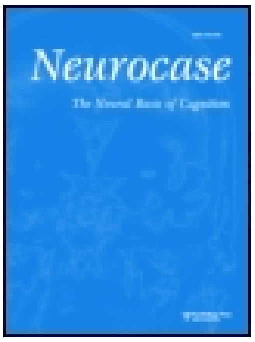

Neurocase

The Neural Basis of Cognition

ISSN: 1355-4794 (Print) 1465-3656 (Online) Journal homepage: http://www.tandfonline.com/loi/nncs20

Sustained attention training reduces spatial bias in Parkinson’s disease: a pilot case series

Joseph DeGutis, Mallory Grosso, Thomas VanVleet, Michael Esterman, Laura Pistorino & Alice Cronin-Golomb

To cite this article: Joseph DeGutis, Mallory Grosso, Thomas VanVleet, Michael Esterman, Laura Pistorino & Alice Cronin-Golomb (2015): Sustained attention training reduces spatial bias in Parkinson’s disease: a pilot case series, Neurocase

To link to this article: http://dx.doi.org/10.1080/13554794.2015.1088035

NEUROCASE, 2015
http://dx.doi.org/10.1080/13554794.2015.1088035

Routledge
Taylor & Francis Group

Sustained attention training reduces spatial bias in Parkinson's disease: a pilot case series

Joseph DeGutis[a,b,c], Mallory Grosso[a,b], Thomas VanVleet[d], Michael Esterman[a,b,e], Laura Pistorino[f] and Alice Cronin-Golomb[f]

[a]Boston Attention and Learning Laboratory, Boston Division VA Healthcare System, Boston, MA, USA; [b]Geriatric Research Education and Clinical Center (GRECC), Boston Division VA Healthcare System, Boston, MA, USA; [c]Department of Medicine, Harvard Medical School, Boston, MA, USA; [d]Department of Medical Research, VA Northern California Healthcare System, Martinez, CA, USA; [e]Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA; [f]Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA

ABSTRACT

Individuals with Parkinson's disease (PD) commonly demonstrate lateralized spatial biases, which affect daily functioning. Those with PD with initial motor symptoms on the left body side (LPD) have reduced leftward attention, whereas PD with initial motor symptoms on the right side (RPD) may display reduced rightward attention. We investigated whether a sustained attention training program could help reduce these spatial biases. Four non-demented individuals with PD (2 LPD, 2 RPD) performed a visual search task before and after 1 month of computer training. Before training, all participants showed a significant spatial bias and after training, all participants' spatial bias was eliminated.

ARTICLE HISTORY
Received 16 March 2015
Accepted 25 August 2015

KEYWORDS
Parkinson's disease; spatial bias; cognitive training; visual search; sustained attention

Parkinson's disease (PD) is a prevalent neurodegenerative disorder, affecting approximately 1% of people over the age of 60 (de Lau & Breteler, 2006). PD has traditionally been characterized by motor disability, which includes tremor, postural rigidity, slowness of movement, and disturbance of posture, gait, and balance (National Institute of Neurological Disorders and Stroke, http://www.ninds.nih.gov). In addition to these classic motor symptoms, non-motor issues such as sleep, mood disturbances, and cognitive dysfunction are quite common in PD (Barber & Dashtipour, 2012; Gallagher & Schrag, 2012; Litvan et al., 2011). These non-motor symptoms may precede motor symptoms (Bhidayasiri & Truong, 2012; Sjodahl Hammarlund, Hagell, & Nilsson, 2012) and are often reported to be more distressing and functionally limiting than motor symptoms (Cronin-Golomb, 2013; Duncan et al., 2014; Klepac, Trkulja, Relja, & Babic, 2008). They have also been shown to increase caregiver burden, health-related costs, risks for nursing home admission, and duration of hospital stays (Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006; Vossius, Larsen, Janvin, & Aarsland, 2011). Unfortunately, in contrast to PD motor dysfunctions that can be ameliorated with dopaminergic treatments (Baker et al., 2009), there is currently a dearth of treatments that effectively relieve non-motor impairments in PD. The goal of the current study is to test whether a novel cognitive training program can enhance an aspect of non-motor function in PD, specifically spatial attention.

Researchers have characterized cognitive deficits in PD in the domains of executive function, visuospatial attention, and sustained attention (Dirnberger & Jahanshahi, 2013; Miller, Neargarder, Risi, & Cronin-Golomb, 2013; Pfeiffer, Lokkegaard, Zoetmulder, Friberg, & Werdelin, 2014). Visuospatial deficits are particularly associated with compromised functional outcomes in PD, such as impaired navigation and driving ability (Amick, Grace, & Ott, 2007; Davidsdottir, Wagenaar, Young, & Cronin-Golomb, 2008), more so than motor symptoms (Uc et al., 2007). Abnormalities have been found on a variety of visuospatial tasks; in particular, several studies have shown that individuals with PD motor symptoms starting on the left body side (LPD) have more severe visuospatial deficits (Bowen, Hoehn, & Yahr, 1972; for review, see Cronin-Golomb, 2010; Verreyt, Nys, Santens, & Vingerhoets, 2011) and more lateralized spatial biases (toward the side of greater damage, ipsilesional) than those with right-sided motor onset (RPD) (Harris, Atkinson, Lee, Nithi, & Fowler, 2003; Lee, Harris, Atkinson, & Fowler, 2001). For example, Harris et al. (2003) found that when those with PD were asked to judge the height or width of a target rectangle compared to a comparison rectangle, LPD tended to perceive rectangles on the left side of space as smaller and those on the right side of space as larger, whereas RPD and control participants did not exhibit this bias.

Several of the visuospatial deficits found in PD are similar to (though milder than) those suffering from hemispatial neglect, a disorder characterized by severe visuospatial deficits, including not attending or not responding to stimuli presented to the side of the body contralateral to the predominant brain lesion, as well as nonspatial deficits such as difficulty sustaining attention (Corbetta & Shulman, 2011). For example, several PD studies show lateralized spatial biases analogous to neglect on tasks of line bisection (Laudate, Neargarder, & Cronin-Golomb, 2013; Lee et al., 2001), navigation (Davidsdottir et al., 2008; Young et al., 2010), and visual exploration (Ebersbach et al., 1996). On tasks of line bisection, Lee et al. (2001) found that LPD, but not RPD, showed midpoint deviations that were similar to individuals with

CONTACT: Joseph DeGutis ✉ degutis@wjh.harvard.edu

hemispatial neglect, and Laudate et al. (2013) reported that LPD tended to explore the right side more than the left side of the line. Ebersbach et al. (1996) demonstrated that when given a visual exploration task, LPD showed a bias to start exploring on the right side of the array, which is similar to findings in hemispatial neglect patients (Manly et al., 2009), whereas control participants and RPD had a bias to start exploring on the left side of the array. It has also been shown that some RPD experience a leftward spatial bias, which could be seen as similar to the minority of patients with neglect for right side of space (Beis et al., 2004; Davidsdottir et al., 2008). An important point was made recently by Norton, Jaywant, Gallart-Palau, and Cronin-Golomb (2015) that spatial biases may characterize individuals with either side of disease onset and that they are due to attentional biases rather than lower-level perceptual dysfunction such as perceived compression of, or weakened signal strength in, one visual hemi-field or by abnormal eye movements.

In regard to the neural mechanisms underlying visuospatial deficits in PD, studies have implicated the dorsal attention network (DAN), involved in goal-directed attention, and the ventral attention network (VAN), involved in sustaining attention and processing unexpected, behaviorally relevant stimuli (Shine et al., 2014; Vossel, Geng, & Fink, 2014). In particular, Shine et al. (2014) found that PD with poor visuospatial performance (discriminating complex monostable stimuli from bistable stimuli) had less gray matter volume in the right anterior insula, a key node in the VAN. Further, they showed reduced connectivity between VAN and DAN at rest and reduced DAN connectivity during task performance. Disruptions to these networks in PD could have direct causes (neurodegenerative processes in these regions) or indirect causes (e.g., neurodegenerative processes in the striatum, which may reduce communication with VAN regions, as shown in Putcha, Ross, Cronin-Golomb, Janes, & Stern, 2015). Though the specific cause of these network disruptions remains unclear, it is noteworthy that disruptions of similar areas occur in those suffering from hemispatial neglect. Typical lesions causing more chronic and severe hemispatial neglect implicate the right-sided VAN and typically spare the bilateral DAN regions (Karnath, Fruhmann Berger, Kuker, & Rorden, 2004). Damaging the VAN in hemispatial neglect disrupts network connections between the VAN and DAN and functionally suppresses activity in the DAN, most notably in the intraparietal sulcus (IPS) (He et al., 2007). This functional suppression can lead to an imbalance between left and right IPS regions, and the persistence of this imbalance has been related to persistence of spatial biases in neglect (Corbetta & Shulman, 2011). The implication of the VAN and DAN in hemispatial neglect, as well as in visuospatial defcits in PD, suggests that these phenomena have at least partially overlapping neural mechanisms.

Over the last 7 years, our group has demonstrated that several hours (e.g., 6 hrs) of computer-based sustained attention training (Tonic And Phasic Attention Training, TAPAT) can significantly reduce spatial biases in those with chronic hemispatial neglect following right hemisphere damage (DeGutis & Van Vleet, 2010; Van Vleet & DeGutis, 2013). Studies have implicated the right-lateralized VAN and bilateral DAN in sustained attention (Esterman, Noonan, Rosenberg, & DeGutis, 2013; Esterman et al., 2015; for review, see Langner & Eickhoff, 2013). Accordingly, we suggest that there are two potential models for the therapeutic effects of sustained attention training: (1) training particularly enhances mechanisms in the right hemisphere (e.g., perilesional VAN activity/connectivity), or (2) training works by enhancing more bilateral mechanisms (e.g., activity/connectivity in the intact bilateral DAN). In patients with right hemisphere damage, improved functioning of the right-lateralized VAN could potentially re-establish VAN/DAN connections and enhance right-sided DAN activity/connectivity (e.g., IPS) more than the left, allowing a greater balance of activity between the right and left DAN regions (e.g., IPS regions), which has been associated with reduced spatial bias (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). This model predicts that TAPAT would help participants with right-sided damage, but would be less effective or even potentially exacerbate spatial biases for those with left hemisphere damage. An alternative explanation of the effectiveness of TAPAT is that sustained attention training rebalances goal-directed spatial attention in general, possibly by generally stimulating and enhancing connectivity between DAN regions. This predicts that TAPAT would reduce spatial biases for participants with both right- and left-sided damage. Testing the effectiveness of TAPAT in participants with spatial biases resulting from either greater left or right hemisphere compromise could provide a unique opportunity to test the mechanisms of this training program.

In the current study, we sought to test whether the sustained attention training program that we have used with success in hemispatial neglect would reduce spatial biases in PD, in light of the similarity in direction of spatial bias in LPD (rightward) to left hemispatial neglect, and RPD (relatively slightly leftward) to right hemispatial neglect. The second goal was to determine whether training would improve spatial biases in LPD more than in RPD. This would help determine if the therapeutic effect of TAPAT is more from stimulating right hemisphere regions or from stimulating bilateral regions.

Methods

Design

We employed a pre/post longitudinal design in which participants were assessed on a conjunction search task before and after 1 month of at-home sustained attention/inhibitory control training (see below). Search performance on the “intact” side of space (ipsilesional) was considered as the control condition (e.g., accounting for test–retest effects), whereas the condition of interest was search performance on the impaired side of space (contralesional). Other tasks were included in the pre/post battery (landmark task, attentional blink, and sustained attention task), though unfortunately there were technical problems with these tasks in some of the participants so we do not report these results.

Participants

The study included four participants with idiopathic PD (three women; ages 58–65 years, M 62.3, SD 3.1; all right-handed). Two participants had initial motor symptoms on the right side (RPD)

Table 1. Demographic and clinical characterization of the current PD sample.

	Participants			
	PD001	PD002	PD003	PD004
Side of onset	Left	Right	Left	Right
Sex	Female	Male	Female	Female
Age	65	64	62	58
Education (years)	16	16	20	17
Disease duration (years)	2.8	5.6	7	14.7
Hoehn and Yahr stage	2	3	2	2
UPDRS total	47	64	27	25
MMSE Score	29.2	28.7	29.2	28.7
BDI-II Score	3	12	2	10
BAI Score	0	12	7	4

Notes: UPDRS = Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, BDI-II = Beck Depression Inventory- 2nd Edition, BAI = Beck Anxiety Inventory.

and two had initial motor symptoms on the left (LPD). Participants were recruited from the Parkinson's Disease Clinic at the Boston Medical Center, the Michael J. Fox Foundation Trial Finder, and through local PD support groups. Data were obtained in compliance with regulations of the Institutional Review Board of Boston University, in accordance with the Declaration of Helsinki. All participants provided informed consent.

Potential participants were interviewed about their medical history to rule out confounding diagnoses such as stroke, head injury, and serious medical illness (e.g., diabetes). No participant had undergone surgery affecting the thalamus, basal ganglia, or other brain regions. None of the participants were found, on exam or by history, to have any ocular illnesses or abnormalities that would have influenced performance on the visually presented measures of interest. Near binocular acuity was assessed at 16″ for each participant, with none worse than 20/40 Snellen. Participant characteristics are provided in Table 1.

All participants were non-demented, as indexed by their scores on the modified Mini-Mental State Examination (MMSE, score converted to standard MMSE, cut-off score = 27) (Stern, Mayeux, Sano, Hauser, & Bush, 1987). Depressive and anxiety symptoms were measured by the Beck Depression Inventory-2nd Edition (BDI-II) (Beck, Steer, Ball, & Ranieri, 1996) and the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988), with all participants scoring within the minimal range on both assessments. Participants were staged according to the Hoehn & Yahr scale of motor disability (Hoehn & Yahr, 1967), with three having a disability stage of 2 and one a stage of 3 (PD002). Disease severity was determined with the use of the Unified Parkinson's Disease Rating Scale (UPDRS, Sections 1–3) (Fahn, Elton, & UPDRS Development Committee, 1987; Levy et al., 2005). PD001 had a total UPDRS score of 47, PD002 had a total score of 64, PD003 had a total score of 27, and PD004 had a total score of 25. All PD participants were taking medication for their Parkinsonian symptoms and were in their "on" period at the time of testing (Levodopa equivalent dosage). Participants did not report making any medication changes during training.

Assessments and training

Conjunction search

The conjunction search requires observers to search for a target object (e.g., red square) among a display of 13 or 14 distractors that are either the same color or the same shape as the target object (e.g., red triangles and blue squares, see List et al., 2008 for a more complete description). The participants were instructed to look at the fixation cross in the center of the screen at the beginning of each trial, and then to verbally indicate whether the target was present or not by verbalizing "yes" or "no". The examiner entered the responses.

To determine the psychophysical threshold for each side of the display, we used a yes–no adaptive staircase procedure described by Kaernbach (1990). The initial display duration was set at 2000 ms, and we manipulated the display duration to reach an adjusted accuracy rate of 75% (further details of this procedure are provided in List et al., 2008). Staircases terminated after 10 reversals (when the answer from one trial to the next went from correct to incorrect or vice versa). A threshold presentation time (TPT) was calculated by averaging the stimulus durations over the final eight reversal points. This adaptive procedure has been successful in detecting lateralized biases in patient populations, such as those with hemispatial neglect (List et al., 2008). Additionally, this task has shown minimal practice effects (DeGutis & Van Vleet, 2010; List et al., 2008; Van Vleet & DeGutis, 2013), making it a good measure to study potential training-related improvements.

Tonic And Phasic Attention Training

Our group has developed a cognitive training program targeting sustained attention over the last 7 years, TAPAT (DeGutis & Van Vleet, 2010; Van Vleet, Chen, Vernon, Novakovic-Agopian, & D'Esposito, 2014; Van Vleet & DeGutis, 2013). The idea is that by having participants practice sustained engagement with the training task (tonic, sustained attention) and exercising response inhibition during rare no-go trials (phasic, transient acts of inhibitory control), TAPAT would foster a focused, engaged state of attention and help participants exercise inhibitory control. To promote this more engaged state, TAPAT employs a continuous performance task and includes several key elements: (1) a rare target format that requires frequent responding, as well as inhibitory control (withhold response on 10% of trials); (2) jittered inter-stimulus intervals (ISIs), which have been shown to promote attentional engagement and response control in individuals with attention deficit hyperactivity disorder (Ryan, Martin, Denckla, Mostofsky, & Mahone, 2010); and (3) rich, novel stimuli, which have also been shown to engage attention (Johnston, Hawley, Plewe, Elliott, & DeWitt, 1990). In addition, we utilized methods to individualize and adapt the training program as participants improve. In particular, participants started at ISIs of 1000/1500/2000 and as they improved above 90% accuracy for the session, for the next session they received less jittered (i.e., more consistent and challenging) ISIs (e.g., 1100/1500/1900, then 1200/1500/1800). Additionally, if participants fell below 80%, the ISIs became more jittered (e.g., 1100/1500/1900, then 1000/1500/2000). This has resulted in a simple, yet challenging and effective sustained attention/inhibitory control training paradigm. Participants performed 30 min/day of training (3 × 10 min rounds).

Results

Training performance

Participants performed TAPAT training for an average of 14.5 sessions, or 7.3 hrs (PD001: 4 hrs, PD002: 10 hrs, PD003: 7.5 hrs, PD004: 7.5 hrs). On the first day of training, all participants could successfully perform the training task, achieving a mean accuracy of 87% (SD = .10) (PD001 = .91, PD002 = .94, PD003 = .90, PD004 = .72). With practice, all participants improved their training task performance and accordingly, ISIs were reduced to make training more challenging (better performance = lower ISIs). As can be seen in Figure 1, all participants had significantly shorter ISIs (i.e., more difficult, less jittered) during the second half of training compared to the first half of training (PD001: 1st half = 350 ms, 2nd half = 25 ms, $t(3) = 6.789$, $p = 0.006$; PD002: 1st half = 173 ms, 2nd half = 17 ms, $t(9) = 3.168$, $p = 0.011$; PD003: 1st half = 258 ms, 2nd half = 29 ms, $t(6) = 5.065$, $p = 0.002$; PD004: 1st half = 450 ms, 2nd half = 357 ms, $t(6) = 5.164$, $p = 0.002$). These results indicate that all participants could successfully perform the training and improved with practice.

Figure 1. Mean ISI for the first and second halves of training. A smaller ISI indicates that the task becomes more difficult (less jittered). All subjects showed significant improvements.

Conjunction search performance

We first examined participants' spatial search bias on the conjunction search prior to training. As can be seen in Figure 2, participants required longer presentation times to detect the search target on their contralesional side compared to their ipsilesional side (spatial bias difference scores for PD001: 282 ms, PD002: 346 ms, PD003: 320 ms, and PD004: 246 ms).

The leftward search biases for RPD and rightward search biases for LPD were very similar ($M = 301$ ms, $M = 296$ ms, respectively). To test whether these search differences were significant, for each participant the last eight reversals for each condition (left vs. right target; 16 reversals) were randomly resampled into pairs of eight, 10,000 times (there are 12,870 possible combinations of this), and a noise distribution of differences between left and right was created. Based on this empirical noise distribution, the probability of the observed differences (or greater) was considered as the actual p-value. As can be seen in Table 2, all four PD participants showed a significant difference in spatial bias prior to training (p-values of 0.004, 0.0002, 0.0049, 0.0048, respectively). The size of these

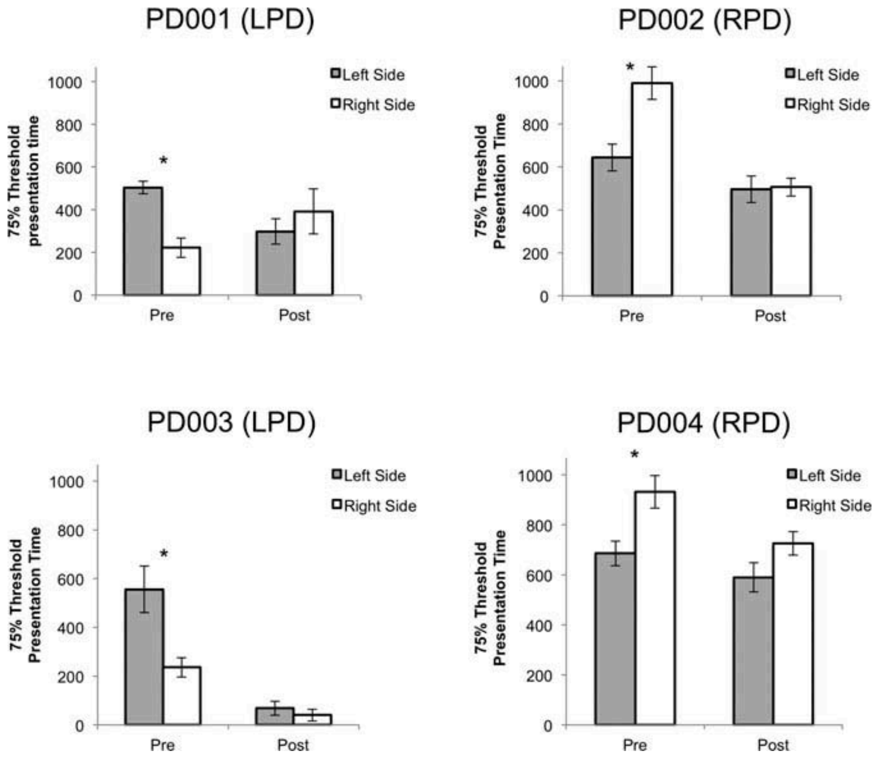

Figure 2. Conjunction search performance before and after training. The dependent variable is the presentation time needed to detect the search target 75% of the time. * indicates $p < 0.05$.

Table 2. Randomization/resampling analysis of conjunction search contrasts.

	Pre: left vs. right		Post: left vs. right		Intact side: pre vs. post		Impaired side: pre vs. post	
Participant	Difference	*p*-value	Difference	*p*-value	Difference	*p*-value	Difference	*p*-value
PD001 (LPD)	282 ms	0.0004	94 ms	0.21	170 ms	0.07	208 ms	0.004
PD002 (RPD)	346 ms	0.0002	10 ms	0.46	148 ms	0.06	484 ms	<0.0001
PD003 (LPD)	320 ms	0.005	28 ms	0.28	196 ms	0.0005	488 ms	0.0005
PD004 (RPD)	246 ms	0.005	136 ms	0.053	96 ms	0.12	206 ms	0.01

Notes: For each participant, the last eight reversals for each condition (e.g., left vs. right target) were randomly resampled into pairs of eight, 10,000 times, and a noise distribution of differences (e.g., between left and right) was created. Based on this empirical noise distribution, the probability of the observed differences (or greater) was considered as the actual *p*-value.

search biases was approximately half of that reported in hemispatial neglect patients performing the identical task (*M* difference = 298.5 ms in the current study vs. hemispatial neglect patients *M* difference = 589 ms from List et al., 2008).

After training, the four PD participants were tested again on the same conjunction search task to determine if their spatial bias was reduced. They were tested an average of 5.5 days after completing training (PD001: 11 days; PD002: 2 days; PD003: 4 days; PD004: 5 days). Note that in three previous hemispatial neglect studies, this task showed no significant test–retest effects, with hemispatial neglect patients maintaining their significant left vs. right spatial biases at retest several weeks later (DeGutis & Van Vleet, 2010, Session 1 M left–right difference: 1023 ms, Session 2 M left–right difference: 1006 ms; List et al., 2008, Session 1 M left–right difference: 536 ms, Session 2 M left–right difference: 476 ms; Van Vleet & DeGutis, 2013, Session 1 M left–right difference: 879 ms, Session 2 M left–right difference: 723 ms). All four PD participants reduced their spatial bias after training to the point where none showed a significant difference between the left and right sides of space when using the same randomization procedure as above (spatial bias difference scores for PD001: 94 ms, $p = 0.21$; PD002: 10 ms, $p = 0.46$; PD003: 28 ms, $p = 0.28$; and PD004: 136 ms, $p = 0.05$). Participants achieved this more balanced pattern of visual search by particularly improving search performance on their contralesional side. In particular, LPD showed a significant improvement in performing leftward searches (*p*-values of 0.0036 and 0.0005) and similarly, RPD showed a significant improvement in performing rightward searches (*p*-values of <0.0001 and 0.0107). In terms of the ipsilesional search (participants' intact side before training), only one (PD003, LPD) significantly improved, and this improvement was numerically smaller than improvements on the contralesional side (ipsilesional difference pre/post = 488, contralesional difference pre/post = 196). Together, these results demonstrate that sustained attention training improved contralesional visual search in both LPD and RPD to the point where there was no significant spatial bias in visual search performance.

Discussion

The aim of this case series was to determine if a sustained attention training program could attenuate spatial biases in PD, and whether training would have differential effects depending on the side of motor symptom onset. Before training, both LPD and RPD required significantly more time to detect the search target when it was presented on their contralesional side compared to their ipsilesional side. After 1 month of TAPAT training (*M* = 7.3 hrs), all participants significantly improved at searching the contralesional side, to the point where no participant demonstrated a significant search bias. We did not find any numeric improvement differences between LPD and RPD, suggesting that training enhanced attention mechanisms in a bilateral manner (e.g., engaged bilateral DAN regions). These results provide proof of concept that lateralized spatial biases in PD can be reduced through cognitive training that targets sustained attention.

These results have important implications for improving non-motor deficits in PD. Improving visuospatial attention is particularly important, because it is critical to improving daily functioning, such as driving and navigation. This study suggests that these visuospatial deficits may not be permanent, but instead are at least partially remediable with short-term cognitive training. These findings are consistent with those of other recent cognitive training studies in PD, which have shown that training can improve processing speed, attention, and visuospatial abilities (Edwards et al., 2013; París et al., 2011; Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006). For example, Edwards et al. (2013) found that compared to a test–retest PD control group, PD participants who completed 20 hrs of speed of processing training improved on a visuospatial assessment related to driving ability (Useful Field of View Test). París et al. (2011) had participants with PD perform a 4-week program targeting selective attention, working memory, processing speed, psychomotor speed, executive functioning, and visuospatial processing. Compared with the PD control group that performed speech therapy, the experimental group improved on standard tests of attention, processing speed, memory, visuospatial processing, and executive function. The current study extends these findings by showing that it is possible to improve spatial biases and that training is effective for both RPD and LPD. Accordingly, the current training program could be an important component of treatments for non-motor symptoms of PD.

In addition to these treatment implications, the current results provide important insights into the mechanisms of sustained attention training. First, the results demonstrate that the therapeutic effect of sustained attention training on spatial attention is not specific to hemispatial neglect, but also occurs in those with PD with lateralized spatial biases. Importantly, the current results extend the previous hemispatial neglect findings by showing that participants with either a leftward or rightward spatial bias benefit from TAPAT. Our previous explanation of TAPAT's therapeutic effect (DeGutis & Van Vleet, 2010) was that TAPAT enhances general intrinsic alertness, which is thought to be a right hemisphere lateralized process (e.g., right VAN, Clemens et al., 2011). We suggested that increased intrinsic alertness leads to more of a leftward shift in spatial attention, similar to what is found in healthy controls (see Manly, Dobler, Dodds, & George, 2005). However, the current results suggest that, rather than a unidirectional effect, TAPAT has a "rebalancing" effect and moves spatial biases to the right or left, depending on the participant's most deficient side. This suggests that TAPAT's therapeutic effects may not simply be due to enhancing general right hemisphere alertness mechanisms, but rather due to enhancing attention functioning in a more bilateral manner.

Though there are several possibilities for the neural mechanisms of these therapeutic effects, one potential explanation is that training engages and rebalances bilateral DAN regions. Sustained attention tasks have shown to reliably recruit bilateral DAN regions (Esterman et al., 2013; Langner & Eickhoff, 2013) and DAN recruitment during sustained attention has been associated with fewer attentional lapses (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009). Practicing to improve at sustaining attention may foster bilateral recruitment of DAN regions and increase functional connectivity between nodes in this network. These training-related improvements in DAN connectivity may be a general phenomenon, being present when participants perform other tasks such as visual search. This potentially increased DAN connectivity during spatial search is particularly relevant to spatial biases, because increased connectivity between left and right IPS (key DAN nodes) has been associated with reduced spatial bias in neglect (He et al., 2007). An alternative mechanism is that training engages right-hemisphere VAN regions, which could indirectly increase DAN (and IPS) connectivity. Future task- and resting-state fMRI studies would be useful to uncover the neural mechanisms of these training-related improvements.

Despite these promising results, there are several limitations to this study. The sample size is small and may not be representative of the PD population in general. Additionally, the current study did not characterize the longevity of the training effects. That said, PD001 was tested 11 days after she stopped training, suggesting that the effects last a minimum of 11 days. Another limitation is that the pre-/post-assessment consisted of only one task, and including a broader battery of tasks could help better understand the effects of sustained attention training on cognitive performance and daily life. A final limitation is that we did not include a control group (e.g., test/retest control group), leaving open the possibility that practice effects influenced the results. Though a possibility, the fact that previous studies using the identical task showed minimal practice effects (DeGutis & Van Vleet, 2010; List et al., 2008; Van Vleet & DeGutis, 2013) suggests that practice effects did not produce the current spatial bias improvements. Furthermore, participants improved at searching their impaired side (i.e., condition of interest) relative to their good side (i.e., control condition), providing additional evidence that the improvements were not due to practice effects.

In summary, we present a pilot case series where we find that sustained attention training can reduce visuospatial deficits in PD, independent of side of motor onset. This not only has important treatment implications, but also provides important insights into understanding the relationship between sustained (nonspatial) attention and spatial attention mechanisms.

Acknowledgments

We are grateful to Marie Saint-Hilaire, M.D., and Cathi Thomas, R.N., M.S.N., of Boston Medical Center Neurology Associates for their support of this pilot study, and to Boston area Parkinson's disease support groups and the Michael J. Fox Foundation Trial Finder. We thank Olivier Barthelemy, Abhishek Jaywant, and Robert Salazar for their assistance on this project. We are especially grateful to the individuals who participated in this study.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the National Institute of Neurological Disorders and Stroke [grant number ROI NS067128] and the Massachusetts Chapter of the American Parkinson's Disease Association.

References

Amick, M. M., Grace, J., & Ott, B. R. (2007). Visual and cognitive predictors of driving safety in Parkinson's disease patients. *Archives of Clinical Neuropsychology*, *22*, 957–967. doi:10.1016/j.acn.2007.07.004

Baker, W. L., Silver, D., White, C. M., Kluger, J., Aberle, J., Patel, A. A., & Coleman, C. I. (2009). Dopamine agonists in the treatment of early Parkinson's disease: A meta-analysis. *Parkinsonism & Related Disorders*, *15*, 287–294. doi:10.1016/j.parkreldis.2008.07.004

Barber, A., & Dashtipour, K. (2012). Sleep disturbances in Parkinson's disease with emphasis on rapid eye movement sleep behavior disorder. *The International Journal of Neuroscience*, *122*, 407–412. doi:10.3109/00207454.2012.677882

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*, 893–897. doi:10.1037/0022-006X.56.6.893

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of Beck depression inventories-IA and-II in psychiatric outpatients. *Journal of Personality Assessment*, *67*, 588–597. doi:10.1207/s15327752jpa6703_13

Beis, J.-M., Keller, C., Morin, N., Bartolomeo, P., Bernati, T., Chokron, S., … Azouvi, P. (2004). Right spatial neglect after left hemisphere stroke: Qualitative and quantitative study. *Neurology*, *63*, 1600–1605. doi:10.1212/01.WNL.0000142967.60579.32

Bhidayasiri, R., & Truong, D. D. (2012). Therapeutic strategies for nonmotor symptoms in early Parkinson's disease: The case for a higher priority and stronger evidence. *Parkinsonism & Related Disorders*, *18*, S110–S113. doi:10.1016/S1353-8020(11)70035-9

Bowen, F. P., Hoehn, M. M., & Yahr, M. D. (1972). Parkinsonism: Alterations in spatial orientation as determined by a route-walking test. *Neuropsychologia*, *10*, 355–361. doi:10.1016/0028-3932(72)90027-9

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences*, *106*, 8719–8724. doi:10.1073/pnas.0900234106

Clemens, B., Zvyagintsev, M., Sack, A. T., Heinecke, A., Willmes, K., & Sturm, W. (2011). Revealing the functional neuroanatomy of intrinsic alertness using fMRI: Methodological peculiarities. *PLoS One*, *6*, e25453. doi:10.1371/journal.pone.0025453

Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., & Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature neuroscience*, *8*, 1603–1610. doi:10.1038/nn1574

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

Cronin-Golomb, A. (2010). Parkinson's disease as a disconnection syndrome. *Neuropsychology Review*, *20*, 191–208. doi:10.1007/s11065-010-9128-8

Cronin-Golomb, A. (2013). Emergence of nonmotor symptoms as the focus of research and treatment of Parkinson's disease: Introduction to the special section on nonmotor dysfunctions in Parkinson's disease. *Behavioral Neuroscience*, *127*, 135–138. doi:10.1037/a0032142

Davidsdottir, S., Wagenaar, R., Young, D., & Cronin-Golomb, A. (2008). Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease. *Brain*, *131*, 2882–2893. doi:10.1093/brain/awn237

de Lau, L. M., & Breteler, M. M. (2006). Epidemiology of Parkinson's disease. *The Lancet Neurology*, *5*, 525–535. doi:10.1016/S1474-4422(06)70471-9

DeGutis, J. M., & Van Vleet, T. M. (2010). Tonic and phasic alertness training: A novel behavioral therapy to improve spatial and non-spatial attention in patients with hemispatial neglect. *Frontiers in Human Neuroscience*, *4*. doi:10.3389/fnhum.2010.00060

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: A review. *Journal of Neuropsychology*, *7*, 193–224. doi:10.1111/jnp.12028

Duncan, G. W., Khoo, T. K., Yarnall, A. J., O'Brien, J. T., Coleman, S. Y., Brooks, D. J., … Burn, D. J. (2014). Health-related quality of life in early Parkinson's disease: The impact of nonmotor symptoms. *Movement Disorders*, *29*, 195–202. doi:10.1002/mds.25664

Ebersbach, G., Trottenberg, T., Hattig, H., Schelosky, L., Schrag, A., & Poewe, W. (1996). Directional bias of initial visual exploration. A symptom of neglect in Parkinson's disease. *Brain*, *119*, 79–87. doi:10.1093/brain/119.1.79

Edwards, J. D., Hauser, R. A., O'Connor, M. L., Valdes, E. G., Zesiewicz, T. A., & Uc, E. Y. (2013). Randomized trial of cognitive speed of processing training in Parkinson disease. *Neurology*, *81*, 1284–1290. doi:10.1212/WNL.0b013e3182a823ba

Esterman, M., Liu, G., Okabe, H., Reagan, A., Thai, M., & DeGutis, J. (2015). Frontal eye field involvement in sustaining visual attention: Evidence from transcranial magnetic stimulation. *NeuroImage*, *111*, 542–548. doi:10.1016/j.neuroimage.2015.01.044

Esterman, M., Noonan, S. K., Rosenberg, M., & DeGutis, J. (2013). In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. *Cerebral Cortex*, *23*, 2712–2723. doi:10.1093/cercor/bhs261

Fahn, S., Elton, R. L., & UPDRS Development Committee. (1987). Unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, M. Goldstein, & D. B. Calne (Eds.), *Recent developments in Parkinson's disease* (Vol. 2, pp. 153–163). Florham Park, NJ: Macmillan Healthcare Information.

Gallagher, D. A., & Schrag, A. (2012). Psychosis, apathy, depression and anxiety in Parkinson's disease. *Neurobiology of Disease*, *46*, 581–589. doi:10.1016/j.nbd.2011.12.041

Harris, J. P., Atkinson, E. A., Lee, A. C., Nithi, K., & Fowler, M. S. (2003). Hemispace differences in the visual perception of size in left hemiParkinson's disease. *Neuropsychologia*, *41*, 795–807. doi:10.1016/S0028-3932(02)00285-3

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*, *53*, 905–918. doi:10.1016/j.neuron.2007.02.013

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology*, *17*, 427–442. doi:10.1212/WNL.17.5.427

Johnston, W. A., Hawley, K. J., Plewe, S. H., Elliott, J. M., & DeWitt, M. J. (1990). Attention capture by novel stimuli. *Journal of Experimental Psychology: General*, *119*, 397–411. doi:10.1037/0096-3445.119.4.397

Kaernbach, C. (1990). A single-interval adjustment-matrix (SIAM) procedure for unbiased adaptive testing. *The Journal of the Acoustical Society of America*, *88*, 2645–2655. doi:10.1121/1.399985

Karnath, H. O., Fruhmann Berger, M., Kuker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: A study of 140 patients. *Cereb Cortex*, *14*, 1164–1172. doi:10.1093/cercor/bhh076

Klepac, N., Trkulja, V., Relja, M., & Babic, T. (2008). Is quality of life in non-demented Parkinson's disease patients related to cognitive performance? A clinic-based cross-sectional study. *European Journal of Neurology*, *15*, 128–133. doi:10.1111/j.1468-1331.2007.02011.x

Langner, R., & Eickhoff, S. B. (2013). Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*, *139*, 870–900. doi:10.1037/a0030694

Laudate, T. M., Neargarder, S., & Cronin-Golomb, A. (2013). Line bisection in Parkinson's disease: Investigation of contributions of visual field, retinal vision, and scanning patterns to visuospatial function. *Behavioral Neuroscience*, *127*, 151–163. doi:10.1037/a0031618

Lee, A. C., Harris, J. P., Atkinson, E. A., & Fowler, M. S. (2001). Evidence from a line bisection task for visuospatial neglect in left hemiparkinson's disease. *Vision Research*, *41*, 2677–2686. doi:10.1016/S0042-6989(01)00129-8

Levy, G., Louis, E. D., Cote, L., Perez, M., Mejia-Santana, H., Andrews, H., … Marder, K. (2005). Contribution of aging to the severity of different motor signs in Parkinson's disease. *Archives of Neurology*, *62*, 467–472.

List, A., Brooks, J. L., Esterman, M., Flevaris, A. V., Landau, A. N., Bowman, G., … Schendel, K. (2008). Visual hemispatial neglect, re-assessed. *Journal of the International Neuropsychological Society*, *14*, 243–256. doi:10.1017/S1355617708080284

Litvan, I., Aarsland, D., Adler, C. H., Goldman, J. G., Kulisevsky, J., Mollenhauer, B., … Weintraub, D. (2011). MDS task force on mild cognitive impairment in Parkinson's disease: Critical review of PD-MCI. *Movement Disorders*, *26*, 1814–1824. doi:10.1002/mds.23823

Manly, T., Dobler, V. B., Dodds, C. M., & George, M. A. (2005). Rightward shift in spatial awareness with declining alertness. *Neuropsychologia*, *43*, 1721–1728. doi:10.1016/j.neuropsychologia.2005.02.009

Manly, T., Dove, A., Blows, S., George, M., Noonan, M. P., Teasdale, T. W., … Warburton, E. (2009). Assessment of unilateral spatial neglect: Scoring star cancellation performance from video recordings–method, reliability, benefits, and normative data. *Neuropsychology*, *23*, 519–528. doi:10.1037/a0015413

Miller, I. N., Neargarder, S., Risi, M. M., & Cronin-Golomb, A. (2013). Frontal and posterior subtypes of neuropsychological deficit in Parkinson's disease. *Behavioral Neuroscience*, *127*, 175–183. doi:10.1037/a0031357

Norton, D. J., Jaywant, A., Gallart-Palau, X., & Cronin-Golomb, A. (2015). Normal discrimination of spatial frequency and contrast across visual hemifields in left-onset Parkinson's disease: Evidence against perceptual hemifield biases. *Vision Research*, *107*, 94–100. doi:10.1016/j.visres.2014.12.003

París, A. P., Saleta, H. G., de la Cruz Crespo Maraver, M., Silvestre, E., Freixa, M. G., Torrellas, C. P., … Bayés, À. R. (2011). Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. *Movement Disorders*, *26*, 1251–1258. doi:10.1002/mds.23688

Pfeiffer, H. C., Lokkegaard, A., Zoetmulder, M., Friberg, L., & Werdelin, L. (2014). Cognitive impairment in early-stage non-demented Parkinson's disease patients. *Acta Neurologica Scandinavica*, *129*, 307–318. doi:10.1111/ane.12189

Putcha, D., Ross, R. S., Cronin-Golomb, A., Janes, A. C., & Stern, C. E. (2015). Altered intrinsic functional coupling between core neurocognitive networks in Parkinson's disease. *NeuroImage: Clinical*, *7*, 449–455. doi:10.1016/j.nicl.2015.01.012

Ryan, M., Martin, R., Denckla, M. B., Mostofsky, S. H., & Mahone, E. M. (2010). Interstimulus jitter facilitates response control in children with ADHD. *Journal of the International Neuropsychological Society: JINS*, *16*, 388–393. doi:10.1017/S1355617709991305

Sammer, G., Reuter, I., Hullmann, K., Kaps, M., & Vaitl, D. (2006). Training of executive functions in Parkinson's disease. *Journal of the Neurological Sciences*, *248*, 115–119. doi:10.1016/j.jns.2006.05.028

Schrag, A., Hovris, A., Morley, D., Quinn, N., & Jahanshahi, M. (2006). Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism & Related Disorders*, *12*, 35–41. doi:10.1016/j.parkreldis.2005.06.011

Shine, J. M., Halliday, G. M., Gilat, M., Matar, E., Bolitho, S. J., Carlos, M., … Lewis, S. J. G. (2014). The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. *Human Brain Mapping*, *35*, 2206–2219. doi:10.1002/hbm.22321

Sjodahl Hammarlund, C., Hagell, P., & Nilsson, M. H. (2012). Motor and non-motor predictors of illness-related distress in Parkinson's disease.

Parkinsonism & Related Disorders, *18*, 299–302. doi:10.1016/j.parkreldis.2011.10.015

Stern, Y., Mayeux, R., Sano, M., Hauser, W. A., & Bush, T. (1987). Predictors of disease course in patients with probable Alzheimer's disease. *Neurology*, *37*, 1649-1649. doi:10.1212/WNL.37.10.1649

Uc, E. Y., Rizzo, M., Anderson, S. W., Sparks, J. D., Rodnitzky, R. L., & Dawson, J. D. (2007). Impaired navigation in drivers with Parkinson's disease. *Brain*, *130*, 2433–2440. doi:10.1093/brain/awm178

Van Vleet, T. M., Chen, A., Vernon, A., Novakovic-Agopian, T., & D'Esposito, M. T. 2014. Tonic and phasic alertness training: A novel treatment for executive control dysfunction following mild traumatic brain injury. *Neurocase*, *21*, 1–10.

Van Vleet, T. M., & DeGutis, J. M. (2013). Cross-training in hemispatial neglect: Auditory sustained attention training ameliorates visual attention deficits. *Cortex*, *49*, 679–690. doi:10.1016/j.cortex.2012.03.020

Verreyt, N., Nys, G. M., Santens, P., & Vingerhoets, G. (2011). Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. *Neuropsychology Review*, *21*, 405–424. doi:10.1007/s11065-011-9182-x

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *The Neuroscientist*, *20*, 150–159. doi:10.1177/1073858413494269

Vossius, C., Larsen, J. P., Janvin, C., & Aarsland, D. (2011). The economic impact of cognitive impairment in Parkinson's disease. *Movement Disorders*, *26*, 1541–1544. doi:10.1002/mds.23661

Young, D. E., Wagenaar, R. C., Lin, C.-C., Chou, Y.-H., Davidsdottir, S., Saltzman, E., & Cronin-Golomb, A. (2010). Visuospatial perception and navigation in Parkinson's disease. *Vision Research*, *50*, 2495–2504. doi:10.1016/j.visres.2010.08.029