Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research Report

Uncovering the (un)attended: Pupil light responses index persistent biases of spatial attention in neglect

Antonia F. Ten Brink [a,1], *Marlies van Heijst* [a], *Brendan L. Portengen* [a,b], *Marnix Naber* [a] and *Christoph Strauch* [a,*,1]

[a] *Utrecht University, Experimental Psychology, Helmholtz Institute, Utrecht, the Netherlands*
[b] *University Medical Center Utrecht, Ophthalmology, Utrecht, the Netherlands*

ARTICLE INFO

Article history:
Received 30 March 2023
Reviewed 13 May 2023
Revised 31 May 2023
Accepted 26 June 2023
Action Editor Paolo Bartolomeo
Published online 20 July 2023

Keywords:
Unilateral neglect
Pupillometry
Hemianopia
Spatial attention
Covert attention

ABSTRACT

Visuospatial neglect is a frequent and disabling disorder, mostly after stroke, that presents in impaired awareness to stimuli on one side of space. Neglect causes disability and functional dependence, even long after the injury. Improving measurements of the core attentional deficit might hold the key for better understanding of the condition and development of treatment. We present a rapid, pupillometry-based method that assesses automatic biases in (covert) attention, without requiring behavioral responses. We exploit the phenomenon that pupil light responses scale with the degree of covert attention to stimuli, and thereby reveal what draws (no) attention. Participants with left-sided neglect after right-sided lesions following stroke ($n = 5$), participants with hemianopia/quadrantanopia following stroke ($n = 11$), and controls ($n = 22$) were presented with two vertical bars, one of which was white and one of which was black, while fixating the center. We varied which brightness was left and right, respectively across trials. In line with the hypotheses, participants with neglect demonstrated biased pupil light responses to the brightness on the right side. Participants with hemianopia showed similar biases to intact parts of the visual field, whilst controls exhibited no bias. Together, this demonstrates that the pupil light response can reveal not only visual, but also attentional deficits. Strikingly, our pupillometry-based bias estimates were not in agreement with neuropsychological paper-and-pencil assessments conducted on the same day, but were with those administered in an earlier phase post-stroke. Potentially, we pick up on persistent biases in the covert attentional system that participants increasingly compensate for in classical neuropsychological tasks and everyday life. The here proposed method may not only find clinical application, but also advance theory and aid the development of successful restoration therapies by introducing a precise, longitudinally valid, and objective measurement that might not be affected by compensation.

* *Corresponding author.*
E-mail address: c.strauch@uu.nl (C. Strauch).
[1] These authors contributed equally to this work.
https://doi.org/10.1016/j.cortex.2023.06.008

1. Introduction

Unilateral spatial neglect (hereafter "neglect") is a severe clinical syndrome during which attention to one side of space is substantially reduced, which cannot be explained by damage to the sensory system (Bartolomeo & Chokron, 2002; Parton, Malhotra, & Husain, 2004). The core component of neglect is a deficit in attentional orienting to the contralesional side of space (Heilman & Van Den Abell, 1979; Husain, 2019). Most notably, neglect presents in ~30% of stroke participants with a prevalence up to 71% after a right-hemispheric stroke when ecological assessment methods are used (Esposito, Shekhtman, & Chen, 2021), persists longer than one year for about a third of these cases (Durfee & Hillis, 2023; Nijboer, Kollen, & Kwakkel, 2013), and is one of the most disabling conditions post-stroke (Buxbaum et al., 2004; Spaccavento, Cellamare, Falcone, Loverre, & Nardulli, 2017). Despite numerous efforts to develop treatments, and apparent improvement of patients on neuropsychological tests throughout recovery (Cassidy, Lewis, & Gray, 1998; Nijboer et al., 2013), the latest Cochrane review and meta-analysis concludes none of the treatments to be convincingly proven effective (Longley et al., 2021). Therapeutic approaches can be classified to aim at *compensation* or *restoration* (Luauté, Halligan, Rode, Rossetti, & Boisson, 2006), however, existing outcome measures do not dissociate between these levels. If restoration therapies are to ever succeed, our discipline must be able to measure the core deficit underlying neglect. Precise, sub-behavioral, objective, and longitudinally reliable measurements that directly target the source of neglect are therefore most urgently needed. Only then we will be able to understand neglect in-depth and to track the efficacy of therapies over time. Here, we present a novel approach that exploits the phenomenon that pupil light responses are modulated by covert attention (Binda, Pereverzeva, & Murray, 2013; Haab, 1886; Mathôt, van der Linden, Grainger, & Vitu, 2013; Naber, Alvarez, & Nakayama, 2013) and are able to track the most fundamental attentional deficit in neglect via weakened pupil light responses to stimuli in neglected hemifields. The here presented method shows promise for sensitive and specific longitudinal measurement—with potential for both research and clinical applications.

Neglect has major consequences for the individual, making research into this deficit all the more urgent. People with neglect show an ipsilesional bias in active behavior, such as exploratory movements, but also in spontaneous eye and head position, even when situated in complete darkness (Danckert & Ferber, 2006; Fruhmann-Berger & Karnath, 2005; Karnath, 1997). Even if mild, neglect in the acute phase is one of the most (Jehkonen et al., 2000; Patel, Coshall, Rudd, & Wolfe, 2003) predictive factors for adverse functional outcomes: increased risks of falls, prolonged hospitalization, long-term care placement, increased burden on caregivers, and many others (Buxbaum et al., 2004; Spaccavento et al., 2017). Neglect is a heterogeneous syndrome that can result from lesions in different brain areas, mostly in the right hemisphere (Moore, Milosevich, Mattingley, & Demeyere, 2023; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017), and can manifest in different modalities (e.g. visual, auditory, tactile; Jacobs, Brozzoli, & Farnè, 2012), reference frames (e.g. egocentric, allocentric; Chechlacz et al., 2010), and distances (e.g. personal, peripersonal, extrapersonal space; Aimola, Schindler, Simone, & Venneri, 2012; Van der Stoep et al., 2013).

Although there is no gold standard for diagnosis, a combination of paper-and-pencil neuropsychological tasks complemented with structured clinical observations is the typical assessment (e.g., Azouvi et al., 2006; Esposito et al., 2021). The neuropsychological tasks have serious drawbacks, among which are flooring/ceiling effects and the huge influence of compensation strategies and practice effects (Bonato & Deouell, 2013; Deouell, Sacher, & Soroker, 2005; Spreij, Ten Brink, Visser-Meily, & Nijboer, 2020). Although there is little to no debate that spatial attention, serving to prioritize information, is severely impaired and driving the symptoms observed in neglect, this impairment could originate on different levels. Neuropsychological assessments require the patient to actively interact with the external world and/or to overtly respond, thereby introducing effects of top-down or controlled attention. Behavioral estimates therefore disallow to monitor possible restoration of the underlying attentional systems, as apparent improvements can merely be due to a learned compensation strategy rather than to a restoration of attentional biases. One explanation for the improvement over time of many patients with neglect on neuropsychological tasks (Cassidy et al., 1998; Nijboer et al., 2013) therefore lies in the development of increasingly automatized top-down changes in *overt* attention. Consequently, assessments that feature overt behavioral responses are plagued by the inability to longitudinally assess neglect reliably, which hinders the evaluation—or even development—of effective restoration therapies (Bonato & Deouell, 2013; Deouell et al., 2005). Eye or head movements (overt shifts in attention) can be considered more automatic than many other overt responses needed in neuropsychological tasks. This makes eye movement-based outcomes, such as the field of exploration and saccade amplitudes, highly sensitive measures to complement paper-and-pencil tests (Cox & Aimola Davies, 2020), although still these are under conscious control.

Shifts in *covert* attention (shifts in absence of eye movements; von Helmholtz, 1866) in turn underlie and precede eye movements (Deubel & Schneider, 1996). An automatic attention bias in covert attention is proposed to drive the core deficit in neglect (Husain, 2019). However, covert attention is an inherently hidden state and therefore hard to assess. Addressing this issue, cueing or detection tasks have been proposed to more directly probe the deficit-underlying attentional system and have shown to disclose signs of neglect in patients who perform within the normal range on paper-and-pencil tasks (e.g., Bartolomeo, 1997, 2000; Bonato, 2015; Bonato, Priftis, Marenzi, & Zorzi, 2009, 2013; Losier & Klein, 2001). Besides a lateralized attention bias in explicit (motor or verbal) responses on such tasks, reduced pupil dilations have been reported for invalid targets in the neglected field, whilst (unseen) targets in the non-neglected field were associated with enhanced pupil dilations (Lasaponara et al., 2021). Still, even these tasks require behavioral responses that are likely to interfere with (spatial) attention itself.

We here propose and evaluated a pupillometry-based method as a novel way to directly assess automatic, covert attention in participants with neglect—requiring no overt interaction with or responses to a task. This method builds on existing work, so-called pupil perimetry, that demonstrated pupil light responses to be able to map out deficits linked to the *sensory* domain—e.g., in the visual cortex. Hereby, bright or dark stimuli are flashed across the visual field. Depending on whether these stimuli fall in intact or damaged parts of the visual field, pupil light responses are substantially stronger or weaker, respectively (Kardon, Kirkali, & Thompson, 1991; Maeda et al., 2017; Naber et al., 2018; Portengen et al., 2021; Skorkovská, Wilhelm, Lüdtke, & Wilhelm, 2009) – and thereby give away functional brain damage. But how could this help identify deficits in *attention* instead of more low-level sensory areas? We exploit the phenomenon that pupil light responses are not purely reflexive, but heavily modulated by attention (Binda & Murray, 2015; Naber, Frässle, & Einhäuser, 2011, 2013; Strauch, Wang, Einhäuser, Van der Stigchel, & Naber, 2022): At constant fixation, shifts in covert attention towards dark or bright parts of an object/visual scene result in pupil dilations or constrictions, respectively (Binda et al., 2013; Haab, 1886; Mathôt et al., 2013; Naber et al., 2013; Strauch, Wang, et al., 2022). To elucidate the potential to capture attentional (instead of sensory) deficits, we tested whether subtle, yet systematic attentional biases towards the left side of the visual field described in younger controls ('pseudoneglect') would be revealed by changes in pupil size (Bowers & Heilman, 1980; Jewell & McCourt, 2000; Strauch, Romein, Naber, Van der Stigchel, & Ten Brink, 2022). We presented healthy participants, who fixated the center of a monitor, with vertical white and black bars in opposite sides of the visual field. We expected pupil light responses to more closely correspond to the left rather than the right side of the screen, due to the overall leftward attention bias. Indeed, the brightness of the left side modulated pupil size stronger than the brightness of the right side, uncovering pseudoneglect (Strauch, Romein, et al., 2022).

In the current study, we tested whether this pupillometry-based method would be able to measure the rightward attentional bias in participants with left-sided neglect. We specifically predicted (and here now tested) in our paper about pseudoneglect "[…] pupil light responses to disproportionately reflect the brightness of the right side of the display in patients with left-sided neglect. In other words, we anticipate a weaker pupil constriction for white/black stimuli and a stronger constriction for black/white stimuli with similar overall brightness between both configurations, as the right side would be (covertly and unconsciously) attended stronger" (p. 269; Strauch, Romein, et al., 2022). We therefore hypothesized pupil light responses to disproportionally reflect the brightness of the right side of the display in participants with left-sided neglect, as compared to controls.

A similar (or perhaps even stronger) effect was hypothesized for participants with cortical impairments that affect the sensory rather than the attentional domain. As for participants with neglect, sensory deficits should be associated with spatially selective weakened responses relative to controls (see Fig. 1 for a visualization of our hypotheses). By including individuals with primary visual field deficits alongside those with neglect, we could better interpret the degree of the imbalance in pupil light responses in neglect, and ensure the reliability of the current method through replication of previous reported findings (Kardon et al., 1991; Maeda et al., 2017; Naber et al., 2018; Portengen et al., 2021; Skorkovská et al., 2009).

2. Materials and methods

The research and consent procedures were performed in accordance with the standards of the Declaration of Helsinki and were approved by the Ethics Committee of De Parkgraaf Rehabilitation center and the Utrecht University Faculty of Social and Behavioural Sciences Ethics Review Board (protocol numbers 21–403 and 20–238). Participants were recruited from February 2022 to February 2023. As effects were of unknown size, no power estimation could be conducted. For diagnosis, however, only substantial effect sizes would be of relevance, which is why effects should show with even very small sample sizes. No part of the study procedures or

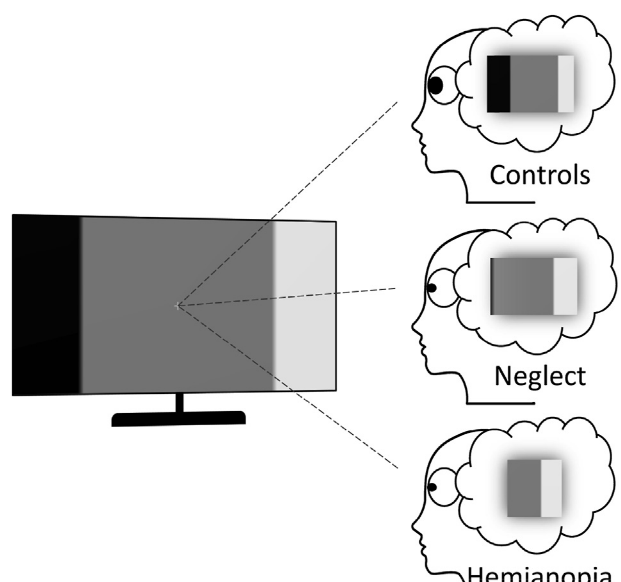

Fig. 1 – Hypothesized mechanism and findings. Example stimulus as presented to participants, hypothesized mental representation of the stimulus, and hypothesized pupil sizes. We expected participants with left-sided neglect to attentionally overrepresent the right visual field, which becomes visible in pupil sizes responding more to the right than to the left side of the screen. Participants with hemianopia were expected to show a bias in pupil size towards the undamaged part of the visual field, which might be even stronger or similar as for participants with neglect. For controls, we expected a slight leftward bias or no bias, which would show in a pupil response that matches the overall luminance.

analysis plans was preregistered prior to the research being conducted. However, the experiment followed the specific predictions made in Strauch, Romein, et al. (2022).

2.1. Participants

2.1.1. Controls

Inclusion criteria were corrected-to-normal vision and no reported psychiatric or neurological diseases in the past. A convenience sample of twenty-two right-handed healthy participants were assessed as controls, including eleven older ($M_{Age} = 53.7$ years, $SD_{Age} = 9.7$ years) and eleven younger participants ($M_{Age} = 23.4$ years, $SD_{Age} = 1.2$ years). Healthy controls were considered for the younger/older group if younger/older than 40 years of age.

2.1.2. Participants with neglect

Seven participants with left-sided neglect admitted to an inpatient geriatric rehabilitation clinic provided consent to participate, and completed the calibration and at least one experimental block. Two of these participants were excluded due to perceptual problems (holes in the macula, $n = 1$; perceiving visual information as being displaced, $n = 1$). Five participants with neglect after a first-ever stroke were eventually included ($M_{Age} = 64.8$ years, $SD_{Age} = 16.7$ years, all right-handed; one only completed the first block). For demographic and stroke-related characteristics, and scores on neuropsychological tests per participant, see Table 1 and Table 2, respectively. For a description of neuropsychological tests, see Supplementary Material 1, and for computer tomography scans of brain lesions, see Supplementary Material 2.

2.1.3. Participants with hemianopia and other visual field deficits

Eleven individuals with quadrantanopia or hemianopia were included ($M_{Age=}54.9$ years, $SD_{Age} = 16.5$ years). Of these eleven, four were diagnosed with hemianopia for the left visual field, two for the right visual field. The remaining five participants were diagnosed with quadrantanopia or had other visual field deficits in varying parts of the visual field. For perimetry maps, see Supplementary Material 3. The visual field loss in all participants was a result of strokes in the occipital cortex. In two participants, strokes occurred after resection of either a tumor in the left frontal cortex or an arteriovenous malformation. No brain scans were available. Due to the spatially smaller and differing deficits in quadrantanopia, which prohibit group-based analyses, we here give their data only where individual data is reported.

2.2. Apparatus

Healthy controls and participants with quadrant-/hemianopia were binocularly tracked using a video-based Eyelink 2000 tracker. The left eye of participants with neglect was tracked using a (largely similar) Eyelink 1000 tracker (both trackers SR research; 1000 Hz). A few participants were accidently tracked at 500 Hz. Upsampling to 1000 Hz and a z-transformation of pupillometric data within participants (see '2.5 Data processing') ensured comparability across participants. For all participants, stimuli were presented on an Asus ROG PG278Q

Table 1 – Demographic and clinical characteristics of participants with neglect ($N = 5$).

ID	Age	Sex	Days post-stroke at rehabilitation centre	Days post-stroke at test session	Stroke characteristics	Barthel Index[a] (0–20) [days post-stroke]	Motricity Index Arm[a] (0–100) [days post-stroke]	Motricity Index Leg[a] (0–100) [days post-stroke]
N1	80	M	10	130	Ischemic stroke, frontal right peri-insular (middle cerebral artery)	15 [149 days]	84 [103 days]	83 [103 days]
N2	56	M	15	28	Ischemic stroke, right hemisphere (middle cerebral artery)	5 [28 days]	0 [16 days]	21 [16 days]
N3	67	M	40	61	Parenchymal hemorrhage with intraventricular extension, right thalamus	1 [41 days]	0 [41 days]	34 [41 days]
N4	41	F	44	121	Ischemic stroke and edema, right frontoparietal	4 [45 days]	0 [44 days]	0 [44 days]
N5	80	M	7	20	Hemorrhage, right basal ganglia	13 [6 days]	91 [8 days]	70 [8 days]

[a] The Barthel Index and Motricity Index were administered in the hospital or rehabilitation center, the number of days post stroke are given between brackets. Higher scores indicate more functional independence (Barthel Index) or more motor strength in the arm or leg (Motricity Index). All participants were right-handed, all participants included were diagnosed with neglect after their first ever stroke.

Table 2 – **Performance on neglect assessment of participants with neglect ($N = 5$) at the day of the testing session.**

ID	Star cancellation, omissions (0–28)[a]	Line bisection paper, deviation in % of line length[b]	Line bisection digitized, deviation in % of line length[b]	Line bisection digitized, endpoint weightings bias[b]	Line bisection digitized, endpoint weightings sum[c]	Greyscales (0–1)[d]	Catherine Bergego Scale, total score (0–30)[e]	Pupil index[f]
N1	9 left, 1 right [30 days]; 8 left, 0 right [130 days]	13.54	1.75	0	.95	.96	8.9	.61
N2	28 left, 12 right [21 days]; 14 left, 0 right [28 days]	−1.76	−9.53	−.06	.89	1	16.7	1.08
N3	5 left, 0 right [55 days]; 0 left, 0 right [61 days]	5.15	2.76	−.02	.97	.88	17.5	.85
N4	28 left, 21 right [<44 days]; 0 left, 0 right [121 days]	na	−.87	.40	.80	1	9	1.24
N5	1 left, 0 right [13 days]; 1 left, 0 right [20 days]	6.50	1.91	.07	1.03	1	13.3	.34

[a] The star cancellation was administered twice: once at an earlier measuring point and once as part of the testing session. The number of days post-stroke are given between brackets. A higher number of omissions is indicative of more severe neglect.

[b] Line bisection deviation and endpoint weightings bias: values < 0 indicate a leftward, and values > 0 indicate a rightward deviation/bias. For the fourth patient, the line bisection on paper was not administered due to a lack of time.

[c] Line bisection endpoint weightings sum: lower scores reflect less overall attention allocated.

[d] Greyscales: values < .5 indicate a leftward, and values > .5 indicate a rightward bias.

[e] Catherine Bergego Scale: occupational therapists filled out the scale on the day of the test assessment, based upon observations that were made on that day and the week before. The number of items that could be observed and scored were 9, 9, 8, 10, and 9, respectively for patient one to five. The total score is the sum of scored items divided by the number of scored items, multiplied by 10. Higher scores indicate more neglect-related behaviour in daily life.

[f] The pupillometric bias estimate is calculated by subtracting the difference between all trials with luminance composition white/black–black/white per participant, starting 550 ms after stimulus onset. More positive values indicate stronger rightward biased pupil light responses.

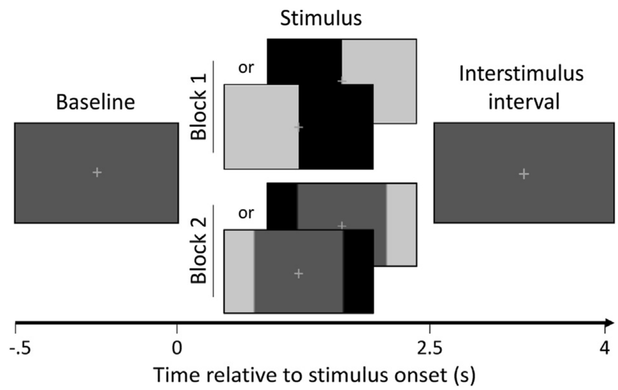

Fig. 2 – Stimuli and task. Participants self-initiated trials by looking at a central fixation cross for minimally .5 sec. Participants were then presented with black/white or white/black stimuli for 2.5 sec (Block 1: full hemifields; Block 2: peripheral bars). Upon valid trial completion (no blinks and central gaze), an interstimulus interval of 1.5 sec followed. Invalid trials were fed back to the participant with the central cross turning red, the trial would then be repeated at a random later point.

monitor (99 Hz, 2560*1440 px, 67.5 cm distance from eye-position) in a light and sound-attenuated room. The participants' head was positioned in a chin and forehead rest. A standard keyboard was positioned in between the headrest and monitor. Psychopy version 2021.2.3 (Peirce et al., 2019) was used for the implementation of the experiment.

2.3. *Procedure and material*

After giving written informed consent, participants gave their data on age, handedness, and sex. Subsequently, participants underwent the eye-tracking experiment. For participants with neglect, star cancellation (Wilson, Cockburn, & Halligan, 1987), line bisection (McIntosh, Schindler, Birchall, & Milner, 2005; Wilson et al., 1987), and greyscales tasks (Mattingley, Bradshaw, Nettleton, & Bradshaw, 1994; Nicholls, Bradshaw, & Mattingley, 1999) were additionally administered, and an occupational therapist filled out the Catherine Bergego Scale (Azouvi et al., 2003; Ten Brink et al., 2013), based upon observations of neglect behavior that were made in the week before and on the day of the assessment (for details on these tasks, see Supplementary Material 1). Depending on the speed of the participant, the assessments took up to 1 h in total.

2.4. *Task*

First, a 9-point calibration and validation procedure of the eye-tracker was performed. The task itself consisted of two blocks. In both blocks, participants were presented with a central fixation cross (light grey), .34° visual angle, presented on an intermediate grey background (Fig. 2). As soon as gaze position was registered for longer than .5 sec within an (invisible) oval shaped fixation region (horizontal radius: 1.74° visual angle; vertical radius: 3.48° visual angle) for participants with neglect or visual field deficits, and within an invisible circle (radius: 1.74° visual angle, i.e., slightly stricter for controls as they were better able to maintain fixation than participants with neglect or visual field deficits) for controls, a trial started. In the first block, one side of the screen (1280*1440 pixels, 24.9*28.0° visual angle) was presented in black, whereas the opposing side was presented in white (i.e., full hemifields). In the second block, these two vertical bars were spaced out by a central vertical grey bar in (518*1440 pixels, 10.2*28.0° visual angle), in line with the stimuli (peripheral bars) used in our previous investigation (Strauch, Romein, et al., 2022). Crucially, between trials, it was randomized whether stimuli would be white/black or black/white. Stimulus presentation lasted 2.5 sec. Upon trial completion, a grey screen was presented. Trials were spaced out by at least an additional 1.5 sec to the .5 sec needed to start a trial. Trials in which participants blinked or did not maintain central gaze position were considered invalid and disregarded. Blocks lasted until ten valid trials were completed per condition (white/black, black/white). This resulted in a testing duration of around 5 min per participant if optimally performed, but the test duration occasionally increased to approximately half an hour due to difficulties in estimating gaze position with the eye tracker (e.g., due to eye lids covering the pupil) or invalid trials.

2.5. *Data processing*

All eye tracking data was processed using a Python (3.8) script. Pupil size was segmented in trial epochs of 2.5 sec starting at stimulus onset and then baseline corrected by subtracting the average pupil size during the first 200 ms after stimulus onset (when the stimulus could not yet have affected pupil size) and z-transformed to make traces directly comparable between setups. Visual inspection ensured no outliers, blinks, or other artefacts affecting pupil measurements. Left/rightward bias in the pupil light response ('pupil bias score') was determined per participant using the average pupil size change relative to baseline starting from 550 ms after stimulus presentation, separately for white/black and black/white displays and then subtracting these average changes, pooling data of both blocks (as no differences were observed between blocks). In other words, this value indicates how much more the pupil responded to what was presented on the right (positive values) or on the left (negative values; zero means similar responses).

2.6. *Statistical analyses*

Bayesian statistics were conducted in JASP (0.14.1; JASP Team, 2021) using the default settings. All other statistics were conducted using custom Python 3.8 scripts (using the statsmodels and scipy.stats packages for statistics). All statistical tests were performed two-sided.

To be able to statistically compare differences between participants with hemianopia and neglect, data from participants with hemianopia with deficits in the right visual field were inverted and combined with data from participants with hemianopia in the left visual field. To statistically test whether white/black and black/white displays resulted in differential pupil responses across groups, a one-way repeated measures ANOVA and, due to the small group sizes, a non-parametric alternative (Kruskal–Wallis test and post-hoc Mann–Whitney *U* test) were fitted. Bayesian Mann–Whitney *U* tests were conducted to further substantiate any absence of effects.

In addition to these arguably more intuitive analyses, we fitted three linear mixed models that take the data structure into account best, i.e., trials being nested in conditions and participants, by using random effects and random slopes for luminance composition (white/black, black/white) and bar width (full, peripheral).[2] Here, we additionally included age as a covariate, as pseudoneglect in healthy participants reduces or disappears with age (Benwell, Harvey, & Thut, 2014; Learmonth, Benwell, Thut, & Harvey, 2017; Schmitz & Peigneux, 2011). As only difference between models, we once tested with participants of all three groups, and once for participants with neglect and once for participants with hemianopia against controls, respectively. Per model, we interpreted the interaction of luminance composition and group to answer our main question.

We assessed whether results could have been confounded by differences in horizontal gaze position with Mann–Whitney *U* tests. If participants with neglect would have fixated more rightward than controls, slightly different retinal images for the different luminance compositions could have driven pupil size due to a higher luminance for black/white displays as compared to white/black displays to drive the observed pupillometric effects.

Finally, to compare the pupil bias score with established neuropsychological tasks, exploratory Spearman correlations were conducted between the pupil bias score and star cancellation (total number of omitted targets), line bisection (endpoint weightings bias), and Catherine Bergego Scale (total score) for the participants with neglect. We abstained from significance testing given the small sample size and low power.

2.7. Data availability

Raw data, materials, and analysis scripts are available via the open Science Framework https://osf.io/hs73k/.

3. Results

Pupils constricted upon stimulus onset in all conditions. As hypothesized, this constriction was modulated by the luminance composition (white/black or black/white) and the participant group. Fig. 3 visualizes these pupil size changes to baseline per participant group (green: controls; blue: neglect; red: hemianopia right; orange: hemianopia left), split per block. The differences in pupil responses between white/black and black/white give an indication of covert attentional biases (Fig. 3: bottom plots, split for blocks; colors indicate groups). The individual pupil bias scores are visualized in Fig. 4 on a left to right axis together with estimated distributions overlaid for controls and participants with neglect (see Supplementary Material 2 and 3 for more detailed information on all participants with neglect or visual field deficits; and Table 2 for the bias estimates for the participants with neglect).

Both parametric and non-parametric tests with group (i.e., controls, neglect, hemianopia) as a predictor were found to significantly predict the difference in pupil size between white/black and black/white displays (ANOVA: $F\,(2{,}31) = 18.65$, $P < .001$, $\eta_{part}{}^2 = .55$; non-parametric Kruskal–Wallis test: $H\,(2) = 17.93$, $P < .001$). Post-hoc non-parametric Mann–Whitney *U* tests revealed significant differences between controls and participants with neglect ($U = 5.0$, $P = .001$; Cohen's $d = 2.37$), as well as significant differences between controls and participants with hemianopia ($U = 6.0$, $P < .001$; Cohen's $d = 2.33$), but no significant differences between participants with neglect and participants with hemianopia ($U = 11.0$, $P = .261$; Cohen's $d = .33$). For the latter analysis, the sample sizes make it hard to conclude whether biases were *similar* between participants with neglect and hemianopia, yet a Bayesian Mann–Whitney *U* test favored similarity ($BF_{01} = 1.78$).

Linear mixed models showed that pupil size was significantly predicted by the decisive interaction of luminance composition and group in all three models (all $P \leq .01$), but not by any other main effect or interaction. Again, no significant differences were found for the decisive interaction between luminance composition and group when comparing participants with hemianopia and neglect with each other (see Supplementary Material 5 for full results and details).

Finally, horizontal gaze position did not differ between groups, as assessed with Mann–Whitney *U* tests (all $P > .08$, descriptively most *left*ward for participants with neglect; see Supplementary Material 6 for full results). Therefore, pupillometric biases cannot be the result of (subtle) differences in gaze position.

In sum, all analyses demonstrate that participants with neglect and participants with hemianopia showed more biased pupil light responses than controls—effects that cannot be explained by age, nor by gaze position. The bias of participants with neglect did not differ from participants with hemianopia with tentative support for similar effect sizes between these groups.

The exploratory comparison of assessed attentional bias with the pupil method versus established neuropsychological tasks in participants revealed an interesting pattern: Participants who omitted many targets in the cancellation task during the first weeks after the stroke (more acute phase), showed strong biases in the pupillometric score at a later time-point post-stroke (Spearman's $\rho = .87$; Fig. 4, bottom left). In contrast, the omitted targets in the same task, but assessed later post-stroke (i.e., at the same time as the pupillometry experiment) did not relate to the pupillometric bias ($\rho = -.21$; Fig. 4, bottom second left). Similarly, the pupillometric bias neither scaled with line bisection scores ($\rho = 0$; Fig. 4, bottom second right) nor with the scores on the Catherine Bergego Scale ($\rho = .10$; Fig. 4, bottom right), which were also measured during the more chronic phase. Correlations with small *n* necessitate caution in interpretation, yet the overall picture of results might suggest that the obtained pupillometric bias

[2] Model equation using mixedLM from statsmodels: Pupil ~ luminance_composition + full_peripheral + age + group + group: luminance_composition:age + group: luminance_composition + age: luminance_composition + age:full_peripheral:group + group: luminance_composition:full_peripheral:age + age:full_peripheral: luminance_composition + group:full_peripheral. With random slopes specified as re_formula = "~luminance_composition*full_peripheral" and groups as ID.

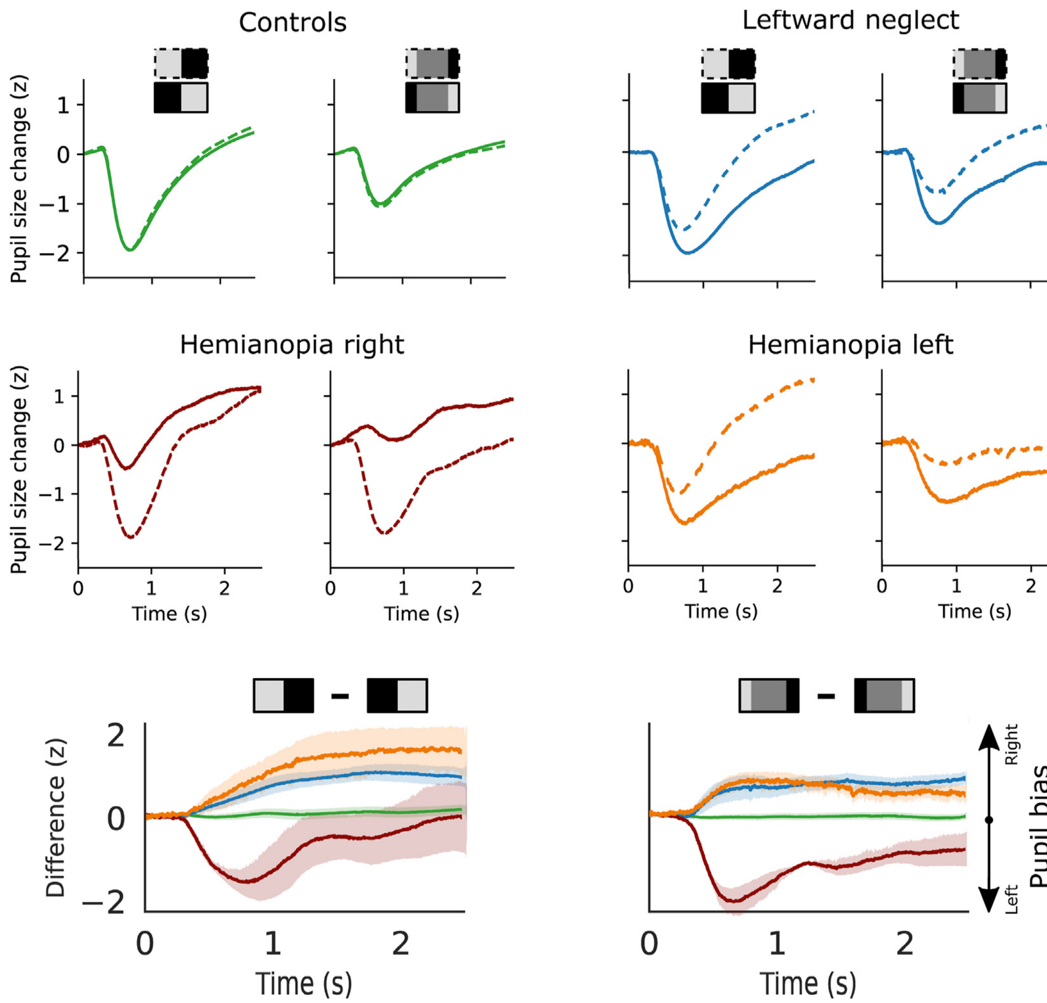

Fig. 3 – Average pupil responses over time split for luminance composition and group of participants. *Top*: The lines reflect the change in pupil size with respect to baseline, locked to stimulus onset across luminance composition (white/black and black/white) and the two bar widths (full hemifields, peripheral bars) across participant groups (controls $n = 22$; leftward neglect $n = 5$; hemianopia right $n = 2$; hemianopia left $n = 4$). Pupil responses were averaged split for luminance composition and participants, showing similar traces for white/black and black/white displays for healthy controls (green), but different traces for participants with neglect (blue) and hemianopia (left-sided: red; right-sided: orange), disproportionally more driven by the non-neglected or non-blind sides. The change in pupil size in trials with white/black stimuli are represented by dashed lines, the change in pupil size in trials with black/white stimuli are represented by solid lines. *Bottom:* differences in pupil size changes between white/black and black/white displays split per group of participants (left: full hemifields, right: peripheral bars). Shaded bars represent standard error of the mean across average differences per participant.

corresponds to neglect in the more acute phase post-stroke, but not to the degree of bias as shown in assessments in a more chronic phase or problems in daily life (Catherine Bergego Scale).

4. Discussion

4.1. *Present findings and theoretical contributions*

We described a pupillometry-based method which showed capable to assess biases in covert spatial attention in controls, participants with neglect, and visual field deficits in participants with hemianopia. In participants with left-sided neglect (an attentional deficit), the pupil responded stronger to the luminance on the right side of the visual display as compared to the left, indicating a rightward bias in automatic, covert attention. A similar pattern was observed for visual field deficits (a sensory deficit): the pupil responded stronger to the intact rather than defective parts of the visual field. This supports the central hypotheses at very large effect size. As in Strauch, Romein, et al. (2022), bar width (full hemifields, peripheral bars) showed no effect on the difference in pupil light response.

In all individuals with left-sided neglect, pupil responses indicated a rightward bias. However, the strength of this bias

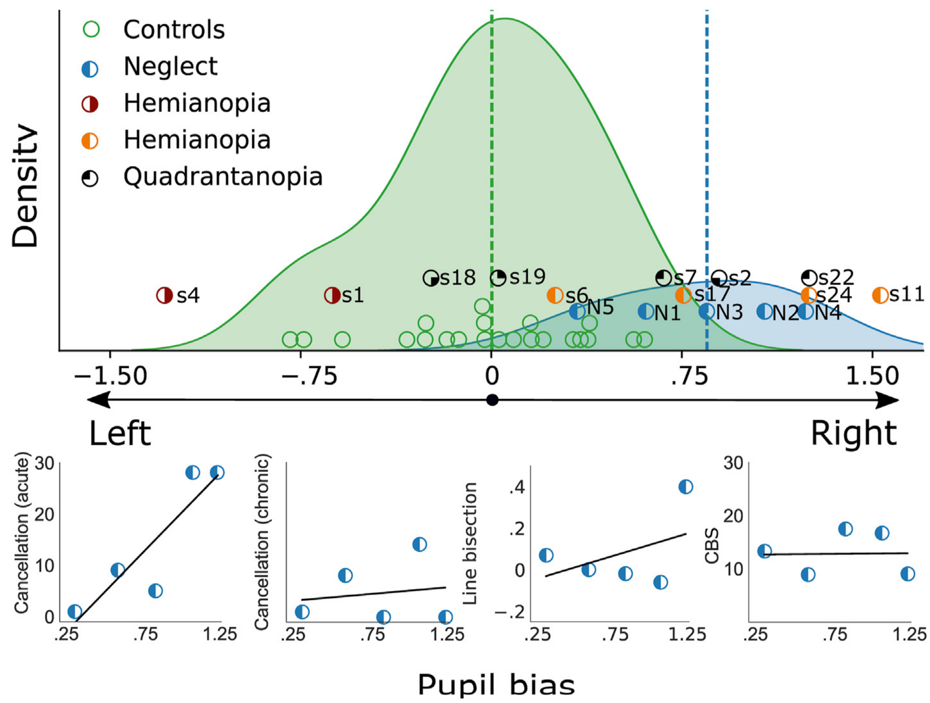

Fig. 4 – **Averaged measures for horizontal bias per participant and pupil bias against classical neuropsychological tests. *Top*: Difference between the pupil size change in trials with white/black and black/white stimuli, averaged across both blocks (full hemifields, peripheral bars), per participant (averaged difference across period 550–2450 ms). Values close to the horizontal 0-point reflect unbiased pupil responses, negative values (to the left) indicate a leftward bias, i.e., stronger pupil responses to the luminance of the left side of the screen, and positive values (to the right) indicate a rightward bias, i.e., stronger pupil responses to the luminance of the right side of the screen. Groups are denoted by colors and schematic drawings of visual/attentional field defects (green: controls; blue: neglect; orange: hemianopia left; red: hemianopia right; black: quadrants and other visual field deficits); vertical dashed lines denote medians for controls and participants with neglect. Labels denote individual participants as given in the tables and supplementary material *Bottom*: scores on neuropsychological tests per participant with neglect scattered against assessed pupil bias. *Left*: Total number of targets omitted in the star cancellation task during the more acute phase after stroke (see Table 2 for the number of days post-stroke at the moment of assessment). A higher number of omissions indicates more neglect. All remaining scores were assessed on the same day, or shortly previous to it (i.e., Catherine Bergego Scale; CBS). *Second left*: Total number of targets omitted in the star cancellation task at the day of the test session, i.e., in a later phase. *Second right*: Endpoint weightings bias taken from the line bisection task. Positive values indicate a leftward attention bias, negative values a rightward attention bias. *Right*: Total score on the CBS. For all participants, at least 7 items of the CBS were scored. The total score was computed by multiplying the average of the scored items by 10. Higher scores reflect more neglect behavior in daily life, as observed by the occupational therapist.**

varied between participants with neglect, and two of the five participants with neglect had scores descriptively similar to controls. Neglect severity measured in clinical tasks (cancellation, line bisection) during a later, more chronic phase did not link to the degree of bias observed in our pupillometry-based measurements. This could suggest that the pupil picked up on the automatic attentional bias present in earlier post-stroke phases, but with increasing awareness and increasingly learned coping mechanisms, behavioral and covert attentional biases diverged.

For all five participants with neglect, including those two for whom the pupillometry-based bias was in the range of healthy controls, practitioners observed neglect behaviour in daily life as assessed with the Catherine Bergego Scale. One may argue that the pupillometric estimate proposed here therefore carries little value, as the Catherine Bergego Scale is considered a highly sensitive measures for effects of neglect on daily life (Azouvi et al., 1996). However, the high sensitivity comes with a low specificity, and a low precision in assessing individual subprocesses of attention. First, the low specificity of the Catherine Bergego Scale might have led to some behaviour observed by practitioners being misdiagnosed as neglect. Determining whether observed behaviour is specifically related to neglect or due to, for instance, apraxia or a severe primary sensory or motor deficit is difficult (Azouvi et al., 1996; Menon & Korner-Bitensky, 2004). This is why standardized neuropsychological tests are designed to assess cognitive functions in isolation. Of course, not knowing what exactly caused a specific behaviour is also the case for standardized tests (i.e., the problem of task impurity), but most likely even more so for observed behaviour in a more complex and dynamic context. Thus, other factors than a bias in lateralized attention might as well have influenced ratings on the Catherine Bergego Scale. Speculatively, this might explain the results of participant N5, who did not show neglect on the star cancellation task (not even in the acute phase) but for whom points were assigned on the Catherine Bergego Scale. Second, the pupil bias score measures a specific aspect of neglect, namely a "default" lateralized covert attention bias. For some individuals, neglect might only show in situations with higher attentional demands (e.g., when dual-tasking is required) or in which there is competition between (relevant) ipsilesional and contralesional information. The latter might underlie the results of participant N1, whose pupil bias score was comparable to most severe biases in healthy controls, but who omitted 8 left targets on the star cancellation task, in which ipsilesional stimuli are present.

Whilst data of five participants warrants further replication, our findings raise the question whether covert attentional biases present chronically persistent. In line with this notion, recent auditory-based ERP measures as a proxy for attention showed no improvement of automatic attentional biases in left-sided neglect after rehabilitation treatment, despite improvement on classical neuropsychological tests (Hildebrandt, Notbohm, Duning, & Schweser, 2023). If follow-up research confirms that the automatic attention bias in participants with neglect indeed does not resolve, this would have substantial implications for understanding the recovery of neglect. Generally, it is thought that recovery of the *impairment itself*—restoration of the underlying attentional system—takes place within the first three months post-stroke (Durfee & Hillis, 2023; Kerkhoff & Schenk, 2012; Nijboer et al., 2013). After this initial period, recovery is thought to be mainly driven by compensatory strategies. The results from the current study, however, lead to the hypothesis that already in the first three months, other processes (e.g., top-down attention) become involved for the compensation for the automatic attention bias (Hildebrandt et al., 2023), which itself may never recover.

Biases were found to be comparable in strength for participants with damages to sensory (hemianopia) and attentional (neglect) systems. Together with previous findings (Binda et al., 2013; Binda & Murray, 2015; Haab, 1886; Kardon et al., 1991; Maeda et al., 2017; Mathôt et al., 2013; Naber et al., 2011, 2018; Portengen et al., 2021; Skorkovská et al., 2009; Strauch, Wang, et al., 2022), this supports the notion that the pupil light response is not solely reflexive, but heavily modulated by attention and thus cortical processing. Such cortical influences hereby must pass the parietal areas damaged in neglect and with it the attentional system and more frontal areas, likely via the frontal eye fields, to affect the brainstem circuit around the superior colliculus that brings about related modulations in pupil size (Strauch, Wang, et al., 2022; Wang & Munoz, 2018).

Furthermore, previous studies have shown that hemianopia and neglect share anatomical substrates. For example, damage to the optic tracks, linking the lateral geniculate nucleus to the primary visual cortex, could cause hemianopia but is also related to visuospatial neglect (Toba et al., 2020). All participants with neglect had no reported concurrent diagnosis of visual field deficits by the hospital and rehabilitation center, still, we did not obtain information on how this was tested. Possibly undiagnosed visual field deficits could thus have contributed to biased pupil light responses in a subset of participants with neglect.

Importantly, participants with visual field deficits versus those with neglect were not comparable regarding time post-injury, which argues for caution when comparing these groups.

4.2. *A roadmap to solve outstanding questions and challenges*

The here introduced method might hold the key to solve a number of longstanding theoretical and applied challenges that neglect continues to pose, which are discussed in the following. On a fundamental level, pupillometry has the potential to uncover the extent to which neglect arises from attentional competition between stimuli or from an inherent bias in spatial attention towards the right (Husain, 2019; Karnath, 2015). To this end, an additional condition featuring a single stimulus on either the left or right side of the intermediate gray display could be incorporated. If pupil light responses were similar for presentation on the right and on the left, this would be in favor of a competition account—as position would be irrelevant in isolation. If, however, pupil light responses were substantially stronger for the stimulus presented on the right than on the left, this would argue for a default bias to the right, independent of interference from the left. Responses falling between these two extremes would support an integrated view of both accounts and indicate the extent to which neglect is shaped by attentional competition versus default attentional biases.

Adding dual tasks to increase attentional demands has been shown to reveal hidden biases in many neuropsychological tasks that might otherwise go undetected in chronic stages (e.g., Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Robertson & Frasca, 1991; Russell, Malhotra, & Husain, 2004). But is mental effort interfering with the interhemispheric balance of dorsal networks (Paladini et al., 2020), directly on the level of the spatial attentional system (Corbetta & Shulman, 2011; Kinsbourne, 1993), or is effort interfering with (highly automatized, yet effortful) compensation strategies instead (Villarreal et al., 2022)? If the account of persistently unaltered pupillometric biases was correct, pupillometric biases should present also without the induction of effort—any further enhancement with effort would argue for an effect of effort on spatial attention in turn. If, however, biases would not enhance, then this would suggest that effort interferes only on the level of executive control needed for compensatory strategies.

Besides these fundamental questions, the here presented method could be useful to dissociate between subtypes of neglect. We propose that, for instance, connected black/white or white/black stimuli that are positioned on both hemifields should go in hand with a much stronger pupillometric bias in allocentric than in egocentric neglect, although, as for the other predictions made in this section above, this remains to be tested. In combination with the aforementioned manipulations this could adequately address the individual, here clustered as a participant with neglect. Neglect is a heterogenous syndrome with a plethora of potential subtypes and possibly different underlying neural substrates and attentional mechanisms at play.

Successful clinical use of the here presented method for diagnosis as an enhancement to existing diagnostic tools will critically depend on iterative improvements to be made for increased feasibility/usability with patients and practitioners as stakeholders. This could be achieved by using gaze-contingent displays, allowing participants to blink, and using eye trackers that are robust to noise. Hereby, a sweet spot in the trade-off between diagnostic properties, cost effectiveness, and burden put on the participants must be found—these considerations could for instance concern the number of trials or the length of stimulus presentation. Furthermore, a study with a large sample size is needed, preferably including participants with left- and right-brain damage following stroke, with and without neglect as determined based upon existing measures to assess reliability, validity, sensitivity, and specificity. This should then also result in a threshold bias score that divides patients with neglect from those without. The estimation of the pupil bias per participant could ideally be determined flexibly, for instance by either reaching a predefined Bayes factor for a null effect or a clear bias, respectively, and then stopping the assessment.

To conclude, our objective, rapid pupillometry-based method allows to directly assess the core deficit of neglect, namely the ipsilesional (covert) attentional bias in absence of any task beyond simple fixation. Participants with deficits in vision, a sensory function, showed almost similarly biased pupil responses as participants with deficits in attentional function. Our initial data further reveals that covert attention is persistently altered in participants with neglect, even weeks or months after stroke. We expect insights into mechanisms of spatial attention, subtypes of neglect, recovery over time, or the effectiveness and working principles of therapies. This method should next be evaluated on larger scale for the clinical diagnosis of neglect, especially in a more chronic phase post-stroke because of its potential robustness to compensation.

Open practices section

The study in this article earned Open Data and Open Material badges for transparent practices. The data and materials used in this study are available at https://osf.io/hs73k/.

Funding

M. Naber was funded by an UitZicht grant 2018–10 (Rotterdamse Stichting Blindenbelangen). B.L. Portengen was funded by the ODAS foundation (grant number 2017–03), the Rotterdamse Stichting Blindenbelangen (grant number B20170004), the F.P. Fischer Foundation (grant number 170511), and the Janivo Foundation (grant number 2017170). The funders had no role in the study design, collection, management, analysis and interpretation of data.

Author contributions

C. Strauch and A.F. Ten Brink conceptualized the studies. C. Strauch, A.F. Ten Brink, and M. Van Heijst contributed to the study design under assistance of M. Naber. Implementation and data curation were performed by M. Van Heijst and A.F. Ten Brink with assistance by B.L. Portengen under supervision of A.F. Ten Brink and C. Strauch. C. Strauch and M. Van Heijst performed the data analysis. C. Strauch and A.F. Ten Brink wrote the draft of the manuscript, C. Strauch performed the visualization of results, A.F. Ten Brink, C. Strauch, B.L. Portengen and M. Naber provided critical review & editing.

Declaration of competing interest

None.

Acknowledgements

We thank all participants for their time. We would like to thank rehabilitation centre De Parkgraaf, in particular Mieke Wilms and Ingrid den Ouden, for their time and help with data collection. We thank Alex J. Hoogerbrugge and Damian Koevoet for discussing visualizations.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.06.008.

REFERENCES

Aimola, L., Schindler, I., Simone, A. M., & Venneri, A. (2012). Near and far space neglect: Task sensitivity and anatomical substrates. *Neuropsychologia*, 50(6), 1115–1123. https://doi.org/10.1016/j.neuropsychologia.2012.01.022

Azouvi, P., Bartolomeo, P., Beis, J., Perennou, D., Pradat-diehl, P., & Rousseaux, M. (2006). A battery of tests for the quantitative assessment of unilateral neglect. *Restorative Neurology and Neuroscience*, 24(4–6), 273–285.

Azouvi, P., Marchal, F., Samuel, C., Morin, L., Renard, C., Louis-Dreyfus, A., et al. (1996). Functional consequences and awareness of unilateral neglect: Study of an evaluation scale. *Neuropsychological Rehabilitation*, 6(2), 133–150. https://doi.org/10.1080/713755501

Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., & Tesio, L. (2003). Behavioral assessment of unilateral neglect: Study of the psychometric properties of the Catherine Bergego Scale. *Archives of Physical Medicine and Rehabilitation*, 84(1), 51–57. https://doi.org/10.1053/apmr.2003.50062

Bartolomeo, P. (1997). The novelty effect in recovered hemineglect. *Cortex; a Journal Devoted To the Study of the Nervous System and Behavior*, 33(2), 323–333. https://doi.org/10.1016/S0010-9452(08)70008-X

Bartolomeo, P. (2000). Inhibitory processes and spatial bias after right hemisphere damage. *Neuropsychological Rehabilitation, 10*(5), 511–526. https://doi.org/10.1080/09602010050143577

Bartolomeo, P., & Chokron, S. (2002). Orienting of attention in left unilateral neglect. *Neuroscience and Biobehavioral Reviews, 26*, 217–234. https://doi.org/10.1016/S0149-7634(01)00065-3

Benwell, C. S. Y., Harvey, M., & Thut, G. (2014). On the neural origin of pseudoneglect: EEG-correlates of shifts in line bisection performance with manipulation of line length. *Neuroimage, 86*, 370–380. https://doi.org/10.1016/j.neuroimage.2013.10.014

Binda, P., & Murray, S. O. (2015). Keeping a large-pupilled eye on high-level visual processing. *Trends in Cognitive Sciences, 19*(1), 1–3. https://doi.org/10.1016/j.tics.2014.11.002

Binda, P., Pereverzeva, M., & Murray, S. O. (2013). Attention to bright surfaces enhances the pupillary light reflex. *The Journal of Neuroscience, 33*(5), 2199–2204. https://doi.org/10.1523/JNEUROSCI.3440-12.2013

Bonato, M. (2015). Unveiling residual, spontaneous recovery from subtle hemispatial neglect three years after stroke. *Frontiers in Human Neuroscience, 9*(July), 1–9. https://doi.org/10.3389/fnhum.2015.00413

Bonato, M., & Deouell, L. Y. (2013). Hemispatial neglect: Computer-based testing allows more sensitive quantification of attentional disorders and recovery and might lead to better evaluation of rehabilitation. *Frontiers in Human Neuroscience, 7*(May), 162. https://doi.org/10.3389/fnhum.2013.00162

Bonato, M., Priftis, K., Marenzi, R., Umiltà, C., & Zorzi, M. (2010). Increased attentional demands impair contralesional space awareness following stroke. *Neuropsychologia, 48*(13), 3934–3940. https://doi.org/10.1016/j.neuropsychologia.2010.08.022

Bonato, M., Priftis, K., Marenzi, R., & Zorzi, M. (2009). Normal and impaired reflexive orienting of attention after central nonpredictive cues. *Journal of Cognitive Neuroscience, 21*(4), 745–759. https://doi.org/10.1162/jocn.2009.21054

Bonato, M., Priftis, K., Umiltà, C., & Zorzi, M. (2013). Computer-based attention-demanding testing unveils severe neglect in apparently intact patients. *Behavioural Neurology, 26*(3), 179–181. https://doi.org/10.3233/BEN-2012-129005

Bowers, D., & Heilman, K. M. (1980). Pseudoneglect: Effects of hemispace on a tactile line bisection task. *Neuropsychologia, 18*(4–5), 491–498. https://doi.org/10.1016/0028-3932(80)90151-7

Buxbaum, L. J., Ferraro, M. K., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., et al. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology, 62*(5), 749–756. https://doi.org/10.1212/01.WNL.0000113730.73031.F4

Cassidy, T. P., Lewis, S., & Gray, C. S. (1998). Recovery from visuospatial neglect in stroke patients. *Journal of Neurology, Neurosurgery, and Psychiatry, 64*(4), 555–557. https://doi.org/10.1136/jnnp.64.4.555

Chechlacz, M., Rotshtein, P., Bickerton, W.-L., Hansen, P. C., Deb, S., & Humphreys, G. W. (2010). Separating neural correlates of allocentric and egocentric neglect: Distinct cortical sites and common white matter disconnections. *Cognitive Neuropsychology, 27*(3), 277–303. https://doi.org/10.1080/02643294.2010.519699

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience, 34*(1), 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Cox, J. A., & Aimola Davies, A. M. (2020). Keeping an eye on visual search patterns in visuospatial neglect: A systematic review. *Neuropsychologia, 146*(June), Article 107547. https://doi.org/10.1016/j.neuropsychologia.2020.107547

Danckert, J., & Ferber, S. (2006). Revisiting unilateral neglect. *Neuropsychologia, 44*(6), 987–1006. https://doi.org/10.1016/j.neuropsychologia.2005.09.004

Deouell, L. Y., Sacher, Y., & Soroker, N. (2005). Assessment of spatial attention after brain damage with a dynamic reaction time test. *Journal of the International Neuropsychological Society: JINS, 11*(6), 697–707. https://doi.org/10.1017/S1355617705050824

Deubel, H., & Schneider, W. X. (1996). Saccade target selection and object recognition: Evidence for a common attentional mechanism. *Vision Research, 36*(12), 1827–1837. https://doi.org/10.1016/0042-6989(95)00294-4

Durfee, A. Z., & Hillis, A. E. (2023). Unilateral spatial neglect recovery poststroke. *Stroke; a Journal of Cerebral Circulation,* 54(1), 10–19. https://doi.org/10.1161/STROKEAHA.122.041710

Esposito, E., Shekhtman, G., & Chen, P. (2021). Prevalence of spatial neglect post-stroke: A systematic review. *Annals of Physical and Rehabilitation Medicine, 64*(5), Article 101459. https://doi.org/10.1016/j.rehab.2020.10.010

Fruhmann-Berger, M., & Karnath, H.-O. (2005). Spontaneous eye and head position in patients with spatial neglect. *Journal of Neurology, 252*(10), 1194–1200. https://doi.org/10.1007/s00415-005-0831-y

Haab, O. (1886). Vortrag gesellschaft der Ärzte in zürich am 21. november 1885. *Korrespondenzbl. f. Schweizer Ärzte, 16*, 153.

Heilman, K. M., & Van Den Abell, T. (1979). Right hemispheric dominance for mediating cerebral activation. *Neuropsychologia, 17*(3–4), 315–321. https://doi.org/10.1016/0028-3932(79)90077-0

Hildebrandt, H., Notbohm, A., Duning, T., & Schweser, I. (2023). Is recovery from left-sided neglect based on changes in automatic attention? An auditory event related potentials study. *Applied Neuropsychology Adult, 0*(0), 1–11. https://doi.org/10.1080/23279095.2022.2163173

Husain, M. (2019). Visual attention: What inattention reveals about the brain. *Current Biology, 29*(7), R262–R264. https://doi.org/10.1016/j.cub.2019.02.026

Jacobs, S., Brozzoli, C., & Farnè, A. (2012). Neglect: A multisensory deficit? *Neuropsychologia,* 50(6), 1029–1044. https://doi.org/10.1016/j.neuropsychologia.2012.03.018

JASP Team. (2021). *JASP*.

Jehkonen, M., Ahonen, J.-P., Dastidar, P., Koivisto, A.-M., Laippala, P., Vilkki, J., et al. (2000). Visual neglect as a predictor of functional outcome one year after stroke. *Acta Neurologica Scandinavica, 101*(3), 195–201. https://doi.org/10.1034/j.1600-0404.2000.101003195.x

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: A review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia, 38*(1), 93–110. https://doi.org/10.1016/S0028-3932(99)00045-7

Kardon, R. H., Kirkali, P. A., & Thompson, H. S. (1991). Automated pupil perimetry pupil field mapping in patients and normal subjects. *Ophthalmology, 98*(4), 485–496. https://doi.org/10.1016/S0161-6420(91)32267-X

Karnath, H.-O. (1997). Spatial orientation and the representation of space with parietal lobe lesions. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 352*(1360), 1411–1419. https://doi.org/10.1098/rstb.1997.0127

Karnath, H.-O. (2015). Spatial attention systems in spatial neglect. *Neuropsychologia, 75*, 61–73. https://doi.org/10.1016/j.neuropsychologia.2015.05.019

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia,* 50(6), 1072–1079. https://doi.org/10.1016/j.neuropsychologia.2012.01.024

Kinsbourne, M. (1993). Orientational bias model of unilateral neglect: Evidence from attentional gradients within hemispace. In I. H. Robertson, & J. C. Marshall (Eds.), *Brain damage, behaviour & cognition series. Unilateral neglect: Clinical and experimental studies* (pp. 63–86). Lawrence Erlbaum Associates.

Lasaponara, S., Fortunato, G., Conversi, D., Pellegrino, M., Pinto, M., Collins, D. L., et al. (2021). Pupil dilation during orienting of attention and conscious detection of visual targets in patients with left spatial neglect. *Cortex; a Journal Devoted To the Study of the Nervous System and Behavior, 134*, 265–277. https://doi.org/10.1016/j.cortex.2020.10.021

Learmonth, G., Benwell, C. S. Y., Thut, G., & Harvey, M. (2017). Age-related reduction of hemispheric lateralisation for spatial attention: An EEG study. *Neuroimage, 153*(June 2016), 139–151. https://doi.org/10.1016/j.neuroimage.2017.03.050

Longley, V., Hazelton, C., Heal, C., Pollock, A., Woodward-Nutt, K., Mitchell, C., et al. (2021). Non-pharmacological interventions for spatial neglect or inattention following stroke and other non-progressive brain injury. *[The Cochrane Database of Systematic Reviews Electronic Resource], 2021*(7). https://doi.org/10.1002/14651858.CD003586.pub4

Losier, B. J., & Klein, R. M. (2001). A review of the evidence for a disengage deficit following parietal lobe damage. *Neuroscience and Biobehavioral Reviews, 25*(1), 1–13. https://doi.org/10.1016/S0149-7634(00)00046-4

Luauté, J., Halligan, P., Rode, G., Rossetti, Y., & Boisson, D. (2006). Visuo-spatial neglect: A systematic review of current interventions and their effectiveness. *Neuroscience and Biobehavioral Reviews, 30*, 961–982. https://doi.org/10.1016/j.neubiorev.2006.03.001

Maeda, F., Kelbsch, C., Straßer, T., Skorkovská, K., Peters, T., Wilhelm, B., et al. (2017). Chromatic pupillography in hemianopia patients with homonymous visual field defects. *Graefe's Archive for Clinical and Experimental Ophthalmology, 255*(9), 1837–1842. https://doi.org/10.1007/s00417-017-3721-y

Mathôt, S., van der Linden, L., Grainger, J., & Vitu, F. (2013). The pupillary light response reveals the focus of covert visual attention. *Plos One, 8*(10), Article e78168. https://doi.org/10.1371/journal.pone.0078168

Mattingley, J. B., Bradshaw, J. L., Nettleton, N. C., & Bradshaw, J. A. (1994). Can task specific perceptual bias be distinguished from unilateral neglect? *Neuropsychologia, 32*(7), 805–817. https://doi.org/10.1016/0028-3932(94)90019-1

McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cancer Biotherapy & Radiopharmaceuticals, 25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

Menon, A., & Korner-Bitensky, N. (2004). Evaluating unilateral spatial neglect post stroke: Working your way through the maze of assessment choices. *Topics in Stroke Rehabilitation, 11*(3), 41–66. https://doi.org/10.1310/KQWL-3HQL-4KNM-5F4U

Moore, M. J., Milosevich, E., Mattingley, J. B., & Demeyere, N. (2023). The neuroanatomy of visuospatial neglect: A systematic review and analysis of lesion-mapping methodology. *Neuropsychologia, 180*(January), Article 108470. https://doi.org/10.1016/j.neuropsychologia.2023.108470

Naber, M., Alvarez, G. A., & Nakayama, K. (2013). Tracking the allocation of attention using human pupillary oscillations. *Frontiers in Psychology, 4*(DEC), 1–12. https://doi.org/10.3389/fpsyg.2013.00919

Naber, M., Frässle, S., & Einhäuser, W. (2011). Perceptual rivalry: Reflexes reveal the gradual nature of visual awareness. *Plos One, 6*(6), Article e20910. https://doi.org/10.1371/journal.pone.0020910

Naber, M., Roelofzen, C., Fracasso, A., Bergsma, D. P., van Genderen, M., Porro, G. L., et al. (2018). Gaze-contingent flicker pupil perimetry detects scotomas in patients with cerebral visual impairments or glaucoma. *The Florida Nurse, 9*(JUL), 1–12. https://doi.org/10.3389/fneur.2018.00558

Nicholls, M. E. R., Bradshaw, J. L., & Mattingley, J. B. (1999). Free-viewing perceptual asymmetries for the judgement of brightness, numerosity and size. *Neuropsychologia, 37*(3), 307–314. https://doi.org/10.1016/S0028-3932(98)00074-8

Nijboer, T. C. W., Kollen, B. J., & Kwakkel, G. (2013). Time course of visuospatial neglect early after stroke: A longitudinal cohort study. *Cortex; a Journal Devoted To the Study of the Nervous System and Behavior, 49*(8), 2021–2027. https://doi.org/10.1016/j.cortex.2012.11.006

Paladini, R. E., Wieland, F. A. M., Naert, L., Bonato, M., Mosimann, U. P., Nef, T., et al. (2020). The impact of cognitive load on the spatial deployment of visual attention: Testing the role of interhemispheric balance with biparietal transcranial direct current stimulation. *The Florida Nurse, 13*(January), 1–6. https://doi.org/10.3389/fnins.2019.01391

Parton, A., Malhotra, P., & Husain, M. (2004). Hemispatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 75*(1), 13–21.

Patel, M., Coshall, C., Rudd, A. G., & Wolfe, C. D. A. (2003). Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clinical Rehabilitation, 17*(2), 158–166. https://doi.org/10.1191/0269215503cr596oa

Peirce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., et al. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior Research Methods, 51*(1), 195–203. https://doi.org/10.3758/s13428-018-01193-y

Portengen, B. L., Roelofzen, C., Porro, G. L., Imhof, S. M., Fracasso, A., & Naber, M. (2021). Blind spot and visual field anisotropy detection with flicker pupil perimetry across brightness and task variations. *Vision Research, 178*(October 2020), 79–85. https://doi.org/10.1016/j.visres.2020.10.005

Robertson, I., & Frasca, R. (1991). Attentional load and visual neglect. *International Journal of Neuroscience, 62*(1–2), 45–56. https://doi.org/10.3109/00207459108999756

Russell, C., Malhotra, P., & Husain, M. (2004). Attention modulates the visual field in healthy observers and parietal patients. *Neuroreport, 15*(14), 2189–2193. https://doi.org/10.1097/00001756-200410050-00009

Schmitz, R., & Peigneux, P. (2011). Age-related changes in visual pseudoneglect. *Brain and Cognition, 76*(3), 382–389. https://doi.org/10.1016/j.bandc.2011.04.002

Skorkovská, K., Wilhelm, H., Lüdtke, H., & Wilhelm, B. (2009). How sensitive is pupil campimetry in hemifield loss? *Graefe's Archive for Clinical and Experimental Ophthalmology, 247*(7), 947–953. https://doi.org/10.1007/s00417-009-1040-7

Spaccavento, S., Cellamare, F., Falcone, R., Loverre, A., & Nardulli, R. (2017). Effect of subtypes of neglect on functional outcome in stroke patients. *Annals of Physical and Rehabilitation Medicine, 60*(6), 376–381. https://doi.org/10.1016/j.rehab.2017.07.245

Spreij, L. A., Ten Brink, A. F., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2020). Increasing cognitive demand in assessments of visuo-spatial neglect: Testing the concepts of static and dynamic tests. *Journal of Clinical and Experimental Neuropsychology, 42*(7), 675–689. https://doi.org/10.1080/13803395.2020.1798881

Strauch, C., Romein, C., Naber, M., Van der Stigchel, S., & Ten Brink, A. F. (2022). The orienting response drives pseudoneglect—evidence from an objective pupillometric method. *Cortex; a Journal Devoted To the Study of the Nervous System and Behavior, 151*, 259–271. https://doi.org/10.1016/j.cortex.2022.03.006

Strauch, C., Wang, C.-A., Einhäuser, W., Van der Stigchel, S., & Naber, M. (2022). Pupillometry as an integrated readout of distinct attentional networks. *Trends in Neurosciences, 45*(8), 635–647. https://doi.org/10.1016/j.tins.2022.05.003

Ten Brink, A. F., Nijboer, T. C. W., Van Beekum, L., Van Dijk, J., Peeters, R., Post, M. W. M., et al. (2013). De nederlandse catherine Bergego schaal: Een bruikbaar en valide instrument in de CVA zorg. *Wetenschappelijk Tijdschrift voor Ergotherapie, 6*(3), 27–36.

Ten Brink, A. F., Verwer, J. H., Biesbroek, J. M., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2017). Differences between left- and right-sided neglect revisited: A large cohort study across multiple domains. *Journal of Clinical and Experimental Neuropsychology, 39*(7), 707–723. https://doi.org/10.1080/13803395.2016.1262333

Toba, M. N., Zavaglia, M., Malherbe, C., Moreau, T., Rastelli, F., Kaglik, A., et al. (2020). Game theoretical mapping of white matter contributions to visuospatial attention in stroke patients with hemineglect. *Human Brain Mapping, 41*(11), 2926–2950. https://doi.org/10.1002/hbm.24987

Van der Stoep, N., Visser-Meily, J., Kappelle, L., de Kort, P., Huisman, K., Eijsackers, A., et al. (2013). Exploring near and far regions of space: Distance-specific visuospatial neglect after stroke. *Journal of Clinical and Experimental Neuropsychology, 35*(8), 799–811. https://doi.org/10.1080/13803395.2013.824555

Villarreal, S., Linnavuo, M., Sepponen, R., Vuori, O., Bonato, M., Jokinen, H., et al. (2022). Computer-based assessment: Dual-task outperforms large-screen cancellation task in detecting contralesional omissions. *Frontiers in Psychology, 12*(January), 1–15. https://doi.org/10.3389/fpsyg.2021.790438

von Helmholtz, H. (1866). *Treatise on physiological optics*. Dover Publication.

Wang, C.-A., & Munoz, D. P. (2018). Neural basis of location-specific pupil luminance modulation. *Proceedings of the National Academy of Sciences, 115*(41), 10446–10451. https://doi.org/10.1073/pnas.1809668115

Wilson, B., Cockburn, J., & Halligan, P. (1987). *Behavioural inattention test*.