1975). The functional implications of hemisphere asymmetries may be better understood by taking inter-individual differences in CR into account. Specifically, changes in hemispheric asymmetries reported in previous studies may, at least partly, result from stronger activation of the right FPN in older adults with higher levels of CR (Fig. 1).

A hallmark of ageing, closely related to functional and structural changes of the FPN, is a decline in visual attention capacity (Madden et al. 2007; Kerchner et al. 2012). Of particular interest is the speed at which visual information is processed, which is associated with functional impairments experienced by older adults in everyday life (Wood and Owsley 2014), and is increasingly considered a promising biomarker for cognitive decline (Ritchie et al. 2014). Similarly, visual short-term storage capacity, the amount of information that can be perceived at one moment in time and will be available for conscious processing, decreases with age (Sander and Werkle-Bergner 2011; McAvinue et al. 2012; Espeseth et al. 2014).

As with many cognitive processes, visual attention capacity does not decline at the same rate, even in healthy aging (McAvinue et al. 2012; Wiegand et al. 2014). Accumulating evidence suggests that individuals brains' differ in their potential

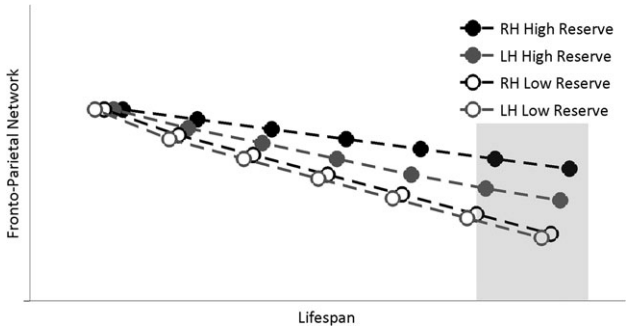

Figure 1. Visualization of Robertson's Neuroscientific Model of CR. Robertson (2013) proposed that CR develops through repeated noradrenaline activation over a lifetime. Given noradrenaline's privileged relationship with right FPN underpinning cognitive operations such as arousal, novelty, and sustained attention, a distinguished role for this network in CR is posited (Robertson 2014). Specifically, throughout a lifetime (X-axis) the continuous engagement of the core cognitive processes supported by the right FPN is assumed to strengthen these networks (Y-axis), thereby cultivating greater levels of CR. In the current study we address whether this network maintains preserved levels of plasticity in later years (shaded in gray) by increasing excitability of the right prefrontal cortex and assessing the effects on aspects of attention. RH denotes right hemisphere, LH denotes left hemisphere.

to compensate for a reduced capacity of early sensory regions to process visual information by increasing recruitment of prefrontal areas (Cabeza 2004; Davis et al. 2008). Recent work combining electrophysiological recordings with the parametric assessment of visual attention based on the formal Theory of Visual Attention (TVA) (Bundesen 1990) in ageing has shown differential involvement of the FPN in older adults with high visual processing speed and high storage capacity, relative to their lower performing peers (Wiegand et al. 2014). Whether the right FPN can be targeted to increase parameters of visual attention capacity in ageing, and whether the visual attention system is mediated by CR remains unexplored.

The current study utilizes TVA to investigate the relationship between distinct aspects of visual attention capacity, hemisphere asymmetries, and CR in ageing. The parameters processing speed *C*, and storage capacity *K* were modeled mathematically independent of each other for each individual, based on performance in a lateralized whole-report paradigm (Duncan et al. 1999a), which permits *C* and *K* to be computed separately for the left and right visual hemifields. Given that visual input elicits strongest activity in the contralateral cortical hemisphere (Heinze et al. 1994; Mangun et al. 1998; Schiffer et al. 2004), this approach provides a psychophysical measure of hemisphere asymmetries in visual attention processes in the older adults.

A question of pressing interest is whether the networks underpinning CR show plasticity in the aging brain, so that reserve may be cultivated later in life. To test this, we employed transcranial direct current stimulation (tDCS) during the whole-report task to increase neuronal excitability in a causal manner. We targeted the right-lateralized FPN to explore 1) whether plasticity of the right FPN can be harnessed in ageing to enhance visual attention and 2) whether this plasticity is related to individuals' levels of CR. We explored this separately for processing speed *C* and storage capacity *K*, to test whether the mechanisms in the FPN underlying these 2 functions could be targeted separately, supporting the distinctiveness of these 2 aspects of visual attention in ageing.

Materials and Methods

Participants

A total of 31 older adults aged between 65 and 85 (M = 71.55, SD = 5.43) completed the current study. All participants were right handed, had no history of neurological illness and no personal or family history of seizures. This study was approved by the Trinity College Dublin School of Psychology Ethics Committee, and written consent was obtained prior to the study.

Study Procedure

Participants in the study attended 4 testing sessions. During the initial test session participants were screened for cognitive impairment using the Montreal Cognitive Assessment (MoCA), and a neuropsychological battery and CR assessment were administered (described below). All participants were familiarized with the TVA task during this first session, and individual exposure durations were identified by a calibration procedure (described below). This was to ensure that each individual's exposure duration spanned from close to their perceptual thresholds to a duration that allowed the participant enough time to reach their full storage capacity, thereby allowing for accurate modeling of the TVA parameters. Following this session, all cognitive healthy older adults (scoring ≥ 23 on the MoCA) were invited to attend 3 TVA-tDCS sessions, where they

received right prefrontal, right parietal, and sham stimulation in a pseudo-random, counter-balanced order.

The Theory of Visual Attention

TVA Whole-Report Task. In each of the 3 TVA-tDCS sessions, participants completed a TVA whole-report experiment divided into 10 blocks, each lasting approximately 3 min (Fig. 2). The task was to verbally report as many letters as possible from a briefly presented letter array. In masked trials, the display was terminated by pattern masks presented for 900 ms on all possible stimulus positions. In unmasked trials, a blank screen with the fixation dot was presented instead. A question mark then appeared on the screen, which indicated to the participants to verbally report the letters seen. The letters could be reported in any order and without any emphasis on speed, and were entered by the experimenter.

Participants were sitting in a comfortable chair with a distance of 47 cm to the screen. The experiment was run on a HP Compaq dc5750 Microtower computer with a 100 Hz refresh rate. The stimuli were arranged in a circle around a fixation dot. Participants were instructed to fixate the dot throughout the whole trial. On each trial, 4 grey letters (Arial font bold) were presented briefly either on the left or right side of a fixation dot. The letters of a given trial were randomly chosen, without replacement, from a pre-specified set (ABDEFGHJKLMNOPRSTVXZ). Four isoluminant scrambled filler grey letters were always presented in the opposite hemifield in order to balance sensory stimulation in the 2 hemifields.

At the beginning of each block, participants were informed about whether letters would be presented in the left or right hemifield. The side on which the letters were presented was constant within one block and systematically alternated between blocks (Cooreman et al. 2015). Participants were instructed to report letters they were "fairly certain" to have seen and refrain from pure guessing. To control for the level of guessing, a feedback was displayed after each block showing the accuracy of the reported letters (i.e., the percentage of correct answers out of all given answers) and participants were advised to adhere to a level of 80–90% correctly reported letters.

Both masked and unmasked letter displays were presented, resulting in 7 different effective exposure durations, which were individually determined in a pre-test (see below). Owing to visual persistence, exposure durations are effectively prolonged in unmasked- compared to masked-array conditions (Sperling 1960). The variation in exposure durations was intended to generate a broad range of performance, specifying the whole probability distribution of the number of correctly reported elements as a function of the effective exposure duration. The whole-report experiment contained 15 trials of each condition (5 masked and 2 unmasked display conditions for both left and right hemifields), resulting in a total amount of 210 trials. Conditions were balanced across blocks and each participant was presented with the same displays in random order, balanced across blocks.

During the initial testing session, participants performed a pre-test to familiarize them with the task and determine the individual distribution of exposure durations. Four practice blocks consisting of 12 trials each were run. As in the experiment, blocks with letters presented in the left and right hemifield alternated. In the practice blocks, 3 trial types were randomly intermixed: 2 "easy" practice trial types with relatively long exposure durations (one 250 ms masked display, and one 200 ms unmasked display) and a calibration trial type to determine the individual lowest exposure duration. Calibration trials always had masked displays and constituted 2/3 of the trials (32 trials) in the practice session. The initial exposure duration of the calibration trials was set to 100 ms. When the participant reported one or more letter correctly in a pair of calibration trials, the exposure duration was lowered 10 ms. If no letter was reported correctly in a pair of calibration trials and an adjustment of exposure duration was just made on the basis of the previous pair of calibration trials, the exposure duration remained. If no letter was reported correctly in a pair of calibration trials and no adjustment of exposure duration was just made on the basis of the previous pair of calibration trials, the exposure duration was increased for 10 ms. The final lowest exposure duration for both masked and unmasked displays was chosen 10 ms lower than the lowest exposure durations determined in the calibration procedure. The final lowest exposure duration could not be less than 10 ms or higher than 200 ms. The long exposure duration for the unmasked displays was always 200 ms. The remaining 4 exposure durations for the masked displays were chosen such that they were equally spaced on a logarithmic scale starting from the final lowest exposure duration to a maximal exposure duration of 190 ms + the final lowest exposure duration. (e.g., if the final lowest exposure duration was found to be 10 ms then 10, 20, 40, 90, and 200 ms were used as exposure duration for the masked displays, whereas 10 and 200 ms were used for the unmasked displays).

TVA Parameter Estimation. Individual parameter estimates for the left and right hemifield were derived separately by using a maximum likelihood procedure described in detail by Dyrholm et al. (2011). Based on the basic equations of TVA (Bundesen 1990; Bundesen et al. 2005; Kyllingsbæk 2006) a participant's accuracy of letter reporting was modeled by an exponential

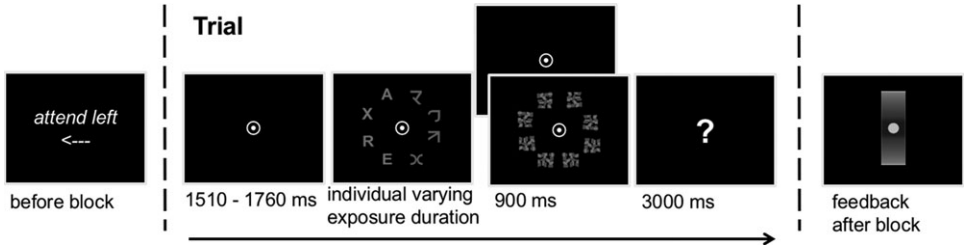

Figure 2. TVA whole-report task. Experimental procedures used for TVA parameter assessment. Four equidistant letters arranged in a half circle were presented in grey, on the left or right side of the display and 5 isoluminant scrambled filler grey letters were always presented in the opposite hemifield. Participants were informed before the beginning of the blocks whether the letters would appear to the right or left. Letters were presented at 5 different individually adapted exposure durations. Feedback was presented visually after each block, and participants were advised to maintain accuracy levels between 80% and 90%, which was visualized as a central green ball in a colored bar; performance below and above this range was visualized as a yellow ball below and above the center of the bar, respectively.

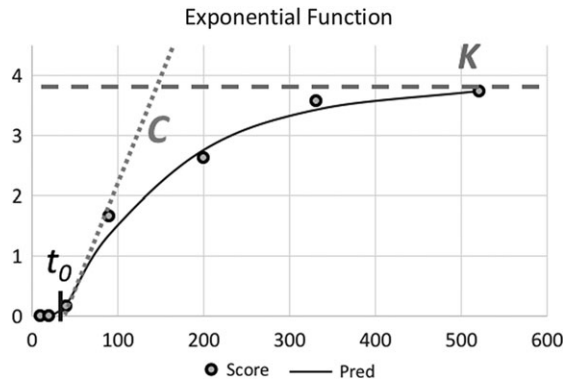

Figure 3. Schematic of the distribution resulting from the TVA modeling procedure. Here parameter t_0 represents the minimal effective exposure duration (in ms), below which information uptake from the display is assumed to be zero. Parameter *C* represents the speed at which items can be processed and is illustrated as the slope of the curve at t_0. Parameter *K* represents storage capacity of vSTM and is illustrated as the asymptotic level of the curve.

growth function as a function of the effective exposure duration (Fig. 3). The function is defined by 4 parameters: 1) parameter *C*, the visual processing speed (elements processed per second); 2) parameter *K*, the storage capacity (maximum number of elements in visual short term memory (vSTM)); 3) parameter t_0, the minimal effective exposure duration (in ms), below which information uptake from the display is assumed to be zero; and 4) parameter μ, the persistence of the iconic memory trace (in ms) in unmasked conditions. The model fitted to the data from each hemifield had 6 degrees of freedom (df): *K*, 3 df (the *K* value reported is the expected *K* given a particular distribution of the probability that on a given trial $K = 1, 2, 3,$ or 4); t_0, 1 df; *C*, 1 df; μ, 1 df. Items were presented at a variety of exposure durations, controlled with a mask (Fig. 2) For those participants whose t0 was fit below 0, the data were re-fitted again fixing t0 to 0. In the present study, parameters t_0 and μ were estimated to obtain valid estimates of the 2 parameters of main interest, *C* and *K*, and will not be discussed.

Assessment of Hemifield Asymmetries in Visual Attention Capacities. To measure the differences in visual attention capacity between hemifields, we modeled the data separately for trials with letters presented in the left and right hemifield (Duncan et al., 1999b). The difference in parameters for right and left hemifields was compared for each parameter separately using paired-samples *t*-tests. In order to explore the hemifield asymmetries in visual attention capacity, laterality indices were computed for both *C* (C_λ) and *K* (K_λ) as the ratio $C_{left}/(C_{left}–C_{right})$ and $K_{left}/(K_{left}–K_{right})$, respectively. Accordingly, an index of 0.5 would indicate balanced processing, an index > 0.5 would denote a leftward processing asymmetry, and an index < 0.5 would denote a rightward processing asymmetry. Overall visual attention capacity for the *C* and *K* parameters were calculated as the average of $C_{left}–C_{right}$ and $K_{left}–K_{right}$, respectively.

CR and Neuropsychological Assessment

During the initial testing session, the following neuropsychological test battery was administered to all participants. The Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) was included as a standardized cognitive screening for age-related cognitive decline. The Cognitive Failures Questionnaire (CFQ) (Broadbent et al. 1982) a self-report measure of everyday absent-mindedness and attentional failures was administered to participants. This was complemented by an informant report of the CFQ, completed by a partner or relative of the participant in order to create a discrepancy score (CFQ-D) to assess the participants' awareness of absent-mindedness and attentional failures (e.g., as used by Harty et al. 2013). Levels of premorbid intelligence were assessed via the National Adult Reading Test (NART (Nelson 1982)). Finally, CR was measured using the CR Index questionnaire (CRIq (Nucci et al. 2012)). This is a validated measure of day-to-day engagements which may contribute to an increased CR with age. The index is comprised of the 3 subscales measuring educational attainment, professional complexity, and leisure activities.

tDCS Targeting the Right Hemisphere

TDCS was employed to increase excitability of prefrontal and parietal regions of the right hemisphere in a single-blind sham controlled, within-subject crossover design. Each participant attended 3 stimulation sessions. Stimulation was administered using a battery-driven DC Brain Stimulator Plus (NeuroConn) with two 5 × 7 cm electrodes used with high-chloride electroencephalography (EEG) gel (Abralyt HiCl, EasyCap). Electrodes were placed according to the 10–20 international EEG system (NA 1991) and kept in place using an EEG cap (Bio-Semi). Stimulation targeting the right prefrontal and right parietal cortical regions was delivered with the center of the anodal electrodes placed over F4 and P4, respectively. The position of the anode was alternated between F4 and P4 across participants during sham stimulation. In all conditions, the cathodal electrode was placed over Cz (vertex).

During active stimulation, 1 mA of tDCS was delivered continuously during the performance of each block, with a ramp-up/ramp-down period of 20 s, resulting in a current density of 0.02857 mA/cm2 at the scalp. During sham stimulation, tDCS was administered at 1 mA for 15 s at the beginning of each block with ramp-up/ramp-down periods of 20 s. This is a commonly used sham procedure to ensure that the sensations regularly experienced during the onset of tDCS are kept constant during real and sham sessions (Gandiga et al. 2006). At the end of both testing sessions, participants were asked to rate the sensations experienced during stimulation using a 5-point likert scale questionnaire for 8 separate sensations (e.g., itchiness, pain, pinching see Fertonani et al. 2010). Please note this questionnaire was added to the study design half way through testing, therefore only $N = 18$ participants completed this questionnaire. The results of the sensations questionnaire were assessed with repeated measures ANOVAS with "Stimulation" (Prefrontal, Parietal, Sham) as a within-subject factor and revealed no differences in the sensations experienced between sham, prefrontal, and parietal tDCS (all $P > 0.05$).

Statistical Analysis

(a) CR analysis. In order to rule out the confound of age on levels of CR (Nucci et al. 2012), participants were classified to their corresponding age class using the computational approach described by Nucci and colleagues. Three linear models were used where the raw scores of the 3 subscores (CRI-*Education*, CRI-*WorkingActivity*, CRI-*LeisureTime*) were set as dependent variables, with age as the independent (or predictor) variable. The 3 CRIq subscores were the residuals of the relative linear models, standardized and transposed to a scale with $M = 100$ and $SD = 15$. This allowed all participants to be systematically classified according to their corresponding age class. Lastly, the total CRI score (CRIq) was the average of the 3 subscores, again

standardized and transposed to a scale with $M = 100$ and $SD = 15$. The higher the CRIq score, the higher the estimated CR.

To examine the baseline relationship between CR and the parameters of visual attention capacity and asymmetry, data from the sham stimulation session were utilized. In order to test relationship between CR and the distinct visual attention indices described above, an across-participant linear regression analysis was conducted (2-tailed Pearson's product–moment correlations) between the CRIq and TVA parameters of interest (C, C_λ, K and K_λ), Bonferroni corrected for multiple comparisons. In order to verify the specificity of any associations between TVA parameters and CR, significant correlations were followed up with a partial correlation analysis, controlling for the parameter of disinterest (i.e., relationship between C_λ and CR was assessed controlling for K_λ). In the text all reported mean values are followed by standard error (i.e., $M \pm SE$).

(b) TVA-FPN stimulation analysis. The effects of right prefrontal and right parietal stimulation on the TVA parameters were assessed using repeated measures ANOVAs with "Stimulation" (Prefrontal, Parietal, Sham) and "Hemifield" (Right, Left) as within-subject factors. Significant main effects and interaction effects were followed up with simple effects analyses. All statistical analyses were performed using SPSS Statistics v21.0.0.1 (IBM) and all figures were designed using customized scripts in MATLAB R2014a 8.3.0.532 (Mathworks, Natick, MA, USA). In all figures, the error bars indicate the standard error of the mean. In the text all reported mean values are followed by standard error (i.e., $M \pm SE$).

To further elucidate the relationship between stimulating the right PFC and improvements in processing speed in ageing, the following follow-up analyses were employed; an across-participant linear regression analysis (2-tailed Pearson's product–moment correlations) was conducted between the changes in C parameter during tDCS and (a) levels of CR (CRIq) and (b) baseline hemifield processing asymmetries (C_λ). Indices of the tDCS-related change of the C parameter were calculated as the difference between real and sham tDCS for each hemifield separately (e.g., $\Delta C_{\text{prefrontal right hemifield}} = [C_{\text{prefrontal right hemifield}} - C_{\text{sham right hemifield}}]$). As there was no significant main effect of stimulation for the K parameter, no follow-up analyses were performed.

Results

Demographic and Neuropsychological Profile

A total of 31 cognitively healthy (≥ 23 of the MoCA) older adults completed the 4 testing sessions (see Table 1 for neuropsychological profiling and demographic information). As expected, the CR index questionnaire (CRIq) was strongly associated with the number formal years in education ($r = 0.70$, $P < 0.0005$), and premorbid intelligence as estimated from the NART ($r = 0.38$, $P = 0.04$). Interestingly, the CRIq was correlated with the CFQ-D ($r = 0.47$, $P = 0.01$) such that lower levels of reserve were associated with less awareness of everyday lapses in attentional control (relative to informant reports). The CRIq was not significantly correlated with scores on the MoCA in this healthy older sample ($r = 0.28$, $P = 0.13$).

CR and Visual Attention

Relationship Between Processing Speed and CR

The mean processing speed for the older adults in the current sample was 18.65 (±1.69) items per second (Table 2). There was no significant difference between processing speed for items in the right ($M = 19.08 \pm 1.74$) versus left hemifield ($M = 18.21 \pm 1.87$; $t(30) = 0.7$, $P = 0.49$). CR (CRIq) was not related to overall processing speed capacity (C; $r = 0.04$, $P = 0.83$). However, a leftward processing asymmetry was predicted by higher levels of CR, as indicated by a positive relationship between the C_λ and CRIq ($r = 0.52$, $P = 0.003$; Fig. 4). This relationship remained significant when controlling for K_λ via a partial correlation ($r = 0.49$, $P = 0.024$).

Relationship Between Storage Capacity and CR

The mean storage capacity for the current ageing sample was 2.42 (±0.57), as estimated from the K parameter (Table 2). There was a trend for higher storage capacity for items in the right ($M = 2.48 \pm 0.11$) versus left hemifield ($M = 2.35 \pm 0.11$). However this failed to reach conventional levels of significance ($t(30) = 1.93$, $P = 0.06$). There was no relationship between the CRIq and overall storage capacity (K; $r = 0.28$, $P = 0.19$), or the degree of hemifield asymmetry in storage capacity (K_λ; $r = -0.2$, $P = 0.29$).

The Effects of tDCS to the Right FPN for each TVA Parameter

Processing Speed C

There was a significant main effect of Stimulation on processing speed ($F_{2,60} = 4.02$, $P = 0.023$, $\eta_p^2 = 0.21$, Fig. 5). Participants were significantly faster at processing visual information during right prefrontal stimulation ($M = 20.60 \pm 1.76$), in comparison to right parietal ($M = 17.47 \pm 1.41$, $P = 0.01$) and sham stimulation ($M = 18.65 \pm 1.69$, $P = 0.05$, Fig. 5). There was no difference between processing speed during right parietal stimulation

Table 1 Demographic and Cognitive Characteristics of the Sample. MoCA denotes Montreal Cognitive Assessment (Nasreddine et al. 2005), a validated cognitive screening tool. PFS IQ denotes predicted full scale IQ as estimated from the National Adult Reading test (NART) (Nelson 1982), a measure of premorbid intelligence. CFQ-D denotes Cognitive Failures Questionnaire Discrepancy Score, the difference between the self (CFQ) and informant (CFQ-other) report of everyday lapses in attention (Broadbent et al. 1982)

Participants ($N = 31$)					
Education					
Age (years)	MoCA	(years)	PFS IQ[a]	CFQ-D[a]	CRIq
71.55 (5.43)	26.97 (1.62)	16.00 (3.58)	121.45 (3.84)	10.94 (17.36)	128.19 (15.68)

[a]Note: Calculation based on $N = 29$ as 2 informant reports and 2 NART questionnaires were not returned/completed. CRIq denotes the total score of the CR Index questionnaire (Nucci et al. 2012).
Values denote mean and standard deviations, M (SD).

Table 2 TVA parameters (processing speed C and storage capacity K) and laterality indices during sham stimulation

TVA parameters				
	C	C_λ	K	K_λ
Mean	18.65	0.48	2.42	0.49
SD	9.43	0.09	0.57	0.04
Range	6.82–54.41	0.29–0.70	1.26–3.53	0.42–0.56

λ denotes laterality indices as described in text. SD denotes standard deviation.

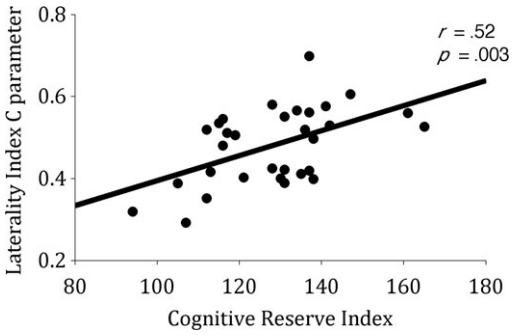

Figure 4. The relationship between Processing Speed Hemifield Asymmetry and CR. Y-axis denotes the Laterality index (C_λ), whereby values greater than 0.5 indicate a leftward asymmetry. X-axis denotes the CR Index questionnaire (CRIq) where greater values indicate higher levels of CR.

relative to sham ($P = 0.33$). Regardless of stimulation, there was no difference in processing speed for items in the right ($M = 19.75 \pm 1.78$) versus left hemifield ($M = 18.06 \pm 1.37$), as evidenced by a non-significant main effect of Hemifield ($F_{1,30} = 2.47$, $P = 0.13$, $\eta_p^2 = 0.08$). There was no interaction between Stimulation and Hemifield ($F_{2,60} = 0.78$, $P = 0.46$, $\eta_p^2 = 0.03$).

Storage Capacity K

There was no difference in Storage Capacity during right prefrontal ($M = 2.38 \pm 0.11$), right parietal ($M = 2.37 \pm 0.10$), and sham stimulation ($M = 2.42 \pm 0.10$) as evidenced by a non-significant main effect of Stimulation ($F_{2,60} = 0.34$, $P = 0.71$, $\eta_p^2 = 0.01$; Fig. 6). Storage Capacity was higher for items presented to the right ($M = 2.51 \pm 0.10$) versus left hemifield ($M = 2.27 \pm 0.10$) as demonstrated by a main effect of Hemifield ($F_{1,30} = 49.95$, $P < 0.0005$., $\eta_p^2 = 0.61$). There was further a significant interaction between Stimulation and Hemifield ($F_{2,60} = 3.91$, $P = 0.025$., $\eta_p^2 = 0.12$; Fig. 6). During sham stimulation there was no significant difference between storage capacity for items in the right ($M = 2.48 \pm 0.11$) versus left hemifield ($M = 2.35 \pm 0.10$, $P = 0.06$). In contrast, during both right prefrontal and right parietal stimulation storage capacity was significantly higher for items in the right than in the left hemifield (prefrontal stimulation: right hemifield $M = 2.55 \pm 0.12$, left hemifield $M = 2.21 \pm 0.10$, $P < 0.0005$, parietal stimulation: right hemifield $M = 2.51 \pm 0.10$, left hemifield $M = 2.24 \pm 0.11$, $P < 0.0005$). Planned comparisons testing effects of tDCS in each hemifield revealed that within the right hemifield there was no significant difference for storage capacity during right prefrontal relative to sham tDCS or during right parietal stimulation relative to sham stimulation (both $P < 0.3$). Within the left hemifield, storage capacity during right prefrontal stimulation was reduced relative to sham ($P = 0.02$). There was no significant difference in storage capacity during parietal relative to sham stimulation, for items in the left hemifield ($P = 0.11$).

The Relationship Between CR and Responsiveness to Right Prefrontal tDCS

Lower levels of CR were associated with greater tDCS-related improvements in processing speed to items in the left ($r = -0.36$, $P < 0.05$) hemifield (Fig. 7*b*). Similarly, a stronger rightward processing speed asymmetry was associated with greater tDCS-related improvements in processing speed for items in the left ($r = -0.64$, $P > 0.0005$) hemifield (Fig. 7*a*). Importantly, these associations were not observed for items in the right hemifield either for levels of CR ($r = 0.04$, $P = 0.83$) or processing asymmetries ($r = 0.11$, $P = 0.56$, Fig. 7*a*,*b*).

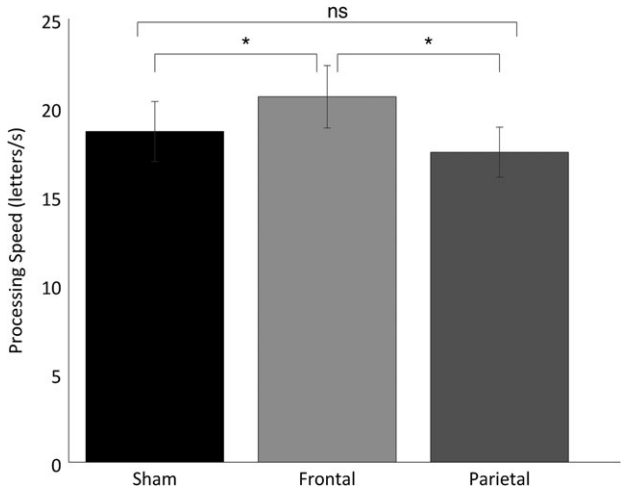

Figure 5. The effect of right prefrontal and right parietal stimulation on processing speed (C). Processing speed was significantly faster during stimulation of the right PFC as compared with during right parietal and sham stimulation. ns denotes not significantly different, *denotes $P < 0.05$.

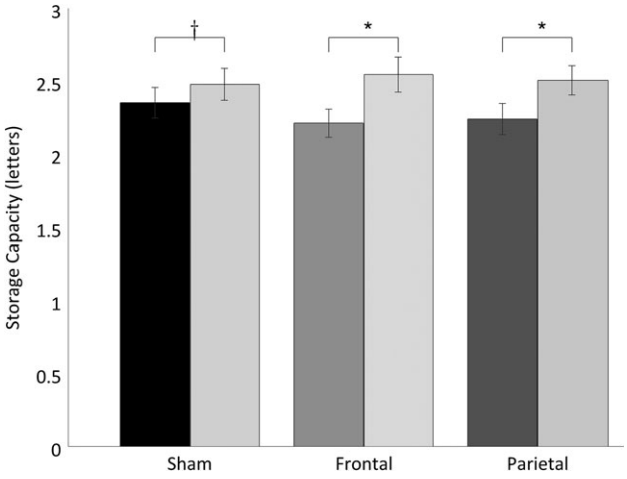

Figure 6. The effect of right prefrontal and right parietal stimulation on storage capacity (K). During sham stimulation, the difference in storage capacity for items in the right (lighter shades) relative to left hemifields was just short of significance. During both right prefrontal and right parietal stimulation, there was a significant difference in storage capacity for the right relative to left hemifield. † denotes $P \leq 0.06$, * denotes $P < 0.05$.

Discussion

The current study provides evidence that high levels of CR are associated with stronger involvement of the right hemisphere during the processing of visual information. At baseline, high reserve individuals demonstrated a leftward processing speed. Correspondingly, when cortical activity in the right PFC was increased using tDCS, processing speed capacity improved. Older adults with lower levels of CR showed tDCS-related benefits to items in the left but not right hemifield such that tDCS temporarily altered their processing speed asymmetry to mimic that of their high reserve peers.

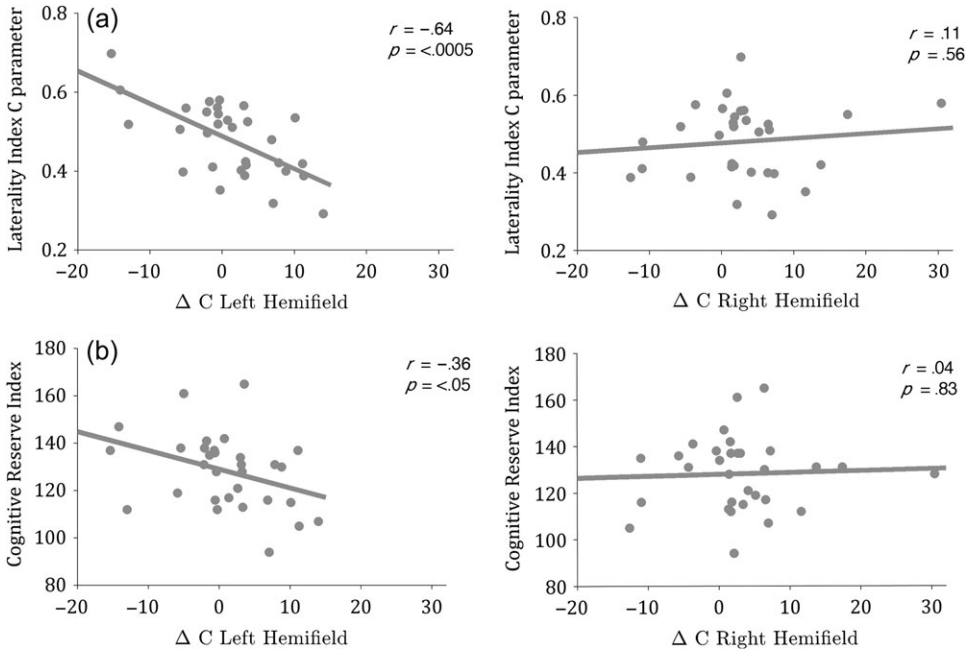

Figure 7. (*a*) The relationship between baseline Processing Speed Asymmetry and tDCS-related improvements per hemifield. (*b*) The relationship between CR and tDCS-related improvements per hemifield. Δ = prefrontal-sham tDCS.

A Role of the Right Hemisphere in CR

The current findings support the recently proposed hypothesis (Robertson 2014) that the right hemisphere is of particular importance for CR in ageing. Firstly, we found that older adults with higher levels of CR showed a processing speed asymmetry towards the left side of space. Recent, unpublished data from the Centre for Visual Cognition, University of Copenhagen using a similar lateralized TVA whole-report task has shown that younger adults display a significantly greater asymmetry in their processing speed capacity to items in the right versus left hemifield (Bart Cooreman, personal communication, see Supplementary Fig. S1). Of note, the asymmetries of overall levels of visual attention capacity described in the present study are not akin to spatial bias measures that refer to the relative distribution of processing resources across both hemifields. This whole-report task requires participants to report visually presented letters within a given hemifield, and has been shown to produce a rightward asymmetry in both processing speed and storage capacity in younger individuals (Kraft et al., 2015 and Supplementary Material), which likely reflects the left hemisphere dominance for processing verbal stimuli (Gross, 1972). The current data thereby suggests that, while elderly individuals with lower levels of CR continue to show the same rightward asymmetry as younger adults, older adults with higher levels of CR demonstrate functional reorganization involving the right hemisphere. This is in line with previous functional neuroimaging findings that mild cognitive impairment and Alzheimer's Disease patients with higher levels of CR show reorganization of several brain areas, even within preserved cognitive domains that are unaffected by the disease (Bosch et al. 2010).

Secondly, we observed that lower levels of CR were associated with less awareness of day-to-day lapses in attentional control (relative to an informant report). Previous work has demonstrated strong associations between awareness of cognitive functioning and the right PFC in healthy ageing (Harty et al. 2014), Alzheimer's Disease (Starkstein et al. 1995; Harwood 2005), and frontotemporal dementia (Mendez and Shapira 2005) and there is strong evidence to suggest that error awareness is a core cognitive process related to CR (Robertson 2014). These findings therefore support the recent proposal that particularly the right hemisphere plays a prominent role in CR (Robertson 2014).

A Causal Role of the Right PFC in Processing Speed Capacity in Ageing

We found that increasing excitability of the right prefrontal enhanced processing speed *C* in older adults. This improvement was location specific and not observed during stimulation of the right parietal cortex. The finding supports previous indirect evidence implicating a role of the right PFC in the processing speed parameter of the TVA including: the assessment of patients with right prefrontal lesions (Habekost and Rostrup 2006), neuroimaging work examining the hemispheric lateralization of white matter tracts connecting frontal and occipital lobes (Chechlacz et al. 2015; Marshall et al. 2015) and experimental manipulations of alertness (Matthias et al. 2009).

With age, increased recruitment of the frontal cortices coupled with pervasive under-activation in more posterior sites in the occipital lobes during the processing of visual information is considered an adaptive compensatory mechanism of frontal regions in response to a reduced capacity for sensory processing (Davis et al. 2008). In line with this, recent work combining a TVA-based assessment with EEG has provided evidence for a particularly important contribution of the PFC to processing speed in older age. Specifically, older adults with higher processing speed levels showed a preserved amplitude of an early electrophysiological marker over frontal scalp regions (i.e., of similar magnitude as younger adults), whereas this signal was markedly reduced in those older individuals whose speed of information processing was considerably slower compared to

younger individuals (Wiegand et al. 2014). Here we show that increasing the availability of the right PFC in older adults supports faster information uptake. This adaptive mechanism presumably helps to engage control processes governed by the PFC (Gbadeyan et al. 2016; Brosnan and Wiegand 2017) that contribute to the speed of visual information processing in ageing (Cabeza 2004; Davis et al. 2008).

Of note, while contralateral organization of the visual processing stream is established (Kastner and Ungerleider 2000; Corbetta and Shulman 2002), there is also evidence suggesting the right PFC processes visual stimuli both contra (left hemifield)- and ipsilaterally (right hemifield) (Duncan et al. 1999b; Sheremata et al. 2010; Shulman et al. 2010). Our results support the proposal that the right PFC may influence bilateral visual attention processes (Corbetta and Shulman, 2011), as increasing activity in the right PFC by tDCS was associated with improvements in processing speed in both the left and the right hemifield.

Preserved Plasticity of the Right PFC in Ageing

Although preliminary evidence suggests it may be possible to increase CR in later years (Lenehan et al. 2016), whether the right-lateralized FPN postulated to underlie CR (Robertson 2014) can be strengthened in older adults is unclear. Here we provide evidence that the right PFC demonstrates preserved levels of plasticity in ageing. Firstly, we show that increasing activity in this brain area in older adults improves visual processing speed, a fundamental cognitive process that is strongly correlated with age-related decline (Gregory et al. 2008; Deary et al. 2010; Ritchie et al. 2014). This finding is of relevance as the basic speed of perceptual processing constitutes a limiting factor on higher level cognitive abilities (Salthouse 1996) and ameliorating deficits in early perceptual processing in ageing may show advantages that cascade throughout the cognitive hierarchy (Mishra et al. 2014, Sep 18) and improve performance on day-to-day tasks (Ball et al. 2010; Rebok et al. 2014). Secondly, we observed that, while the overall effect of processing speed enhancement by tDCS was not dependent on the individuals' level of CR, those older adults with lower levels of CR showed tDCS-related speeding of information processing for visual items in the left and not right hemifield. Increasing activity in the right PFC, therefore temporarily shifted the processing asymmetry leftward in older adults with lower levels of reserve, to resemble that of their high reserve peers. Here, we therefore provide support that plasticity of the right PFC may be harnessed in later life, and most importantly, we demonstrate that lower levels of CR do not limit plasticity of the right PFC. These results support the right PFC as a viable target brain region for mitigating processing speed deficits in ageing using neuromodulatory techniques such as fMRI neurofeedback (deBettencourt et al. 2015; Habes et al. 2016), methods of non-invasive brain stimulation (Gögler et al. 2016, Dec 30), or by combing neuromodulatory approaches with validated behavioral training paradigms (Milewski-Lopez et al. 2014; Rebok et al. 2014) or pharmacological approaches (Newhouse 2004). Moreover, these findings suggest the right PFC may, in fact, play a causal role in cultivating levels of CR thus providing support for the first neuroscientific theory of CR proposed in the literature (Robertson 2013, 2014).

Separate Neural Underpinnings for Visual Processing Speed and Storage Capacity

A major strength of the TVA-based approach is that effects on distinct parameters of visual attention capacity, processing speed and storage capacity, can be independently assessed within one test. In the current sample, the association between visual attention and CR was selective to the hemifield asymmetry in processing speed; neither the absolute individual limit nor hemifield asymmetries of visual storage capacity were associated with levels of CR. Furthermore, tDCS targeting the right dorsolateral PFC was associated with improved processing speed across both hemifields, while a concurrent reduction in storage capacity was observed during stimulation for items in the left hemifield. Our findings therefore are further evidence for a critical assumption of NTVA that at least partially distinct brain networks underlie the 2 TVA parameters of visual attention capacity (Bundesen et al. 2011) and that they are differently affected by aging (Wiegand et al. 2014).

Several studies utilizing behavioral or pharmacological approaches to target the efficiency of the visual attention system have successfully modulated processing speed *C* while storage capacity *K* remained unaffected by experimental manipulations (Matthias et al. 2009; Bublak et al. 2011; Vangkilde et al. 2011), suggesting that processing speed may be a relatively more malleable capacity. Furthermore, although most studies report age-related declines in both processing speed and storage capacity (see Habekost 2015 for a review) there is evidence to suggest that processing speed declines at a more dramatic rate with age (Habekost et al. 2013; Nielsen 2015, Jan 13) and may be more richly associated with general cognitive decline. For example, in a cohort of patients with mild cognitive impairment and AD both storage capacity *K*, and processing speed *C* were related to standardized neuropsychological tests involving visual material, whereas only *C* was additionally correlated with measures of verbal memory (Bublak et al. 2011). Here, we demonstrate another neural dissociation of the functions, specifically, that they are selectively sensitive to plasticity in the attention network induced by tDCS.

One possible explanation for the disruptive effect of tDCS on storage capacity in the left hemifield could be that neuronal activity in the contralateral frontal eye field regions, located posterior to the DLPFC and close to the cathodal electrode, was disrupted by the stimulation. Previous work has demonstrated contralateral processing biases within the frontal eye fields in other short-term and working memory tasks (Hagler and Sereno 2006; Kastner et al. 2007). However, we can only speculate on this based on the present results. Future work combining right PFC tDCS with neuroimaging techniques and computational modeling (Bikson et al. 2012; Bestmann et al. 2015), or the use of a more focal and spatially specific neuromodulatory technique, such as TMS, would shed light on this.

Limitations and Outlook

All older adults in the current study were cognitively healthy as identified by the cognitive screening tool (MoCA). However, in the absence of imaging methods, the possibility that these results may be confounded by pre-clinical Alzheimer's Disease (e.g., as assessed by amyloid PET imaging), which affects the FPNs (Neufang et al. 2011; Sorg et al. 2012) cannot be excluded (Hansson et al. 2006; Koch et al. 2015). Furthermore, as in other tDCS studies (Harty et al. 2014), responsiveness to tDCS varied largely between the older participants in our sample, and the sources of these inter-individual differences remain unclear. Possible mediators might be anatomical properties affecting the current flow such as skull thickness, gyral pattern, and cerebrospinal fluid (Opitz et al. 2015), or the neuro-anatomical connectivity strength between the right PFC and other nodes of the visual attention system (Chechlacz et al. 2015; Ramsey

et al. 2017). Further research is necessary to systematically investigate how anatomical and functional properties contribute to the variability in responsiveness to brain stimulation (Bikson et al. 2012; Berker et al. 2013).

Finally, our result seem to contradict the assumption that individuals who maintain youth-like brain structures are cognitively high-performing in older age; a phenomenon referred to as brain maintenance (Nyberg et al. 2012). We understand CR and brain maintenance as orthogonal concepts (Habeck et al. 2016, Jul 11) which interactively determine an aging individual's cognitive status over the lifespan. Within the present study design, we demonstrate at a single point in time that stronger hemispheric reorganization of a highly specific cognitive function in older adults with higher compared to lower levels of CR, while baseline performance in processing speed was not related to individuals' level of CR. In order to dissociate mechanisms of brain maintenance and reserve within individuals, brain and cognitive measures within a longitudinal design are needed (Raz and Lindenberger 2011). Future studies may further elucidate whether the asymmetry in processing speed is indeed predictive of cognitive (and neural) development in older age.

Conclusions

The worldwide prevalence of Alzheimer's Disease is projected to triple to 135.5 million by 2050 (Langa 2015) which will have devastating implications for patients, families and societies. Understanding the neural underpinnings of how to increase CR, the neurocognitive buffer against age-related neuropathology, is of societal relevance. Here we show using a TVA-based assessment, un-confounded by motor requirements, that leftward asymmetry in the speed of visual processing is associated with CR. We have demonstrated that increasing activity in the right PFC using tDCS facilitates faster processing of visual information in older adults. Moreover, probing this key node in the right-lateralized CR network can temporarily shift the processing speed asymmetry in individuals with low levels of CR to resemble that of their high reserve peers. We therefore demonstrate preserved plasticity of the right PFC in ageing, and the usefulness of targeting this region, even in elderly individuals with lower levels of reserve.

Supplementary Material

Supplementary data is available at *Cerebral Cortex* online.

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References

Alzheimer's Association. 2013. 2013 Alzheimer's disease facts and figures. Alzheimers Dement. 9:208–245.

Ball K, Edwards JD, Ross LA, McGwin GJr. 2010. Cognitive training decreases motor vehicle collision involvement of older drivers. J Am Geriatr Soc. 58:2107–2113.

Berker AO, de, Bikson M, Bestmann S. 2013. Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. Front Hum Neurosci. 7:613.

Bestmann S, de Berker AO, Bonaiuto J. 2015. Understanding the behavioural consequences of noninvasive brain stimulation. Trends Cogn Sci. 19:13–20.

Bikson M, Rahman A, Datta A. 2012. Computational models of transcranial direct current stimulation. Clin EEG Neurosci. 43:176–183.

Bosch B, Bartrés-Faz D, Rami L, Arenaza-Urquijo EM, Fernández-Espejo D, Junqué C, Solé-Padullés C, Sánchez-Valle R, Bargalló N, Falcón C, et al. 2010. Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. Cortex. 46:451–461.

Bowers D, Heilman KM. 1980. Pseudoneglect: effects of hemispace on a tactile line bisection task. Neuropsychologia. 18: 491–498.

Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. 1982. The cognitive failures questionnaire (CFQ) and its correlates. Br J Clin Psychol. 21:1–16.

Brosnan MB, Wiegand I. 2017. The dorsolateral prefrontal cortex, a dynamic cortical area to enhance top-down attentional control. J Neurosci. 37:3445–3446.

Brown JW, Jaffe J. 1975. Hypothesis on cerebral dominance. Neuropsychologia. 13:107–110.

Bublak P, Redel P, Sorg C, Kurz A, Förstl H, Müller HJ, Schneider WX, Finke K. 2011. Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging. 32:1219–1230.

Bundesen C. 1990. A theory of visual attention. Psychol Rev. 97: 523–547.

Bundesen C, Habekost T, Kyllingsbæk S. 2005. A neural theory of visual attention: bridging cognition and neurophysiology. Psychol Rev. 112:291–328.

Bundesen C, Habekost T, Kyllingsbæk S. 2011. A neural theory of visual attention and short-term memory (NTVA). Neuropsychologia. 49:1446–1457.

Cabeza R. 2002a. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 17:85–100.

Cabeza R. 2002b. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 17:85–100.

Cabeza R. 2004. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex. 14:364–375.

Chechlacz M, Gillebert CR, Vangkilde SA, Petersen A, Humphreys GW. 2015. Structural variability within frontoparietal networks and individual differences in attentional functions: an approach using the theory of visual attention. J Neurosci. 35:10647–10658.

Cooreman B, Wiegand I, Petersen A, Vangkilde S, Bundesen C. 2015. Cue-it? We say: block-it! J Vis. 15:1335.

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 3: 215–229.

Corbetta M, Shulman GL. 2011. Spatial neglect and attention networks. Ann Rev Neurosci. 34:569–599.

Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. 2008. Qué PASA? The posterior–anterior shift in aging. Cereb Cortex. 18:1201–1209.

Deary IJ, Johnson W, Starr JM. 2010. Are processing speed tasks biomarkers of cognitive aging? Psychol Aging. 25:219–228.

deBettencourt MT, Cohen JD, Lee RF, Norman KA, Turk-Browne NB. 2015. Closed-loop training of attention with real-time brain imaging. Nat Neurosci. 18:470–475.

Duncan J, Bundesen C, Olson A, Humphreys G, Chavda S, Shibuya H. 1999a. Systematic analysis of deficits in visual attention. J Exp Psychol Gen. 128:450–478.

Duncan J, Bundesen C, Olson A, Humphreys G, Chavda S, Shibuya H. 1999b. Systematic analysis of deficits in visual attention. J Exp Psychol Gen. 128:450–478.

Dyrholm M, Kyllingsbæk S, Espeseth T, Bundesen C. 2011. Generalizing parametric models by introducing trial-by-trial parameter variability: The case of TVA. J Math Psychol. 55: 416–429.

Espeseth T, Vangkilde SA, Petersen A, Dyrholm M, Westlye LT. 2014. TVA-based assessment of attentional capacities-associations with age and indices of brain white matter microstructure. Front Psychol. 5:71.

Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. 2010. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res. 208:311–318.

Gandiga PC, Hummel FC, Cohen LG. 2006. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 117: 845–850.

Gbadeyan O, McMahon K, Steinhauser M, Meinzer M. 2016. Stimulation of dorsolateral prefrontal cortex enhances adaptive cognitive control: a high-definition transcranial direct current stimulation study. J Neurosci. 36:12530–12536.

Gögler N, Willacker L, Funk J, Strube W, Langgartner S, Napiórkowski N, Hasan A, Finke K. 2016 Dec 30. Single-session transcranial direct current stimulation induces enduring enhancement of visual processing speed in patients with major depression. Eur Arch Psychiatry Clin Neurosci. 1–16.

Gregory T, Nettelbeck T, Howard S, Wilson C. 2008. Inspection time: a biomarker for cognitive decline. Intelligence. 36: 664–671.

Gross MM. 1972. Hemispheric specialization for processing of visually presented verbal and spatial stimuli. Percept Psychophys. 12:357–363.

Habeck C, Razlighi Q, Gazes Y, Barulli D, Steffener J, Stern Y. 2016. Cognitive reserve and brain maintenance: orthogonal concepts in theory and practice. Cereb Cortex. 1–8.

Habekost T. 2015. Clinical TVA-based studies: a general review. Front Psychol. 6:290.

Habekost T, Rostrup E. 2006. Persisting asymmetries of vision after right side lesions. Neuropsychologia. 44:876–895.

Habekost T, Vogel A, Rostrup E, Bundesen C, Kyllingsbæk S, Garde E, Ryberg C, Waldemar G. 2013. Visual processing speed in old age. Scand J Psychol. 54:89–94.

Habes I, Rushton S, Johnston SJ, Sokunbi MO, Barawi K, Brosnan M, Daly T, Ihssen N, Linden DE. 2016. fMRI neurofeedback of higher visual areas and perceptual biases. Neuropsychologia. 85:208–215.

Hagler DJJr, Sereno MI. 2006. Spatial maps in frontal and prefrontal cortex. Neuroimage. 29:567–577.

Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. 2006. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol. 5: 228–234.

Harty S, O'Connell RG, Hester R. 2013. Older adults have diminished awareness of errors in the laboratory and daily life. Psychol Aging. 28:1032–1041.

Harty S, Robertson IH, Miniussi C, Sheehy OC, Devine CA, McCreery S, O'Connell RG. 2014. Transcranial direct current stimulation over right dorsolateral prefrontal cortex enhances error awareness in older age. J Neurosci. 34: 3646–3652.

Harwood DG. 2005. Frontal lobe hypometabolism and impaired insight in Alzheimer disease. Am J Geriatr Psychiatry. 13: 934–941.

Heinze HJ, Mangun GR, Burchert W, Hinrichs H, Scholz M, Münte TF, Gös A, Scherg M, Johannes S, Hundeshagen H, et al. 1994. Combined spatial and temporal imaging of brain activity during visual selective attention in humans. Nature. 372:543–546. doi:10.1038/372543a0.

Kastner S, DeSimone K, Konen CS, Szczepanski SM, Weiner KS, Schneider KA. 2007. Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. J Neurophysiol. 97:3494–3507.

Kastner S, Ungerleider LG. 2000. Mechanisms of visual attention in the human cortex. Annu Rev Neurosci. 23:315–341.

Kerchner GA, Racine CA, Hale S, Wilheim R, Laluz V, Miller BL, Kramer JH. 2012. Cognitive processing speed in older adults: relationship with white matter integrity. In: PLoS ONE. 7: e50425.

Koch K, Myers NE, Göttler J, Pasquini L, Grimmer T, Förster S, Manoliu A, Neitzel J, Kurz A, Förstl H, et al. 2015. Disrupted intrinsic networks link Amyloid-β pathology and impaired cognition in prodromal Alzheimer's disease. Cereb Cortex. 25:4678–4688.

Kraft A, Dyrholm M, Kehrer S, Kaufmann C, Bruening J, Kathmann N, Bundesen C, Irlbacher K, Brandt SA. 2015. TMS over the right precuneus reduces the bilateral field advantage in visual short term memory capacity. Brain Stimul. 8: 216–223.

Kyllingsbæk S. 2006. Modeling visual attention. Behav Res. 38: 123–133.

Langa KM. 2015. Is the risk of Alzheimer's disease and dementia declining? Alzheimers Res Ther. 7:34.

Lenehan ME, Summers MJ, Saunders NL, Summers JJ, Ward DD, Ritchie K, Vickers JC. 2016. Sending your grandparents to university increases cognitive reserve: the Tasmanian healthy brain project. Neuropsychology. 30:525–531.

Madden DJ, Spaniol J, Whiting WL, Bucur B, Provenzale JM, Cabeza R, White LE, Huettel SA. 2007. Adult age differences in the functional neuroanatomy of visual attention: a combined fMRI and DTI study. Neurobiol Aging. 28:459–476.

Mangun GR, Buonocore MH, Girelli M, Jha AP. 1998. ERP and fMRI measures of visual spatial selective attention. Hum Brain Mapp. 6:383–389.

Marshall TR, Bergmann TO, Jensen O. 2015. Frontoparietal structural connectivity mediates the top-down control of neuronal synchronization associated with selective attention. In: Behrens T, editor. PLOS Biology. 13:e1002272.

Matthias E, Bublak P, Costa A, Müller HJ, Schneider WX, Finke K. 2009. Attentional and sensory effects of lowered levels of intrinsic alertness. Neuropsychologia. 47:3255–3264.

McAvinue LP, Habekost T, Johnson KA, Kyllingsbæk S, Vangkilde S, Bundesen C, Robertson IH. 2012. Sustained attention, attentional selectivity, and attentional capacity across the lifespan. Atten Percept Psychophys. 74:1570–1582.

Mendez MF, Shapira JS. 2005. Loss of insight and functional neuroimaging in frontotemporal dementia. J Neuropsychiatry Clin Neurosci. 17:413–416.
Milewski-Lopez A, Greco E, van den Berg F, McAvinue LP, McGuire S, Robertson IH. 2014. An evaluation of alertness training for older adults. Front Aging Neurosci. 6:843.
Mishra J, Rolle C, Gazzaley A. 2015. Neural plasticity underlying visual perceptual learning in aging. Brain Res. 1612:140–151.
NA. 1991. American electroencephalographic society guidelines for standard electrode position nomenclature. J Clin Neurophysiol. 8:200–202. https://www.ncbi.nlm.nih.gov/pubmed/16612226
Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 53:695–699.
Nelson HE. 1982. National Adult Reading Test (NART): for the assessment of premorbid intelligence in patients with dementia: Test manual.
Neufang S, Akhrif A, Riedl V, Förstl H, Kurz A, Zimmer C, Sorg C, Wohlschläger AM. 2011. Disconnection of frontal and parietal areas contributes to impaired attention in very early Alzheimer's disease. J Alzheimers Dis. 25:309–321.
Newhouse P. 2004. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol. 4:36–46.
Nicholls MER, Bradshaw JL, Mattingley JB. 1999. Free-viewing perceptual asymmetries for the judgement of brightness, numerosity and size. Neuropsychologia. 37:307–314.
Nielsen S. 2015. Cognitive aging on latent constructs for visual processing capacity: a novel structural equation modeling framework with causal assumptions based on a theory of visual attention. Theories Vis Attent Link Cognit Neuropsychol Neurophysiol. 2:55.
Nucci M, Mapelli D, Mondini S. 2012. Cognitive reserve index questionnaire (CRIq): a new instrument for measuring cognitive reserve. Aging Clin Exp Res 24(3):218–226.
Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. 2012. Memory aging and brain maintenance. Trends Cogn Sci. 16:292–305.
Opitz A, Paulus W, Will S, Antunes A, Thielscher A. 2015. Determinants of the electric field during transcranial direct current stimulation. Neuroimage. 109:140–150.
Ramsey LE, Siegel JS, Lang CE, Strube M, Shulman GL, Corbetta M. 2017. Behavioural clusters and predictors of performance during recovery from stroke. Nat Human Behav. 1:0038. Nature Publishing Group.
Raz N, Lindenberger U. 2011. Only time will tell: cross-sectional studies offer no solution to the age–brain–cognition triangle: comment on salthouse (2011). Psychol Bull. 137:790–795.
Rebok GW, Ball K, Guey LT, Jones RN, Kim H-Y, King JW, Marsiske M, Morris JN, Tennstedt SL, Unverzagt FW, et al. 2014. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. J Am Geriatr Soc. 62:16–24.
Reuter-Lorenz PA, Jonides J, Smith EE. 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci. 12:174–187.
Ritchie SJ, Tucker-Drob EM, Deary IJ. 2014. A strong link between speed of visual discrimination and cognitive ageing. Curr Biol. 24(15):R681–R683.
Robertson IH. 2013. A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. Neurobiol Aging. 34:298–308.
Robertson IH. 2014. A right hemisphere role in cognitive reserve. Neurobiol Aging. 35:1375–1385.
Salthouse TA. 1996. The processing-speed theory of adult age differences in cognition. Psychol Rev. 103:403–428.
Sander MC, Werkle-Bergner M. 2011. Contralateral delay activity reveals life-span age differences in top-down modulation of working memory contents. Cereb Cortex. 21(12):2809–2819.
Schiffer F, Mottaghy FM, Vimal RLP, Renshaw PF, Cowan R, Pascual-Leone A, Teicher M, Valente E, Rohan M. 2004. Lateral visual field stimulation reveals extrastriate cortical activation in the contralateral hemisphere: an fMRI study. Psychiatry Res. 131:1–9.
Sheremata SL, Bettencourt KC, Somers DC. 2010. Hemispheric asymmetry in visuotopic posterior parietal cortex emerges with visual short-term memory load. J Neurosci. 30:12581–12588.
Shulman GL, Pope DLW, Astafiev SV, McAvoy MP, Snyder AZ, Corbetta M. 2010. Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. J Neurosci. 30:3640–3651.
Sorg C, Myers N, Redel P, Bublak P, Riedl V, Manoliu A, Perneczky R, Grimmer T, Kurz A, Förstl H, et al. 2012. Asymmetric loss of parietal activity causes spatial bias in prodromal and mild Alzheimer's disease. Biol Psychiatry. 71:798–804.
Sperling G. 1960. The information available in brief visual presentations. Psychol Monogr: Gen Appl. 74:1–29.
Starkstein SE, Vázquez S, Migliorelli R, Tesón A, Sabe L, Leiguarda R. 1995. A single-photon emission computed tomographic study of anosognosia in Alzheimer's disease. Arch Neurol. 52:415–420.
Stern Y, Alexander GE, Prohovnik I, Mayeux R. 1992. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol. 32:371–375.
Vangkilde S, Bundesen C, Coull JT. 2011. Prompt but inefficient: nicotine differentially modulates discrete components of attention. Psychopharmacology (Berl). 218:667–680.
Voyer D, Voyer SD, Tramonte L. 2012. Free-viewing laterality tasks: a multilevel meta-analysis. Neuropsychology. 26:551–567.
Wiegand I, Töllner T, Dyrholm M, Müller HJ, Bundesen C, Finke K. 2014. Neural correlates of age-related decline and compensation in visual attention capacity. Neurobiol Aging. 35:2161–2173.
Wood JM, Owsley C. 2014. Useful field of view test. Gerontology. 60:315–318.