

# Alertness Training Improves Spatial Bias and Functional Ability in Spatial Neglect

Thomas Van Vleet, PhD <sup>(a)</sup>,<sup>1</sup> Paolo Bonato, PhD,<sup>2,3</sup> Eric Fabara, MD,<sup>3</sup> Sawsan Dabit, BA <sup>(a)</sup>,<sup>1</sup>

Sarah-Jane Kim, MA,<sup>1</sup> Christopher Chiu, BA,<sup>4</sup> Antonio Luigi Bisogno, MD,<sup>5</sup>

Michael Merzenich, PhD,<sup>1,6</sup> Maurizio Corbetta, MD,<sup>5,7,8</sup>

and Joseph DeGutis, PhD<sup>9,10</sup>

**Objective:** We conducted a multisite, randomized, double-blinded, controlled trial to examine the effectiveness of a digital health intervention targeting the intrinsic regulation of goal-directed alertness in patients with chronic hemispatial neglect.

**Methods:** Forty-nine participants with hemispatial neglect, who demonstrated significant spatially biased attention after acquired brain injury, were randomly assigned to the experimental attention remediation treatment or the active control group. The participants engaged with the remotely administered interventions for 12 weeks. The primary outcome was spatial bias on the Posner cueing task (response time difference: left minus right target trials). Secondary outcomes included functional abilities (measured via the Catherine Bergego scale and Barthel index), spatial cognition, executive function, quality of life, and sleep. Assessments were conducted before and immediately after participation in the experimental intervention or control condition, and again after a 3-month no-contact period.

**Results:** Compared with the active control group, the intervention group exhibited a significant improvement in the primary outcome, a reduction in spatially biased attention on the Posner cueing task (p = 0.010, Cohen's d = 0.96), in addition to significant improvements in functional abilities as measured on the Catherine Bergego and Barthel indices (p = 0.027, Cohen's d = 0.24).

**Interpretation:** Our results demonstrate that our attention training program was effective in improving the debilitating attention deficits common to hemispatial neglect. This benefit generalized to improvements in real-world functional abilities. This safe, highly scalable, and self-administered treatment for hemispatial neglect might serve as a useful addition to the existing standard of care.

#### ANN NEUROL 2020;88:747-758

# Introduction

Nearly one-third of all patients suffering unilateral brain injury exhibit a debilitating array of attention deficits known as hemispatial neglect.<sup>1–4</sup> Although signs of neglect can vary greatly in presentation and severity,<sup>5–7</sup> the most widely recognized deficit is failure to attend or respond to stimulation presented to the side of space opposite the lesion (ie,

contralesional).<sup>8–13</sup> Pronounced biases in spontaneous orienting and motor initiation typically resolve in the postacute phase of recovery, whereas deficits in goal-directed spatial attention (eg, searching in an array of stimuli; or shifting attention from stimuli in the ipsilesional to the contralesional visual field [disengagement]) can persist for several years postinsult.<sup>14–16</sup> Patients with neglect consistently score lower

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25862

Received Oct 29, 2019, and in revised form Jul 21, 2020. Accepted for publication Jul 26, 2020.

Address correspondence to Dr Van Vleet, Research and Development, Posit Science, 160 Pine Street, Suite 200, San Francisco, CA 94111. E-mail: tom. vanvleet@positscience.com

Additional supporting information can be found in the online version of this article.

From the <sup>1</sup>Department of Research and Development, Posit Science Inc, San Francisco, CA, USA; <sup>2</sup>Department of Physical Medicine & Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, Boston, MA, USA; <sup>3</sup>Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, USA; <sup>4</sup>Department of Psychology, University of Massachusetts, Boston, MA, USA; <sup>5</sup>Clinica Neurologica, Department of Neuroscience, and Padova Neuroscience Center (PNC), University of Padova, Italy; <sup>6</sup>School of Medicine, University of California, San Francisco, CA, USA; <sup>7</sup>Department of Neurology, Radiology, Neuroscience Washington University School of Medicine, St. Louis, MO, USA; <sup>8</sup>Venetian Institute of Molecular Medicine, VIMM, Padova, Italy; <sup>9</sup>Boston Attention and Learning Laboratory, VA Boston Healthcare System, Boston, MA, USA; and <sup>10</sup>Department of Psychiatry, Harvard Medical School, Boston, MA, USA

at both admission and discharge on established measures of functional ability and activities of daily living.<sup>17–19</sup> Furthermore, the presence of neglect is associated with poor motor recovery, higher rates of disability and poor response to rehabilitation compared with other patient groups with similar lesion extent;<sup>7,20–22</sup> a condition made worse by higher rates of denial (anosagnosia<sup>23</sup>) or apathy towards these deficits relative to patients with similar lesions but without neglect, further complicating recovery and treatment.

Deficits in nonspatially lateralized attention<sup>24-27</sup> are fundamental to the persistence of neglect beyond the acute phase of recovery. Lesions associated with persistent neglect often involve damage to the right ventral attention network (VAN), which supports nonspatially lateralized attention.<sup>28-30</sup> The ensuing functional disconnection between spatial and nonspatial neural systems has been shown to be closely associated with deficits in nonspatially lateralized attention,<sup>31–33</sup> including decreased physiological arousal,<sup>34</sup> poor sustained attention,<sup>35</sup> inefficient updating of visual working memory,<sup>25,27</sup> poor temporal resolution,<sup>36</sup> and slow speed of processing.<sup>37</sup> Crucially, these deficits bias the deployment of spatial attention<sup>38-40</sup> and undermine more complex cognitive functions, such as short-term memory and executive control, resulting in impairments in functional abilities.<sup>41</sup> Notably, the severity of nonspatial deficits in neglect and associated VAN lesions have been shown to be a stronger predictor of the chronicity of neglect than the spatially lateralized deficits.<sup>25,26,42-44</sup> Thus, addressing these deficits is crucial to improving long-term outcomes in neglect.

The current treatment standard for neglect is timelimited sessions of therapist-guided leftward cueing.<sup>45</sup> Although voluntary cueing improves the trained task,<sup>46</sup> it has limited generalization and can easily be overcome by stimuli that automatically attract attention to the right in the presence of a left neglect. Furthermore, therapistadministered behavioral treatments that rely on adequate recall of a new strategy (eg, "look left")<sup>38,47</sup> might not be well suited to patients with limited awareness of their deficits.<sup>48</sup> Pharmacotherapies, which are often administered in parallel, can boost alertness and nonspatial attention. However, they have been generally less effective than behavioral treatments and have shown mixed outcomes, in addition to producing potentially negative side effects (eg, detrimental interactions with other medications).<sup>7,49</sup> In the past decade, computerized behavioral training methods that target nonspatial deficits in neglect have taken a distinctly different approach, providing systematic and adaptive challenges tailored to the specific deficits of the patient. This bottom-up approach to treatment (ie, no explicit strategy required) provides many hundreds to several thousands of learning trials presented across

multiple virtual contexts to engage mechanisms of learning and generalization more fully.<sup>50</sup>

In the present study, we used a computerized intervention that targets both tonic (sustained) and phasic (moment-tomoment) alertness, referred to as tonic and phasic alertness training (TAPAT). Unlike many treatment approaches for neglect, TAPAT does not require deployment of spatial attention. Instead, TAPAT was designed to challenge the ability of patients to sustain nonspatially lateralized attention intrinsically via prolonged training epochs (multiple  $\sim$ 10-minute blocks per session), jittered interstimulus intervals (ISIs),<sup>51,52</sup> and continual and successive signal resolution of stimuli presented at central fixation.<sup>53</sup> The design of the TAPAT intervention was inspired by seminal studies conducted by Ian Robertson and colleagues, in which phasic<sup>40,54</sup> or tonic manipulations of alertness<sup>38,54,55</sup> were shown to decrease deficits and reduce spatial bias, albeit transiently. In TAPAT, patients are required to respond via button press to frequent and centrally presented images, while actively inhibiting their prepotent motor response when an infrequent and randomly presented target image is shown (a new target image was committed to memory before each  $\sim$ 10-minute training epoch). This attention remediation approach, relative to an active control (AC) condition, has been effective in reducing or eliminating spatial bias in all but 2 of 20 patients with neglect in two prior preliminary TAPAT training trials.<sup>56,57</sup> Furthermore, in these studies, improvements in target accuracy (ie, inhibitory control/phasic alertness) were significantly correlated with improvements in sensitive measures of spatial attention.56,57

To examine the efficacy of TAPAT training to improve spatial attention and functional outcomes in patients with neglect, we conducted a definitive multisite, randomized, double-blinded, controlled clinical trial, which was referred to as the REmediation of SPatial NEglect trial or RESPONSE trial (clinicaltrials.gov NCT01965951). Relative to prior studies that have examined the effects of TAPAT in patients with neglect, we increased the total training time from  $\sim 6$  to  $\sim 12$  hours, incorporated functional outcome measures, included a broader array of spatial bias measures and used a previously validated active control condition.<sup>58</sup> Most importantly, we used a sensitive measure of spatial bias, the Posner cueing task, as the primary outcome measure, because of its demonstrated ability effectively to capture spatial bias associated with neglect in the chronic phase of recovery, in addition to its demonstrated sensitivity and specificity relative to other commonly used measures of neglect.<sup>59</sup>

# **Patients and Methods**

#### Trial Registration and Data Access

This trial was preregistered at clinicaltrials.gov (NCT01965951).

#### Design

This was a multisite, randomized, double-blinded, controlled trial conducted at Washington University, St Louis, MO; VA Boston Healthcare System, Boston, MA; and Spaulding Rehabilitation Hospital, Boston, MA.

#### Protocol

The RESPONSE protocol was reviewed and approved by the Western Institutional Review Board (IRB Protocol 20132014) and funded by the US National Institutes of Health (NIH; NINDS R44NS071780). The study protocol and analysis plan was published<sup>60</sup> before completing participant enrollment. The following amendment to the protocol was made by an independent external advisory committee before unblinding. Specifically, owing to technical problems with the administration of an adapted conjunction search task, which prohibited the use of this measure, the Posner cueing task was specified as the primary outcome measure (response time [RT] difference for detecting targets appearing on the left compared with the right side).<sup>59</sup>

Inclusion and exclusion criteria were chosen to identify participants with chronic spatial neglect. Inclusion criteria were  $\geq 3$  months after acquired brain injury that resulted in spatial neglect (ICD-10-CM R41.4) defined as deficient performance on  $\geq 2$  of 4 common measures of spatial attention, including: the Mesulam cancellation task<sup>61</sup> (ages 50 years and younger >0 omissions; 51–80 years > 4 omissions); a tone counting task<sup>26</sup> (<94%) total accuracy); landmark task<sup>57</sup> (deviation from objective center as determined by the 95% confidence interval); and a spatial dual task<sup>62</sup> (>19% difference in accuracy for right-left target trials). For the dual task, if accuracy to correctly identify the symbol in the initial task was <50%, the assessment was repeated once. If accuracy to correctly identify the symbol did not improve to  $\geq 50\%$  in the second administration, inclusion was based on performance consistent with neglect in all the remaining measures. Additional inclusion criteria were ≤8 on the Blessed scale-short form<sup>63</sup> (ie, no residual cognitive impairment or dementia), aged ≥18 years, fluent English speakers, and intact sensorimotor capacity to use the computerized intervention.

Exclusion criteria were complete primary visual field deficit (score of 3 on the NIH Stroke Scale visual field subscale<sup>64</sup>), a diagnosis of an illness or condition with known cognitive consequences (eg, schizophrenia, bipolar disorder, cancer, or multiple sclerosis; however, common comorbidities following brain injury, including post-traumatic stress disorder, mild to moderate depression, and chronic pain were not exclusion criteria), major depression (Beck Depression Inventory, second edition; BDI-II

 $\geq$  29), or evidence of active suicidal ideation or behavior within 1 month of consent on the Columbia-Suicide Severity Rating Scale Scale,<sup>65</sup> (C-SSRS). Participants who appeared to be intoxicated or under the influence of a controlled substance on any day of assessment were rescheduled or discontinued. Participants were also excluded for participation in a concurrent clinical trial that could affect the outcome of this one. Participation in standard treatments, such as occupational therapy or use of prescribed medications (eg, anticoagulant) were not exclusion criteria. Recruitment took place through general internal medicine and neurology clinics at Washington University, Boston VA, and Spaulding Rehabilitation Hospital, in addition to the surrounding communities of St Louis and Boston.

#### Procedures

Institutional review board approval was obtained at the coordinating center (Posit Science) and at each local site. Participants were reimbursed for their participation; those completing all training and assessment visits could earn \$435.00. Written informed consent was obtained from all participants.

The 49 eligible participants were randomized after baseline assessment. Randomization stratified participants based on their age (adults 18–64 years of age or seniors  $\geq$  65 years of age) and severity of spatial neglect symptoms based on performance on a computerized search task (mild–moderate or severe defined as <621 or >620 milliseconds difference in detection of left–right targets, respectively); controlling balance based on random permuted blocks within strata, and blocked according to site.<sup>66</sup> Sites requested randomization allocation by e-mail, and a single coordinating center staff member fulfilled requests through a concealed randomization allocation sequence (Sealed Envelope, London, UK).

Participants and clinician raters were blinded, and participants were reminded regularly not to discuss their training with these clinicians. To maintain the participant blind, consent forms described the study as comparing two distinct types of cognitive training, and study staff described the hypothetical benefits of each type. Site staff who interacted with participants directly during training were not blinded but were instructed with scripts to describe the features of each program as potentially beneficial.

The protocol specified 39 sessions of cognitive training, intended to be delivered in 30-minute sessions over 12 weeks. Participants were given the opportunity (but not required) to extend their participation by  $\leq$ 4 weeks at the end of the 12-week period to make up missed sessions. Participants trained at home, and an unblinded treatment

TABLE 1. Baseline Demographic and Inclusion Measures			
Parameter	ITT group (n = 49)	ET group (n = 24)	AC group $(n = 25)$
Demographic			
Age (yr)	$58.8 \pm 13.9$	$60.5\pm12.9$	$57.1 \pm 14.9$
Education (yr)	$14.7\pm5.2$	$15.0\pm 6.0$	$14.3\pm4.2$
Biological Sex (% male)	66	66	66
Ethnicity (% Caucasian)	77	68	79
Time since ABI (yr)	$2.3\pm2.2$	$2.3 \pm 2.3$	$2.3\pm2.2$
NIH stroke scale (total score)	$5.9 \pm 4.0$	$6.2 \pm 4.3$	$5.5 \pm 3.7$
Short Blessed test (weighted)	$2.5 \pm 3.4$	$3.0 \pm 4.0$	$2.0\pm2.8$
Lesion volume (voxels)	$154,210 \pm 218,126$	$145,530 \pm 162,707$	$162,891 \pm 267,392$
Partial hemianopsia (%)	53	50	54
Full hemianopsia (%)	11	8	17
Screening/inclusion			
Mesulam cancelation (omissions)	$13.7\pm16.0$	$13.5 \pm 15.2$	$13.9\pm17.0$
Dual task (left trials accuracy)	$0.549\pm0.364$	$0.602\pm0.360$	$0.480\pm0.370$
Tone counting task (accuracy)	$0.617\pm0.222$	$0.647\pm0.210$	$0.585\pm0.235$
right	$0.072\pm0.196$	$0.049\pm0.196$	$0.095\pm0.196$
Mean ± 1 standard deviation or percentage of variable. Active Control (AC); Aquired Brain Injury (ABI); Experimental Treatment (ET); Intent To			

Treat (ITT); National Institutes of Health (NIH).

coach was available by telephone for technical assistance or to answer questions. Assessments (see Table 1 and Table S1) were performed at baseline before randomization (V1), after the completion of training ( $\sim$ 3 months after randomization; V2), and again after a 3-month no-training/no-contact follow-up period (V3).

# Conditions

**Experimental Treatment (ET).** The experimental cognitive training program was a commercially available cognitive training exercise (Freeze Frame; BrainHQ, Posit Science, San Francisco, CA) and was based on the TAPAT training approach,<sup>57</sup> with the goal of improving spatial attention and cognitive functions affected by spatial neglect. The exercise targeted sustained goal-directed attention-to-response and inhibitory control (executive function).

**Active Control (AC).** The active control program was designed to provide an experience that was matched to the experimental treatment program in intensity and duration, while plausibly engaging cognitive systems to maintain the patient blind. Previously vetted<sup>58</sup> off-the-shelf computer games were selected (eg, boggle, mahjong) and were delivered with a

schedule identical to the experimental treatment. Crucially, the active control games did not specifically target tonic and phasic alertness or aspects of sustained attention.

# Outcomes

**Primary Outcome.** The primary outcome was the Posner cueing task:<sup>59</sup> RT difference for detecting targets that appeared on the left compared with the right side. The results of a receiver operating characteristic analysis ranking sensitivity and specificity<sup>59</sup> of common spatial bias measures in patients with acute and chronic neglect demonstrated that the Posner cueing task RT difference metric had the highest area under the curve (0.916) and was significantly superior in diagnostic accuracy. Furthermore, the high accuracy of the Posner test in discriminating controls from chronic patients indicated that even in the chronic stage many patients had neglect, and further suggests that RT measures are a sensitive indicator of chronic neglect.

Developed by Posner (1984),<sup>67</sup> the task requires participants to detect visual stimuli at attended or unattended peripheral locations while maintaining central fixation. This task has been used widely in studies of spatial neglect, owing to its sensitivity to detect mild cases. A relative RT delay for targets presented in the contralesional visual field compared with the ipsilesional visual field indexes a lateralized deficit in visual perception and attention. To capture a valid reflection of participants' performance, independent of criterion shifts or trade-offs between speed and accuracy,<sup>68</sup> we used an inverse efficiency scoring approach.<sup>69</sup> Mean RTs were divided by the proportion of correct trials responded to in each specific condition (eg, valid and invalid cue × side). This helps to account for potential differences in accuracy across leftand right-cued trials.

Secondary Outcomes. Secondary outcomes included a composite measure of spatial cognition, composed of performance on the grayscales task<sup>70</sup> and a spatial working memory task.<sup>71</sup> The composite score was used to preserve statistical power and avoid multiple comparisons and was calculated by remapping the intent-to-treat (ITT) population scores for each test to z-scores, which were averaged within each secondary domain (eg, spatial cognition). These measures have been validated empirically in this population and capture components of spatial cognition, including spatial working memory, representational neglect, and saccade bias. The grayscales task captures perceptual bias by presenting two mirror-reversal objects progressively darkened on opposite ends of the object. Participants with spatial neglect can show a bias in judging the object darkened on the ipsilesional side as "darker" than its mirror-reversed analog. The spatial working memory task is a computerized vertical variant of the Corsi task,<sup>72</sup> in which sequences of spatial locations in a vertical column are displayed, and participants are required to judge verbally (yes/no) if a single location (probed visually) had been in the preceding sequence.<sup>71</sup> The composite measure was calculated as an average of z-scores, calculated for each measure, from performance of the entire study cohort at baseline.

Participants also completed two measures of functional performance ability, the neglect-specific Catherine Bergego (CB) scale<sup>73</sup> and the Barthel index,<sup>74</sup> which were combined into a single composite measure of functional performance ability. The composite score was used to preserve statistical power and avoid multiple comparisons and was calculated by remapping the ITT population scores for each test to *z*-scores, which were averaged within each secondary domain (eg, functional performance ability). The Barthel index was chosen to facilitate comparison of treatment effects with the larger medical literature, and the CB scale was thought to provide sufficient sensitivity to the features of spatial neglect.<sup>73</sup>

Additionally, participants completed a set of assessments that composed an executive function composite, including measures of working memory, inhibitory control, and switching.<sup>75</sup> Working memory was evaluated via the Wechsler Adult Intelligennce Scale, fourth edition (WAIS-IV) Digit Span subtest, backward span (eg, participant is read a sequence of numbers and is required to recall the numbers in reverse order). This measure was chosen owing to the difficulty of using visual analogs in this population (ie, unsuitable owing to spatially lateralized stimulus arrays); thus, examining the putative verbal workspace was considered more appropriate. Likewise, to capture fluency and switching abilities, we used the Delis-Kaplan Executive Function System (DKEFS) verbal fluency subtest. This task required participants to produce words spontaneously and rapidly in response to phonemic and semantic cues, and to alternate between two category-based cues. Lastly, inhibitory control was assessed using a continuous performance measure with sound psychometric properties, good validity and generalizability across settings, and adaptability for trials in patients with spatial neglect.<sup>71</sup> The task required sustained engagement (ie, no intertrial break), frequent responses, and inhibitory control to overcome the preponent motor response when presented with an infrequent target item. As stated above, the composite score was used to preserve statistical power and avoid multiple comparisons and was calculated by remapping the ITT population scores for each test to z-scores, which were averaged within each secondary domain (eg, executive function).

Finally, outcomes included a measure of healthrelated quality of life (Short-Form 12 [SF-12v2]), as a measure of the impact of program use on the participants' own view of their impairment and function (ie, quality of life);<sup>76</sup> and quality of sleep, as measured by performance on the Pittsburg sleep quality index. This measure has been used in many outcomes studies, including a prior study of TAPAT outcomes in participants with post-traumatic stress disorder (J DeGutis, A Rosenblatt, R McGlinchey, W Milberg, T Van Vleet, in preparation), in which it effectively captured improvements in sleep quality post-training compared with a waitlist control group.

*Train-to-Task-Related Measure.* A computerized assessment targeting the cognitive operations inherent in the experimental treatment program was used as positive control for task learning and target engagement and was administered at baseline (V1) and immediately after the completion of training (V2). The task consisted of a continuous visual presentation of spatial locations located along the vertical axis, above and below central fixation.<sup>41</sup> After the continuous presentation of several spatial locations, participants were required to determine whether a location-probe matched one of the previously presented stimulus locations.

### Statistical Analysis

A predefined analysis plan specified sample size, various study populations including the ITT population, and the statistical approach (clinicaltrials.gov NCT01965951). The ITT population included all randomized participants who completed their first training session. The trial was powered to test a clinically significant effect size of 0.5 (Cohen's *d*) at 2-sided  $\alpha$  level of 0.05. The primary outcome measure was performance on the Posner cueing task (RT difference: left–right target trials<sup>59</sup>), evaluated at the post-training assessment (V2) time point relative to baseline (V1); the key value for significance was the group-by-time interaction factor for the linear mixed effects model.

Baseline data were compared with Student *t* tests or the  $\chi^2$  test Outcome measures were evaluated using linear mixed effects models. Missing data were accounted for using iterative full-information maximum likelihood estimation. Each model included treatment group and time as fixed factors and site as a random factor. An interaction term (training group × time) estimated the effect of the experimental intervention on outcome measure change. Planned comparisons were performed on the fully evaluated populations using Student *t* tests of difference scores.

Sensitivity analysis were conducted to account for participant drop-out. Missing values were substituted based on the available measurements for participants at other visits, and a multiple monotone imputation method was used to generate five iterations, which were averaged and entered into the linear mixed model.

# Results

#### Participants

Of the 96 participants assessed for eligibility, 51.0% qualified for the study and were randomized (Fig 1), yielding an ITT sample of 49 participants (ET, 24; AC, 25). Achieved power to detect an effect size of 0.5 was 0.593 with this sample size. Recruitment began in June 2014; the final participant completed follow-up assessment in February 2017.

Pretraining demographic and baseline measures are shown in Table 1. Scores on the screening measures, the primary (Posner cueing task) and secondary spatial attention/cognition measures (grayscales, spatial working memory task) indicated significant spatial bias in attention and perception (see Table 1 and Table S1). The participants' average CB scale score of 5.9 (5.2) with a range of 0-25 (maximal score of 30) was significantly lower than the assessors' average score of 9.1 (6.2) with a range of 0-23  $(t_{69} = -2.079, p = 0.04)$ , indicating significant prevalence of anosognosia<sup>8,77</sup> in the ITT population. The average Barthel index scores of 77.5 (20.8), with a range of 20-100, indicated meaningful levels of perceived disability in the ITT population (no significant difference between ET and AC groups). Average performance in the short Blessed test of 1.16 (1.62) did not reveal evidence of cognitive impairment or dementia in the ITT population, and the average BDI score of 10.5 (8.6) indicated a minimal level of depressive symptoms. Likewise, the average performance in the SF-12 mental component of 39.8 (12.3) indicated that mental health issues contributed to minimal restrictions on everyday activities; and



FIGURE 1: Consolidated Standards of Reporting Trials (CONSORT) table. Experimental Treatment (ET); Active Control (AC); V2 (second visit; post-training assessment); V3 (third visit; follow-up assessment).



FIGURE 2: Frequency map shows normalized computed tomography (CT) images and magnetic resonance imaging (MRI) scans (normalized via SPM 12) created via FSL software. The color bar indicates in absolute terms the number (n) of lesions affecting a particular area. Six participants were excluded owing to low-quality neuroimaging or faulty Digital Imaging and Communications in Medicine (DICOM) files.

the average SF-12 physical component score of 53.2 (10.4) indicated moderate contributions of physical issues to restrictions in everyday life.

After randomization, there were no significant differences between the ET and AC groups. Notably, there was no difference in average lesion volume (voxels) between participants in the ET group (145,530.353 [SD = 162,707.098]) versus the AC group (162,891.47 [SD = 267,392.24]), ( $t_{32} =$ -0.229, p = 0.821), nor any difference in lesion location between groups (p = 0.632; see Fig 2). Regarding the source of acquired brain injury, 46 of the 49 participants enrolled suffered a first-time stroke involving the right hemisphere; 3 suffered traumatic brain injury (TBI); 2 of the 3 participants with TBI experienced brief loss of consciousness and both scored 15 on the Glasgow coma scale.

After program set-up and orientation, in the ET group 9 participants dropped out/withdrew and 15 participants completed the final assessment, and in the AC group 9 dropped out/withdrew and 16 participants completed the final assessment. Drop-out/withdrawal rates were not significantly different between the two groups  $(p = 0.554, \chi^2)$ . There were no significant differences between the population that did not complete the final assessment (the drop-out/withdrawal population, n = 18) and those that went on to complete the posttraining assessment (the fully-evaluable [FE] population at V2, n = 31), nor between the ET and AC drop-out/withdrawal groups. Notably, there was no difference between the ET and AC groups in the incidence of anosognosia<sup>8</sup> at baseline (p = 0.549,  $\chi^2$ ): 12 of 16 participants in the ET group (in which both a participant and a care-giver completed the CB assessment) versus 13 of 20 participants in the AC group. Also, there was no difference between groups in those participants who withdrew or were removed from the study. Only three participants were lost to follow-up between V2 and V3 (AC, n = 2; ET, n = 1). Reasons for drop-out/withdrawal were typically the time commitment of study participation (50% of drop-outs),



FIGURE 3: Primary outcome. Index of spatial bias based on performance on the Posner cueing task (left-right target detection latency)

change in life circumstances (eg, relocation, surgery, death; 40% of drop-outs), or lost to follow-up (10% of dropouts). Finally, within the FE-V2 group, 15 of 15 participants in the ET group were considered fully trained, as were 16 of 16 participants in the AC group (completing 100%, 39 of a potential 39 sessions).

#### Effects of Training on Outcome Measures

Within-group change scores, between-group difference scores, and significance for ET and AC comparisons in the ITT group are reported in Table S1. First, on the train-totask measure (a positive control for task learning), administered before and after training, the ET group showed a significant advantage (33% improvement) over the AC group (4% worse) at the post-training time point (p = 0.007, Cohen's d = 1.15). For the primary outcome measure (Fig 3), the ET group showed a significant advantage (228.57 milliseconds less rightward bias) over the AC group (288.33 milliseconds more rightward bias) at the posttraining visit (p = 0.010, Cohen's d = 0.96) and demonstrated a positive trend at the follow-up visit (p = 0.16, Cohen's d = 0.54; ET = 153.92 milliseconds less rightward bias and AC = 148.22 milliseconds more rightward bias). On a within-group basis, improvement in the ET group was 1.8 times larger than that of the AC group at post-training, and 2.0 times larger at follow-up (Table S1).

An analysis of the magnitude of change pre- versus post-training, in which we adopted two criteria (+0.2 standard deviations of the pretraining scores based on recommendations for a minimally clinically important difference in cognitive function<sup>78</sup> and +1.0 standard deviations, as a representative large effect) demonstrated that the participants in the ET group showed reliable changes > three-fold relative to the AC group at both criteria levels (+0.2: 25% in the ET group vs 7% in the AC group; +1.0: 13% in the ET group vs 0% in the AC group).

Preplanned secondary regression analyses showed that the magnitude of spatial bias at baseline was correlated with the magnitude of improvement in the primary outcome in the ET group at the post-training (r = -0.769, n = 16, p = 0.001) and follow-up visits (r = -0.769, n = 16, p = 0.001)



FIGURE 4: Forest plot of effect sizes and 95% confidence intervals. Individual tests that form composite outcome measures are shown in gray. Cohen's *d* effect size was computed for each measure based on the change in performance from post-training minus pretraining (top), and follow-up minus pretraining (bottom). Left (L); Right (R); CB (Catherine Bergego Scale); WM (Working Memory); SF (Short Form); MH (Mental Health); PH (Physical Health); PSQI (Pittsburgh Sleep Quality Index); QOL (Quality of Life); Experimental Treatment (ET); Active Contorl (AC).

Post

-0.928, n = 13, p = 0.0001); participants with greater spatial bias at baseline improved the most. Although the magnitude of spatial bias has previously been shown to be correlated with the degree of anosognosia,<sup>6,77</sup> in the present study the magnitude of denial relative to improvement in the primary outcome reached only trend level at post-training (r = -0.528, n = 16, p = 0.09) and was not correlated at follow-up (p = 0.31).

Finally, to address other potential factors that might have contributed to the outcome, we evaluated regression to the mean via a between-groups analysis of covariance comparing performance on the primary outcome measure at post-training (V2), while controlling for performance at baseline (V1), for the FE AC versus ET groups; this analysis failed to reveal a meaningful contribution of regression to the mean ( $F_{28} = 5.96$ , p = 0.021). Given the drop-out rate, we also conducted a sensitivity analysis, in which we substituted missing values based on the available measurements for participants at other visits using a multiple monotone imputation method (five iterations). Imputed values were included in the model, and the results were consistent with the initial analysis, in that the crucial time  $\times$  group interaction was significant (p = 0.011, Cohen's d = 0.443). Although the beneficial effect of ET on the primary outcome was robust, a shorter initial training period, with follow-up booster training sessions as needed, might improve acceptability and retention.

Regarding the secondary measures, the ET group showed a significant advantage over the AC group (p = 0.027, Cohen's d = 0.24) in the functional composite measure (CB scale; Barthel index) when comparing the pre- versus post-training visit (3.13 points of improvement in the Barthel and 1.06 points improvement in the CB for ET, versus no change in the Barthel and 0.14 points worsening in the CB for the AC group). There was no between-group difference in the functional abilities composite at the follow-up visit (p = 0.65). The ET group also showed a significant advantage over the AC group when comparing the pre- versus post-training visit in the spatial cognition composite measure (p = 0.007, Cohen's d = 0.71; a positive trend favoring the ET group was shown at the follow-up visit (p = 0.12, Cohen's d = 0.46). Notably, between-group analyses of the FE population showed that the ET group demonstrated a significant 5.4% increase in performance accuracy in the spatial working memory task ( $t_{13} = 2.38$ , p = 0.02), relative to a 7.0% decrease in the AC group (Cohen's d = 0.87) at post-training; and a significant 8.0% improvement in spatial working memory in the ET group ( $t_{13} = 2.49$ , p = 0.02) versus a worsening in the AC group of 2.0% at follow-up (Cohen's d = 0.94). Finally, there was no significant between-group difference in the quality-of-life

measures (SF-12 Mental Health and Physical Health scales), sleep measure (Pittsburg Sleep Quality Index), or the executive function composite measure for either comparison (the pre- vs post-training visit or pre- vs the follow-up visit). A forest plot of effect sizes and 95% confidence intervals for all outcome measures, including individual tests composing the functional ability, spatial cognition, and executive function composite measures, is shown in Fig 4.

Preplanned secondary regression analyses examined predictors of change in the primary outcome (Posner bias change score) and revealed a significant correlation with change in spatial working memory span (as span increased, bias was reduced) at the post-training assessment (r =-0.358, n = 29, p = 0.05). However, this relationship did not reach significance at the follow-up visit (p = 0.19). Regression analyses conducted to examine the relationship between the primary and secondary outcomes revealed a trend level association between improvements in spatial bias (primary outcome measure) and physical health at post-training, as reported on the secondary health-related quality of life SF-12v2 measure (r = 0.324, n = 31, p = 0.076).

Ten adverse events were recorded during the study period (ET, 5; AC, 5) and were related to falls, medical management of co-occurring disorders (eg, diabetes, heart disease), and one death. All incidents were reviewed and determined to be unrelated to participation in the study.

## Discussion

The RESPONSE study was a randomized controlled clinical trial of a cognitive training program in participants with hemispatial neglect after an acquired brain injury that met American Academy of Neurology standards for a class I randomized controlled trial. Improvements in spatial attention (the primary outcome) favoring the experimental treatment group (ET) were statistically significant compared with the active control group (AC), with a meaningfully large effect size 1.8-2.0 times larger in the ET versus the AC group. Likewise, improvements in several common measures of neglect (eg, secondary outcome, spatial cognition) favoring the ET group were also statistically significant compared with the AC group when comparing performance pre- versus post-training. Improvements in realworld functional performance favoring the ET group were also statistically significant compared with the AC group at post-training. In fact, benefits in the ET group included improvements in deficits common to neglect, as reflected in performance on the CB scale.

The significant correlation between improvements in training (inhibitory control or reduction in commission

errors) and spatial working memory suggests that the intervention also improved the efficiency of visual working memory updating<sup>25,27</sup> and speed of successive signal resolution;<sup>36</sup> benefits that might indicate a mechanism of action of the treatment. Specifically, improvements in the updating of spatial locations might enable patients to mitigate the gross attention deficits in neglect that bias the deployment of spatial attention.<sup>38–41</sup> Reduction of these deficits might also benefit functional abilities, as demonstrated in the withingroup improvements.

The present results can be compared with common clinical interventions for neglect, which typically involve therapist-administered "top-down" self-cueing strategies (eg, "look left") that typically rely on adequate recall of the behavioral strategy (an approach that might not be conducive for patients with deficit awareness issues)<sup>48</sup> and experimental interventions, which have largely applied "bottom-up" approaches (eg, optokinetic stimulation, repetitive transcranial magnetic stimulation, prism adaptation). Although a lack of shared methods in neglect research has prevented one-to-one comparisons between interventions (eg, 50 different outcome measures were used in a variety of combinations across 20 studies included in a recent meta analysis<sup>79</sup>), notable improvements have been demonstrated across several therapies.<sup>45,79–83</sup> A recent review of intervention trials for neglect<sup>80</sup> found 7 of 15 randomized controlled trials with statistically significant between-group differences in favor of the experimental group, but only 4 studies<sup>84-87</sup> that showed large effect sizes (Cohen's d > 0.80). Notably, the approaches in these 4 studies required a therapistadministered device (virtual reality goggles, transcutaneous electrical nerve stimulation, mirrors, or optokinetic stimulator), and no intervention was amenable to selfadministration at home, as in the present trial.

In addition to the uniquely accessible approach, other strengths of the present study addressed commonly cited concerns regarding methodology<sup>45</sup> and included a well-defined participant population, multisite execution, good match between the expectation of benefit between the intervention and active control group, use of a follow-up assessment after a no-contact period, and use of an a priori statistical plan with an ITT analysis. Weaknesses of the study are that it did not achieve its enrollment goal, and the associated lack of power necessary to explore mechanistic formulations.

In summary, the treatment of individuals who suffer an acquired brain injury or stroke and exhibit neglect is often complicated by patients' gross loss of awareness and highly comorbid denial of deficits (eg, anosognosia). Not surprisingly, these patients exhibit poorer outcomes relative to patients with a similar extent of injury but without neglect. The results of the present trial provide strong evidence that this specific form of self-administered, plasticity-based cognitive training can be incorporated as part of an evidence-based treatment plan to improve awareness, mitigate spatial bias, and improve functional abilities in people with hemispatial neglect after acquired brain injury.

# Acknowledgment

The RESPONSE study was funded by a US National Institutes of Health grant (NINDS R44NS071780) awarded to Posit Science as the coordinating center, with subcontracts issued to each of the individual trial sites.

We thank the participants who participated in the RESPONSE study for their time and effort.

# Author Contributions

T.V.V, J.D., M.M., and M.C. contributed to the study conception and design. T.V.V., J.D., M.C., P.B., E.F., A.L.B., S.D., S.-J.K., and C.C. contributed to the acquisition and analysis of the data. T.V.V, J.D., and A.L.B. contributed to the drafting of the manuscript and figures.

# **Potential Conflicts of Interest**

Posit Science was the sponsor of this trial and is the developer of the BrainHQ cognitive training program used in this study. Posit Science holds patents for and a proprietary interest in this software. T.V.V., M.M., S.D., and S.-J.K. are employees of, and hold equity in, Posit Science.

Other authors have no conflicts to report. Ultimate responsibility for the design, conduct, analysis, and interpretation of the study, in addition to authorship of the report, reside with T.V.V. and J.D.

## References

- Heilman KM, Bowers D, Valenstein E, Watson RT. Disorders of visual attention. Baillieres Clin Neurol 1993;2:389–413.
- Heilman KM, Bowers D, Valenstein E, Watson RT. Hemispace and hemispatial neglect [Internet]. In: Jeannerod M, ed. Advances in psychology. North-Holland, 1987:115-150. Available at: http://www. sciencedirect.com/science/article/pii/S0166411508617112. Accessed September 24, 2019.
- Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990; 28:597–613.
- Halligan PW, Fink GR, Marshall JC, Vallar G. Spatial cognition: evidence from visual neglect. Trends Cogn Sci (Regul. Ed.) 2003;7: 125–133.
- Pedersen PM, Jørgensen HS, Nakayama H, et al. Hemineglect in acute stroke–incidence and prognostic implications. The Copenhagen stroke study. Am J Phys Med Rehabil 1997;76:122–127.

- Appelros P, Karlsson GM, Seiger A, Nydevik I. Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. J Rehabil Med 2002;34:215–220.
- Buxbaum LJ, Ferraro MK, Veramonti T, et al. Hemispatial neglect: subtypes, neuroanatomy, and disability. Neurology 2004;62: 749–756.
- Azouvi P, Olivier S, de Montety G, et al. Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Bergego scale. Arch Phys Med Rehabil 2003;84:51–57.
- Ishiai S, Koyama Y, Seki K, et al. Approaches to subjective midpoint of horizontal lines in unilateral spatial neglect. Cortex 2006;42: 685–691.
- Heilman KM, Bowers D, Coslett HB, et al. Directional hypokinesia: prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect. Neurology 1985;35:855–859.
- Mattingley JB, Husain M, Rorden C, et al. Motor role of human inferior parietal lobe revealed in unilateral neglect patients. Nature 1998;392:179–182.
- Hornak J. Ocular exploration in the dark by patients with visual neglect. Neuropsychologia 1992;30:547–552.
- Driver J, Vuilleumier P. Perceptual awareness and its loss in unilateral neglect and extinction. Cognition 2001;79:39–88.
- Johnston CW, Diller L. Exploratory eye movements and visual hemineglect. J Clin Exp Neuropsychol 1986;8:93–101.
- List A, Brooks JL, Esterman M, et al. Visual hemispatial neglect, reassessed. J Int Neuropsychol Soc 2008;14:243–256.
- Posner MI, Walker JA, Friedrich FJ, Rafal RD. Effects of parietal injury on covert orienting of attention. J Neurosci 1984;4:1863–1874.
- Denes G, Semenza C, Stoppa E, Lis A. Unilateral spatial neglect and recovery from hemiplegia: a follow-up study. Brain 1982;105: 543–552.
- Kalra L, Perez I, Gupta S, Wittink M. The influence of visual neglect on stroke rehabilitation. Stroke 1997;28:1386–1391.
- Jehkonen M, Ahonen JP, Dastidar P, et al. Predictors of discharge to home during the first year after right hemisphere stroke. Acta Neurol Scand 2001;104:136–141.
- Katz N, Hartman-Maeir A, Ring H, Soroker N. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. Arch Phys Med Rehabil 1999;80:379–384.
- Cherney LR, Halper AS, Kwasnica CM, et al. Recovery of functional status after right hemisphere stroke: relationship with unilateral neglect. Arch Phys Med Rehabil 2001;82:322–328.
- Paolucci S, Grasso MG, Antonucci G, et al. Mobility status after inpatient stroke rehabilitation: 1-year follow-up and prognostic factors. Arch Phys Med Rehabil 2001;82:2–8.
- Adair JC, Na DL, Schwartz RL, et al. Anosognosia for hemiplegia: test of the personal neglect hypothesis. Neurology 1995;45: 2195–2199.
- Danckert J, Ferber S. Revisiting unilateral neglect. Neuropsychologia 2006;44:987–1006.
- Husain M, Shapiro K, Martin J, Kennard C. Abnormal temporal dynamics of visual attention in spatial neglect patients. Nature 1997; 385:154–156.
- Robertson IH, Manly T, Beschin N, et al. Auditory sustained attention is a marker of unilateral spatial neglect. Neuropsychologia 1997;35: 1527–1532.
- Van Vleet TM, Robertson LC. Cross-modal interactions in time and space: auditory influence on visual attention in hemispatial neglect. J Cogn Neurosci 2006;18:1368–1379.
- Corbetta M, Shulman GL. Control of goal-directed and stimulusdriven attention in the brain. Nat Rev Neurosci 2002;3:201–215.

- Corbetta M, Shulman GL. Spatial neglect and attention networks. Annu Rev Neurosci 2011;34:569–599.
- Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. Neuron 2008;58: 306–324.
- He BJ, Snyder AZ, Vincent JL, et al. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 2007;53:905–918.
- Baldassarre A, Ramsey L, Hacker CL, et al. Large-scale changes in network interactions as a physiological signature of spatial neglect. Brain 2014;137:3267–3283.
- Ramsey LE, Siegel JS, Baldassarre A, et al. Normalization of network connectivity in hemispatial neglect recovery. Ann Neurol 2016;80: 127–141.
- Heilman KM, Schwartz HD, Watson RT. Hypoarousal in patients with the neglect syndrome and emotional indifference. Neurology 1978; 28:229–232.
- Bartolomeo P, Chokron S. Left unilateral neglect or right hyperattention? Neurology 1999;53:2023–2027.
- Battelli L, Cavanagh P, Intriligator J, et al. Unilateral right parietal damage leads to bilateral deficit for high-level motion. Neuron 2001; 32:985–995.
- Samuelsson H, Hjelmquist EK, Jensen C, et al. Nonlateralized attentional deficits: an important component behind persisting visuospatial neglect? J Clin Exp Neuropsychol 1998;20:73–88.
- Robertson IH, Tegnér R, Tham K, et al. Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. J Clin Exp Neuropsychol 1995;17:416–430.
- Lazar RM, Fitzsimmons B-F, Marshall RS, et al. Reemergence of stroke deficits with midazolam challenge. Stroke 2002;33:283–285.
- Robertson IH, Mattingley JB, Rorden C, Driver J. Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. Nature 1998;395:169–172.
- Malhotra P, Coulthard EJ, Husain M. Role of right posterior parietal cortex in maintaining attention to spatial locations over time. Brain 2009;132:645–660.
- Peers PV, Cusack R, Duncan J. Modulation of spatial bias in the dual task paradigm: evidence from patients with unilateral parietal lesions and controls. Neuropsychologia 2006;44:1325–1335.
- Duncan J, Bundesen C, Olson A, et al. Systematic analysis of deficits in visual attention. J Exp Psychol Gen 1999;128:450–478.
- Hjaltason H, Tegnér R, Tham K, et al. Sustained attention and awareness of disability in chronic neglect. Neuropsychologia 1996;34: 1229–1233.
- Bowen A, Hazelton C, Pollock A, Lincoln NB. Cognitive rehabilitation for spatial neglect following stroke. Cochrane Database Syst Rev 2013;7:CD003586.
- Diller L, Riley E. The behavioural management of neglect. Unilateral neglect: clinical and experimental studies. Mahwah, NJ: Lawrence Erlbaum Associates, Inc., 1993:293-308.
- Gorgoraptis N, Mah Y-H, Machner B, et al. The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke. Brain 2012;135:2478–2491.
- Halligan PW, Robertson I. Spatial neglect: a clinical handbook for diagnosis and treatment. Hove, East Sussex, United Kingdom: Psychology Press, 2014.
- Danckert J, Ferber S, Pun C, et al. Neglected time: impaired temporal perception of multisecond intervals in unilateral neglect. J Cogn Neurosci 2007;19:1706–1720.
- Merzenich M, Van Vleet T, Nahum M. Brain plasticity-based therapeutics. Front Hum Neurosci 2014;8:385.

# ANNALS of Neurology

- Bouret S, Sara SJ. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci 2005;28: 574–582.
- Wodka EL, Simmonds DJ, Mahone EM, Mostofsky SH. Moderate variability in stimulus presentation improves motor response control. J Clin Exp Neuropsychol 2009;31:483–488.
- Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997;275:1593–1599.
- Matthias E, Bublak P, Müller HJ, et al. The influence of alertness on spatial and nonspatial components of visual attention. J Exp Psychol Hum Percept Perform 2010;36:38–56.
- Posner MI. Measuring alertness. Ann NY Acad Sci 2008;1129: 193–199.
- Van Vleet TM, DeGutis JM. Cross-training in hemispatial neglect: auditory sustained attention training ameliorates visual attention deficits. Cortex 2013;49:679–690.
- 57. DeGutis JM, Van Vleet T. Tonic and phasic alertness training: a novel behavioral therapy to improve spatial and non-spatial attention in patients with hemispatial neglect. Front Hum Neurosci 2010;4:60.
- Fisher M, Holland C, Merzenich MM, Vinogradov S. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. Am J Psychiatry 2009;166:805–811.
- Rengachary J, d'Avossa G, Sapir A, et al. Is the posner reaction time test more accurate than clinical tests in detecting left neglect in acute and chronic stroke? Arch Phys Med Rehabil 2009;90: 2081–2088.
- Vleet TV, DeGutis J, Dabit S, Chiu C. Randomized control trial of computer-based rehabilitation of spatial neglect syndrome: the RESPONSE trial protocol. BMC Neurol 2014;14:25.
- Mesulam MM. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos Trans R Soc Lond B Biol Sci 1999;354:1325–1346.
- Bonato M, Priftis K, Marenzi R, et al. Increased attentional demands impair contralesional space awareness following stroke. Neuropsychologia 2010;48:3934–3940.
- Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797–811.
- Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–870.
- Posner K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266–1277.
- 66. Pocock SJ. *Clinical trials: a practical approach*. San Francisco, CA USA: John Wiley & Sons, 2013.
- Posner MI, Walker JA, Friedrich FJ, Rafal RD. Effects of parietal injury on covert orienting of attention. J Neurosci. 1984;4:1863–1874.
- 68. Bruyer R, Brysbaert M. Combining speed and accuracy in cognitive psychology: is the Inverse Efficiency Score (IES) a better dependent variable than the mean Reaction Time (RT) and the Percentage of Errors (PE)? Psychol Belgica 2011;51:5–13.

- Townsend JT, Ashby FG. Methods of modeling capacity in simple processing systems. In Castellan J, Restle F (Eds). *Cognitive theory*.
  Hillsdale, NJ: Erlbaum, 1978;200–239.
- Mattingley JB, Berberovic N, Corben L, et al. The greyscales task: a perceptual measure of attentional bias following unilateral hemispheric damage. Neuropsychologia 2004;42:387–394.
- 71. Malhotra P, Jäger HR, Parton A, et al. Spatial working memory capacity in unilateral neglect. Brain 2005;128:424–435.
- De Renzi E, Faglioni P, Previdi P. Spatial memory and hemispheric locus of lesion. Cortex 1977;13:424–433.
- Chen P, Hreha K, Fortis P, et al. Functional assessment of spatial neglect: a review of the Catherine Bergego scale and an introduction of the Kessler foundation neglect assessment process. Top Stroke Rehabil 2012;19:423–435.
- Collin C, Wade DT, Davies S, Horne V. The Barthel ADL index: a reliability study. Int Disabil Stud 1988;10:61–63.
- Miyake A, Friedman NP, Emerson MJ, et al. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 2000;41: 49–100.
- Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the medical expenditure panel survey. Qual Life Res 2009;18:727–735.
- Grattan ES, Skidmore ER, Woodbury ML. Examining anosognosia of neglect. OTJR (Thorofare N J) 2018;38:113–120.
- Yon A, Scogin F. Procedures for identifying evidence-based psychological treatments for older adults. Psychol Aging 2007;22:4–7.
- Liu KPY, Hanly J, Fahey P, et al. A systematic review and metaanalysis of rehabilitative interventions for unilateral spatial neglect and hemianopia Poststroke from 2006 through 2016. Arch Phys Med Rehabil 2019;100:956–979.
- Lisa LP, Jughters A, Kerckhofs E. The effectiveness of different treatment modalities for the rehabilitation of unilateral neglect in stroke patients: a systematic review. NeuroRehabilitation 2013;33:611–620.
- Azouvi P, Jacquin-Courtois S, Luauté J. Rehabilitation of unilateral neglect: evidence-based medicine. Ann Phys Rehabil Med 2017;60: 191–197.
- Kwon J-S. Therapeutic intervention for visuo-spatial neglect after stroke: a meta-analysis of randomized controlled trials. Osong Public Health Res Perspect 2018;9:59–65.
- Singh-Curry V, Husain M. Rehabilitation in practice: hemispatial neglect: approaches to rehabilitation. Clin Rehabil 2010;24:675–684.
- Polanowska K, Seniów J, Paprot E, et al. Left-hand somatosensory stimulation combined with visual scanning training in rehabilitation for post-stroke hemineglect: a randomised, double-blind study. Neuropsychol Rehabil 2009;19:364–382.
- Thieme H, Bayn M, Wurg M, et al. Mirror therapy for patients with severe arm paresis after stroke-a randomized controlled trial. Clin Rehabil 2013;27:314–324.
- Schröder A, Wist ER, Hömberg V. TENS and optokinetic stimulation in neglect therapy after cerebrovascular accident: a randomized controlled study. Eur J Neurol 2008;15:922–927.
- Kim YM, Chun MH, Yun GJ, et al. The effect of virtual reality training on unilateral spatial neglect in stroke patients. Ann Rehabil Med 2011;35:309–315.