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Research report

Cross-training in hemispatial neglect: Auditory sustained attention training ameliorates visual attention deficits

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ABSTRACT

Prominent deficits in spatial attention evident in patients with hemispatial neglect are often accompanied by equally prominent deficits in non-spatial attention (e.g., poor sustained and selective attention, pronounced vigilance decrement). A number of studies now show that deficits in non-spatial attention influence spatial attention. Treatment strategies focused on improving vigilance or sustained attention may effectively remediate neglect. For example, a recent study employing Tonic and Phasic Alertness Training (TAPAT), a task that requires monitoring a constant stream of hundreds of novel scenes, demonstrated group-level ($n = 12$) improvements after training compared to a test–retest control group or active treatment control condition on measures of visual search, midpoint estimation and working memory (DeGutis and Van Vleet, 2010). To determine whether the modality of treatment or stimulus novelty are key factors to improving hemispatial neglect, we designed a similar continuous performance training task in which eight patients with chronic and moderate to severe neglect were challenged to rapidly and continuously discriminate a limited set of centrally presented *auditory* tones once a day for 9 days (36-min/day). All patients demonstrated significant improvement in several, untrained measures of spatial and non-spatial *visual* attention, and as a group failed to demonstrate a lateralized attention deficit 24-h post-training compared to a control group of chronic neglect patients who simply waited during the training period. The results indicate that TAPAT-related improvements in hemispatial neglect are likely due to improvements in the intrinsic regulation of supramodal, non-spatial attentional resources.

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1. Introduction

The neglect syndrome refers to a collection of spatial and non-spatial attention deficits that can occur after damage to any number of interconnected cortical or subcortical structures, usually in the right hemisphere (e.g., Friedrich et al., 1998; Husain and Kennard, 1996; Karnath et al., 2001; Heilman et al., 1993; Mesulam, 1990; Mort et al., 2003; Posner et al., 1984). While the severity of impairment can vary widely (Hier et al., 1983), the most obvious problem is that patients do not respond to stimuli on the contra-lesional or “neglected” side of space, often seemingly unaware that anything in that space exists (see Driver and Vuilleumier, 2001).

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Patients with neglect also exhibit deficits in attention that are not spatially lateralized such as poor time-challenged successive-signal recognition, poor working memory, and poor sustained attention (Danckert and Ferber, 2006; Heilman et al., 1978; Husain et al., 1997; Malhotra et al., 2005, 2009; Parton et al., 2006; Robertson et al., 1997; Van Vleet and Robertson, 2006). Interestingly, these non-spatial deficits in attention are often stronger predictors of persistent (chronic) spatial neglect in the post-acute stroke recovery phase than are the contra-lesional visuo-spatial deficits themselves (Peers et al., 2006; Duncan et al., 1999; Hjaltason et al., 1996; Husain et al., 1997; Robertson et al., 1997). Irrespective of their association with lateralized deficits, growing evidence suggests that deficits in non-spatial attentional resources are a fundamental contributor to the neglect disorder.

Changes in tonic attention, that fluctuate over minutes to hours, and/or phasic attention, that fluctuate over fractions of a second, have been shown to modulate spatial bias. Tonic attention provides the cognitive tone for more complex functions such as working memory and executive control (Strum et al., 1997; Posner, 2008) and reducing tonic attention via administration of a sedative results in the immediate re-emergence of spatial neglect symptoms in recovered patients (Lazar et al., 2002). Phasic attention is typically associated with brief alerting stimuli (e.g., presentation of a loud tone) or the occurrence of an unpredicted, behaviorally relevant stimulus (DeGutis and Van Vleet, 2010; Singh-Curry and Husain, 2009). Phasic attention supports cognitive operations such as orienting and selective attention (Posner, 2008; Husain and Rorden, 2003), both of which are often compromised in patients with neglect.

Only a few studies have systematically targeted tonic or phasic aspects of attention in patients with neglect (DeGutis and Van Vleet, 2010; Robertson et al., 1995, 1998; Thimm et al., 2006). Studies modulating phasic attention exogenously, from the ‘bottom up’, via presentation of an unexpected alerting tone have shown significant improvement in both time-challenged selective attention [attentional blink (AB); Van Vleet and Robertson, 2006] and spatial attention (Robertson et al., 1998), albeit transiently (on the order of seconds of improvement). Studies modulating phasic attention in a more endogenous manner (‘top–down’), as when waiting for the appearance of a target image in a stream of similar distracters (DeGutis and Van Vleet, 2010) have shown *sustained* improvements (on the order of days to weeks) in selective and spatial attention (see also Thimm et al., 2006).

While several studies have shown a reduction, and in some cases elimination, of patients’ spatial neglect when trained to achieve a more ready and focused attentional state (DeGutis and Van Vleet, 2010; Robertson et al., 1995; Thimm et al., 2006), training focused on both tonic *and* phasic attention may be more effective as robust, group-level effects have been difficult to demonstrate without explicitly training both mechanisms.

In a recent study, DeGutis and Van Vleet (2010) examined the use of a novel training technique designed to engender a sustained focused state of attention. Twelve patients with chronic, moderate to severe neglect were trained in relatively brief daily epochs of Tonic and Phasic Alertness Training (TAPAT) over 9 days. This task required patients to continuously respond via button press to small, briefly displayed scenes presented at central fixation while inhibiting responses to an infrequent target scene. Task improvement was dependent on the ability to intrinsically foster an alert and ready to respond state (tonic attention), but also to periodically and unpredictably inhibit the prepotent motor response (i.e., phasically alter their attention). One day after treatment ended, patients improved to the point where, as a group, they failed to show a spatial bias on sensitive measures of spatial search and object perception as well as a measure of non-spatial, speeded selective attention. Although benefits of training faded over several weeks in the absence of additional training, the magnitude of the training effect was unexpected given the limited training time (4.5 h total).

The therapeutic mechanism(s) of TAPAT warrant further investigation, as a better understanding of the interaction between spatial and non-spatial attention and the plasticity of these attention networks could lead to key insights into the basic mechanisms of interaction between non-spatial and spatial attention and ultimately lead to more effective treatments for patients with hemispatial neglect. First, because TAPAT involves repeatedly and rapidly allocating attention to visual scenes, it could be that improvements in visuo-spatial attention could be related to the visual processing demands. For example, exercising patients’ capacity to quickly grasp the gist of each scene may have led to more efficient recruitment of occipito-temporal (Epstein and Kanwisher, 1998) and posterior parietal regions (Xu and Chun, 2009) involved in gist perception. Alternatively, stimulus novelty (exposure to hundreds of novel images) may have increased patients’ overall level of arousal (Downar et al., 2002) resulting in improved spatial attention. A third possibility is that TAPAT trained patients to more thoroughly engage their intrinsic regulation of attention (see Robertson et al., 1995), allowing both a higher level of attentional engagement/intensity as well as the ability to sustain this level of engagement during demanding tasks.

If enhancing intrinsic alertness is the primary mechanism of TAPAT, the stimulus modality of training should not matter (i.e., intrinsic alertness mechanisms would be similarly engaged by training with auditory stimuli as visual). Additionally, training intrinsic alertness should depend less on external stimulus factors such as novelty or complexity and more on maintaining a consistent level of engagement. To examine these hypotheses, we designed an auditory version of TAPAT which employed substantially fewer and less complex stimuli than the visual training analog (four tones *vs* 981 images). Eight patients with chronic and moderate to severe neglect were required to continuously engage in the rapid discrimination of a small set of auditory tones by initiating a button press to all non-target tones (90% of trials) and inhibiting their response to the presentation of a target tone (10% of trials). All sounds were presented centrally following a variable inter stimulus interval (ISI) and target tones were randomly intermixed. As in the original TAPAT study, patients were trained on the task for 9 days, 36-min/day. Prior to training, and at 1 and 14 days post-training, subcomponents of visual attention were evaluated using the following measures: visual conjunction search (CS) (DeGutis and Van

Vleet, 2010; List et al., 2008; Van Vleet and Robertson, 2006, 2009), subjective midpoint estimation or landmark (LM) task (DeGutis and Van Vleet, 2010) and spatial and non-spatial selective attention (AB; Hillstrom et al., 2004; Van Vleet and Robertson, 2006).

2. Method

2.1. Patients

Sixteen patients (four females) with chronic neglect gave informed consent before participation, in compliance with the Institutional Review Board of the VA Northern California Health Care System in Martinez, California, USA. Their ages spanned 34–78 years, [mean = 66, standard deviation (SD) = 13.6] and all were right-handed (Table 1). Patients were recruited on the basis of a unilateral lesion (all right-sided) to the cerebral cortex, basal ganglia or thalamus (see Table 1 and Fig. 1). Patients were free from seizure disorders, dementia or other neurological impairment and had no substance abuse history.

Patients' performance on sensitive, validated computerized measures of spatial attention (CS task, see List et al., 2008; Van Vleet and Robertson, 2009) and midpoint estimation (LM, see Harvey et al., 1995) was used to establish the presence of neglect. These computerized assessments have been shown to correlate highly with more traditional paper–pencil based clinical measures of neglect, such as line bisection and star cancellation, and due to the use of adaptive algorithms may be more sensitive to the presence of patients' deficits and training-related changes in these deficits (see List et al., 2008). For the current study, patients had to exhibit >20% spatial bias to the left on either task to meet enrollment criteria (e.g., on the CS task, the mean presentation time required to find targets on the left had to exceed the time required to detect targets appearing to the right by no less than 20%).

2.2. Assignment

A minimization procedure (Treasure and MacRae, 1998) was used to assign patients to either the TAPAT-auditory training group or the test–retest control group (see Fig. 2). The first four patients recruited were assigned to the TAPAT-auditory group as proof of principal. The remaining 12 patients were assigned to either treatment or control group based on the following selection factors used to minimize potential imbalance between-groups: age, months since lesion, lesion site and performance on the CS task (see Table 1). Though we did not employ an active control condition in the current study, we previously found that patients with neglect showed no improvements on the outcome measures employed in the current study (AB, CS, LM) after a search training control condition (DeGutis and Van Vleet, 2010). Also, in a healthy population, we recently demonstrated that performance on several physiological indices of arousal did not differ between an object categorization control task and TAPAT, suggesting that the benefits of TAPAT are not due to general arousal effect (Van Vleet et al., 2010) (Fig. 3).

A between-groups AB design was used to compare outcomes, TAPAT-auditory group versus the test–retest control group (see Fig. 2). Both groups were assessed on attention and working memory measures (detailed below) 1 day before and 1 day after either 9 days of TAPAT-auditory

Table 1 – Profile of patients in the auditory (TAPAT-auditory) group and the test–retest control group.

Patient	Age	Sex	Handedness	Lesion location	Months since lesion	Visual field deficit	CS score	LM pixel deviation	AB accuracy
TAPAT – auditory									
EB	34	F	R	R-VP	36	N	.40	−5.0	.95
BW	67	M	R	R-FP	50	Homo	.72	9.0	.40
JS	69	F	R	R-FP	40	N	.39	7.5	.35
DW	64	M	R	R-FP	30	N	.57	−2.0	.86
FR	73	M	R	R-P	32	N	.25	4.5	.43
CW	78	M	R	R-PT	28	N	.22	3.5	.67
TO	69	M	R	R-PS	52	N	.88	29.5	.43
RG	74	M	R	R-FPS	66	N	.59	6.0	.20
Average	**66.0**				**41.8**		**.50**	**6.6**	**.53**
SD	**13.6**				**13.2**		**.23**	**10.3**	**.26**
Control									
DE	76	M	R	R-FP	13	N	.44	24.5	.33
DM	63	M	R	R-PTS	6	N	.82	8.5	.56
GA	77	F	R	R-FP	33	N	.82	27.1	.68
JR	60	M	R	R-FP	48	N	.17	8.5	–
EM	54	M	R	R-S	4	N	.63	1.0	.08
RA	74	M	R	R-PT	24	N	.46	30.0	.83
RP	58	M	R	R-FPS	240	N	.52	8.8	.61
BK	64	F	R	R-VP	12	Homo	.79	−17.5	.30
Average	**65.7**				**47.5**		**.58**	**11.3**	**.48**
SD	**8.8**				**79.1**		**.22**	**15.7**	**.25**

R = right, L = left, V = visual cortex, P = parietal cortex, F = frontal cortex, T = thalamus, S = striatum.

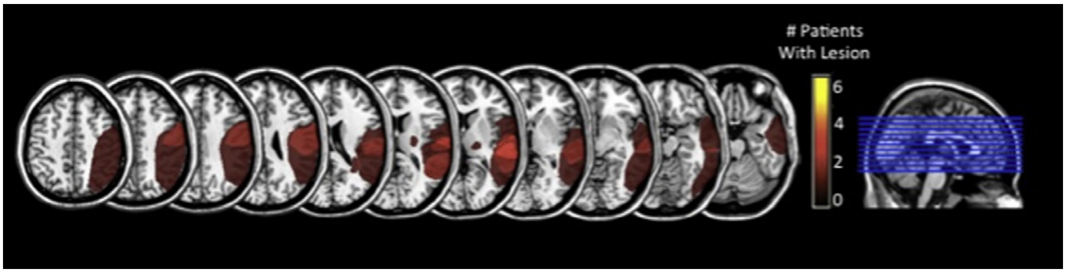

Fig. 1 – Lesion overlap comprising patients in the TAPAT-auditory group ($n = 8$).

training or a 9-day wait period. To measure carryover effects from TAPAT-auditory training, patients in the TAPAT-auditory training group were also assessed 14 days after the completion of training. Additional details regarding participants in each group are reported in Table 1.

2.3. Apparatus

All assessments and training tasks were presented on a widescreen LCD panel (33 cm × 21 cm) of a laptop computer. Screen resolution was 1280 by 800 pixels and the refresh rate was 60 Hz. Patients viewed stimuli from a distance of 60–70 cm, with their line of sight perpendicular to the LCD screen. During training, patients viewed a central fixation cross while responding via spacebar press with their right (dominant) hand to auditory tones presented via two external speakers located on either side of the screen (10° to the left and right of fixation, respectively). Non-targets were presented as two rapid presentations of the same tone frequency (50 msec each with 5 msec of silence between each tone); four possible non-target tone frequencies were randomly intermixed (1000, 800, 400, or 200 Hz, 60 dB, 50 msec). The target tone was a single tone presented at the same duration, but only one presentation (i.e., a single 50 msec tone) and presented at one unique frequency/day (at a different frequency than non-target tones). The limited stimulus variety is a dramatic departure from visual TAPAT training (see DeGutis and Van Vleet, 2010), in which hundreds of novel scenes were presented to participants. Thus, the design of the current study controls for the possible contribution of novelty, by greatly limiting the range of stimuli that patients were required to discriminate. Also, because of speed of auditory recognition processing relative to visual, the inter-stimulus intervals were increased relative to TAPAT-visual (TAPAT-visual: 500, 1000, 2000 msec; TAPAT-auditory: 600, 1800, 3000 msec). Thus, the same number of targets (10% of trials) and non-targets (90% of trials) were presented per 12 min block as TAPAT-visual; patients completed three blocks/training session.

Patients' performance on four experimental attention measures was assessed pre- and post-training: CS task, LM task, AB task (spatial and non-spatial versions). The order of these tasks was kept consistent for all patients for all testing sessions (1-CS, 2-LM, 3,4-AB) (non-spatial then spatial). The following day, patients commenced nine daily sessions of auditory TAPAT, each session lasting approximately 42 min (3 × 12 min of training with a short break between each round). One day (post + 1) and 2 weeks (post + 14) after training was completed, the computer-based assessments were re-administered to assess both immediate and long-term effects of training.

2.4. Training task: auditory tonic and phasic alertness training

Training consisted of three rounds of a 12-min task in which numerous centrally presented tones were briefly presented and patients were required to respond via a button press when the tone was a non-target tone and withhold from responding when the tone was a pre-determined target tone. Each day, the session began with the patients familiarizing themselves with a new target tone while reading the following

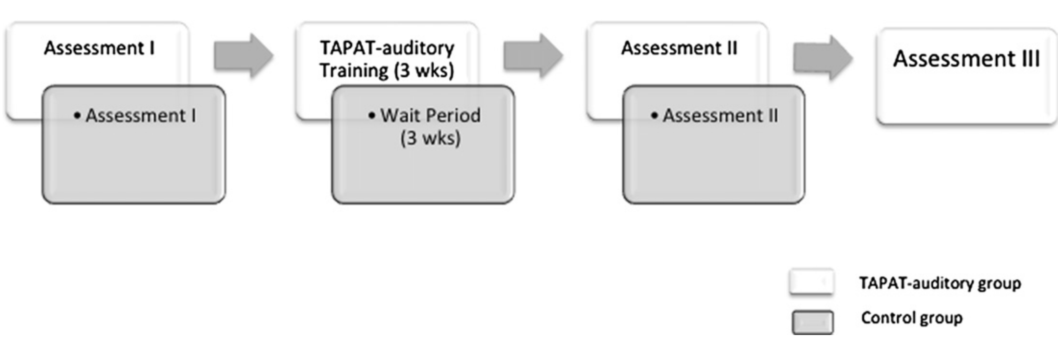

Fig. 2 – Graphical representation of the study design. All participants completed assessment I immediately prior to training (< 48 h) or wait period, and assessment II 3-weeks later. Participants in the TAPAT-auditory group completed assessment III 2 weeks post completion of training.

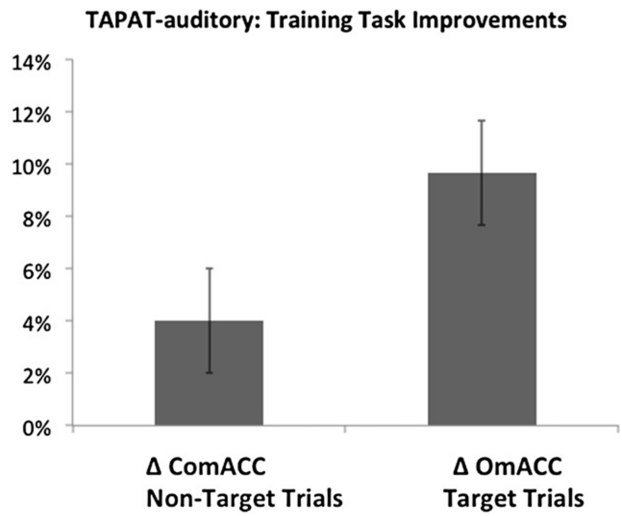

Fig. 3 – TAPAT-auditory group results of performance improvements (Session 1–Session 9) on the training task (error bars represent standard error of the mean).

instructions as the experimenter read them aloud: "You will hear many tones over the next 12 min. Your job is to hit the spacebar as fast as you can for each tone except when the tone is the target tone. When you hear the target tone, do not hit the spacebar. The target tone for today is the following. Please take a minute to memorize this tone." An example of the target tone was played three times or until the patient felt prepared. For each session, the patient was presented with a new target tone, non-target tones remained the same each day. Patients were instructed to keep their eyes on a central fixation "+" while evaluating the sounds presented.

We measured commission accuracy (accuracy at responding to non-targets), correct commission reaction time (reaction time to responding to non-targets), and omission accuracy (accuracy at withholding a response to targets) for every 250 trials, providing nine observations per daily session. This allowed us to calculate a mean and SD for each measure on the first and final day of training and test for significant improvements for each patient.

2.5. *TAPAT-visual training versus TAPAT-auditory*

Because four patients in the TAPAT-auditory group (JS, BW, DW, EB) also completed TAPAT-visual training (14-months prior to enrollment in the current study; DeGutis and Van Vleet, 2010), we were able to evaluate the influence of TAPAT-auditory versus TAPAT-visual on three of four outcomes measures. To accomplish this, we matched four additional patients from the TAPAT-visual study (DS, RL, JF, SV) with the remaining four patients from the current study based on several variables including age, gender, lesion location, time since brain injury and pre-training CS deficit to enable group-level comparisons (see Table 1). CS was chosen as a key behavioral measure for comparison due its sensitivity and significant correlation with conventional, paper–pencil search measures that have been used to diagnose severity of neglect for decades (List et al., 2008).

3. Test–retest control group versus TAPAT-auditory group

3.1. *Outcome measures*

3.1.1. *CS*

The CS task requires searching for a target object (i.e., red square) amongst an array of distracters that include same-colored objects (i.e., red triangles) and same-shaped objects (i.e., blue squares, see List et al., 2008 for a more complete description). Thus, patients cannot simply search for the color of an object or the shape of an object, but are required to search for the conjunction of the particular shape and color. Displays contained a central fixation crosshair and 14 items. Patients were instructed to fixate the central crosshair at the start of each trial, and to indicate whether or not a target was present on each trial by verbally responding "yes" or "no." The experimenter entered patients' responses. Patients were encouraged to report what they saw as accurately as possible and were reminded that the speed of response was not important.

To determine the psychophysical threshold for each side of the display, we adopted a yes–no adaptive staircase procedure described by (Kaernbach, 1990). The initial display duration was set at 2000 msec and we manipulated the display duration to reach an adjusted accuracy rate of 75% (further details of this procedure are described by 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), and a threshold presentation time (TPT) was calculated by averaging the stimulus durations over the final six reversal points. Two separate TPTs were estimated: one from the adaptive staircase for left target detection and one from the adaptive staircase for right target detection. These two estimations occurred simultaneously because all trial types (left target-present, left target-absent, right target-present, right target-absent) were randomly interleaved and equiprobable until one staircase terminated. Thereafter, displays from the completed staircase continued to be presented, including target-present and target-absent trials (each at a reduced probability of .1). These post convergence data points were not included in the TPT calculation.

3.1.2. *Alternative CS*

We administered a CS task as used in prior studies (DeGutis and Van Vleet, 2010; List et al., 2008; Van Vleet and Robertson, 2006) to evaluate the deployment of spatial attention. In this task, a single red square located to the right or left of a central fixation cross was the target object; red triangles and blue squares were used as distracters. After training, we re-administered this task as well as an alternative version for the first time. In the alternate condition, distracters were the same as the original task, but the target was a blue triangle. The inclusion of this alternate version allowed us to compare the results of searching for a novel target before training (original CS) with searching for a novel target after training in the alternate condition.

3.1.3. *LM task*

The LM task was employed as a test of object-based attention and subjective midpoint estimation as described previously (see Harvey et al., 1995; also DeGutis and Van Vleet, 2010). It consisted of a single, black horizontal line that subtended 10° of visual angle (337 pixels) to the left and right of the objective center of the line, and was presented against a gray background. A red vertical reference line or LM that subtended 8 pixels/.125° of visual angle above and below the horizontal bisected the line. For each trial, patients were instructed to first determine the center of the black line and to say whether the LM is to the left or right of their subjective center of the line. There were two types of trials in which separate adaptive staircases were calculated: (1) one in which the LM started from the left (4° from center) and (2) one in which the LM started from the right (4° from center). Right starting trials and left starting trials were randomly intermixed.

If the patient reported that the LM was to the right or left of center on a given trial, on the next trial of that type (right starting trial or left starting trial) the LM was moved incrementally in the opposite direction. Reversals occurred when the patient changed their response for a given type of trial (i.e., went from saying "right of center" to saying "left of center" for a right starting trial). After every two reversals, the increments that the LM was moved between trials decreased (reversals 1 and 2 – 100 pixels/1.48°; reversals 3 and 4 – 50 pixels/.74°; reversals 5 and 6 – 25 pixels/.37°; reversals 7 and 8 – 10 pixels/.15°; reversals 9 and 10 – 5 pixels/.07°). The task ended after 10 left starting trial reversals and 10 right starting trial reversals. The average pixel deviation of the last six reversals for left starting and right starting trials was calculated to obtain a good estimate of the patient's subjective midpoint of the black line.

3.1.4. *AB task: spatial and non-spatial*

We utilized a conventional, non-spatial visual AB task (Raymond et al., 1992; Shapiro et al., 1994) and a spatially lateralized version (Hillstrom et al., 2004; Van Vleet and Robertson, 2006) to examine working memory efficiency. Both tasks consisted of a rapid serial visual presentation (RSVP) of 14 items presented in the center of the screen (subtending 2° of visual angle vertically and 1° horizontally) with the first of two target numbers embedded in 12 or 13 distracter letters presented at central fixation; for the spatially lateralized version, the second target number appeared equally often the left or right of central fixation. Each character was presented on the screen for 120 msec with a 40 msec inter-stimulus interval. The first target number (T1) was red to maximize identification while the distracter letters and second target number (T2), when present, were black and more challenging to identify. T2 appeared either two positions after T1 (200 msec after T1) or six positions after T1 (1040 msec after T1). On both single and dual-task trials, T1 and T2 discrimination was a four alternative forced-choice judgment rather than a presence/absence judgment, preventing patients from conservative reporting of target detection when targets were not clearly attended. Patients verbally reported the identity of the targets and the experimenter coded responses via an external numeric keyboard. Only those trials in which patients correctly identified T1 were used to calculate T2 accuracy.

4. Results

Pre-training, there was no significant difference between the TAPAT-auditory and control group in age [$t(1,14) = -.04$, $p = .96$], time since brain injury [$t(1,14) = .20$, $p = .84$], performance on the CS [$t(1,14) = .68$, $p = .50$], LM [$t(1, 14) = .71$, $p = .49$], or AB [$t(1,13) = -.49$, $p = .63$].

4.1. CS

We performed a repeated-measures analysis of variance (ANOVA) with pre/post and side (L/R) as within-subjects factors and TAPAT-auditory/test–retest control as the between-group factor to determine if TAPAT-auditory training had a larger effect than repeated testing over the same time period. Additionally, to reduce the contribution of general age-related decline in the speed of perceptual processing, we co-varied out patients' age. For the CS, the ANOVA showed a significant main effect of side of display [$F(1,7) = 35.53$, $p < .01$], pre/post [$F(1,7) = 8.88$, $p < .05$] and revealed a significant three-way interaction of side of display × pre/post × TAPAT-auditory/control [$F(1,7) = 6.14$, $p < .05$]. This interaction was driven by greater improvements in searching the left side of the display after TAPAT-auditory training compared to the test–retest control group (see Figs. 4 and 5). In fact, 1 day after TAPAT-auditory training, there was no significant difference between the TPT for the left and right side of the display [mean Left = 360 msec *vs* Right = 270 msec; $t(14) = .81$, $p = .42$]. However, 13 days later, these improvements faded and the difference between detecting left and right targets was not significantly different from before training (Fig. 6).

4.2. LM

The repeated-measures pre/post × TAPAT-auditory/control analysis of pixel deviation from center showed no significant main effects, but demonstrated a trend toward a significant interaction [$F(1,7) = 2.12$, $p < .18$], which appeared driven by a more leftward shift after training in the TAPAT-auditory group compared to repeated testing in the control group (see Figs. 4 and 5). For the TAPAT-auditory group, patients achieved a mean bias at Post + 1 nearly 3 pixels to the *left* of objective center (−2.68 pixels). At time points 3, TAPAT-auditory patients shifted their estimation back to the right of the objective midpoint.

4.3. AB

For the AB task, a repeated-measures pre/post × TAPAT-auditory/control analysis on accuracy of T2 detection for each lag (2 and 6) given accurate T1 identification demonstrated a significant main effect of pre/post for lag 2 [$F(1,7) = 10.95$, $p < .01$] as well as a significant pre/post × TAPAT-auditory/control interaction [$F(1,7) = 11.27$, $p < .01$]. This interaction was driven by patients' greater improvement at lag 2 after TAPAT-auditory training (Mean before training = 48%, Mean Post + 1 Day = 74%). For lag 6, the ANOVA did not demonstrate significant main effects, but did reveal a significant pre/

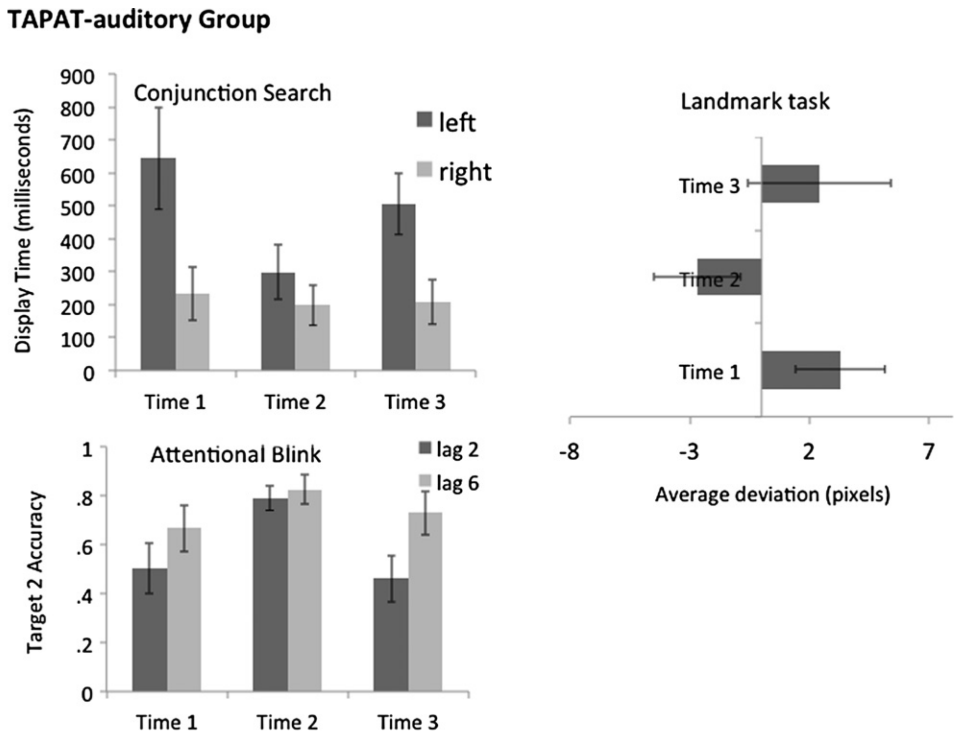

Fig. 4 – TAPAT-auditory group results of performance on three outcome measures (error bars represent standard error of the mean).

post × TAPAT-auditory/control interaction [$F(1,7) = 9.16$, $p < .01$]. Again, this interaction was driven by patients' greater improvement at lag 6 after TAPAT-auditory training (Mean before training = 65%, Mean Post + 1 Day = 82%). After TAPAT-auditory training, patients' performance was similar to unimpaired age-matched controls performing the identical task (Van Vleet and Robertson, 2006). Consistent with the other measures, these improvements faded and failed to be significantly greater than pre-training by time point 3 (Post + 14).

5. Additional outcomes: TAPAT-auditory group

5.1. *Alternative CS*

To assess whether the beneficial effects of training shown in the TAPAT-auditory group generalized to a completely novel condition, we examined patients' search performance for a novel target on an alternative color-shape CS task (blue triangle as target). Patients in the TAPAT-auditory group were assessed on this task at Times 2 and 3 (Post + 1 Day and Post + 14 Days). A 2 × 2 ANOVA with Side (L, R) and Time (2, 3) as factors revealed a significant Main Effect of Time [$F(1,12) = 6.99$, $p < .05$], but not side [$F(1,12) = 3.47$, $p > .09$], nor the interaction of Side × Time [$F(2,24) = 3.50$, $p = .09$]. *T*-tests comparing Right versus Left mean reversal values on the alternative CS task at Post + 1 Day showed that patients exhibited no difference in the detection of Left versus Right targets (i.e., no evidence of a lateralized detection deficit) following training [mean Left reversals = 320 *vs* Right = 291; $t(12) = .437$, $p = .67$], but exhibited a trend toward longer Left target versus Right target TPT at Post + 14 Days [mean Left reversals = 711 *vs* Right = 356; $t(12) = 1.98$, $p < .07$].

5.2. *Spatial AB*

To examine the influence of space on rapid target identification we employed a repeated-measures ANOVA on T2 discrimination accuracy (on correct T1 trials only) with lag (2, 6), Time (1, 2, 3) and Side (L, R) as factors. This analysis revealed significant Main Effects of Time [$F(2,32) = 8.30$, $p < .01$] and lag [$F(1,16) = 4.22$, $p < .05$]. Paired *t*-tests comparing group means before and after training (Post + 1 Day) revealed a significant improvement in T2 accuracy at lag 2 when the second target appeared to the left of central fixation [Mean pre-training = 11%, Mean Post + 1 Day = 39%; $t(5) = 2.50$, $p < .05$]; this benefit faded by 2 weeks post-training [Time 1 *vs* Time 3 T2 accuracy: $t(5) = -.88$, $p = .42$]. At lag 7, T2 accuracy to the left of central fixation showed a trend toward positive improvement [Mean pre-training = 26%, Mean Post + 1 Day = 55%; $t(5) = -2.27$, $p = .07$]. For targets appearing to the right of central fixation, patients demonstrated significant improvement in T2 accuracy at lag 7 [$t(5) = -3.67$, $p < .01$], but not at lag 2 [$t(5) = -1.09$, $p < .32$].

6. TAPAT-visual versus TAPAT-auditory training outcomes

Because four patients in the auditory TAPAT group (JS, BW, DW, EB) also participated in visual TAPAT training

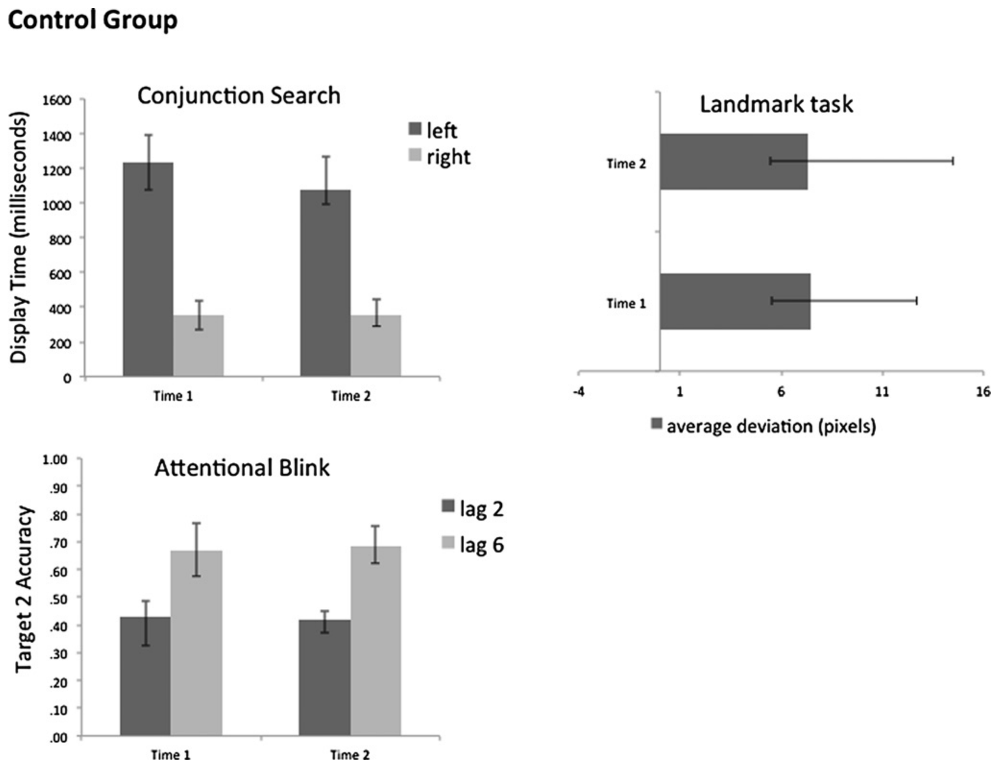

Fig. 5 – Test–retest control group results of performance on three outcome measures (error bars represent standard error of the mean).

(DeGutis and Van Vleet, 2010) >1-year prior to the current study, we were able to evaluate the influence of auditory TAPAT versus visual TAPAT on several outcome measures. First, on the TAPAT-auditory training task we compared the mean commission accuracy, correct commission reaction time, and omission accuracy on the first and last day of training. While there were no significant improvements on commission accuracy, correct commission reaction time, or omission accuracy as a group, individual patients showed marked improvements on several aspects of the task. This variability in patients' TAPAT-auditory task improvement patterns may reflect the use of different task strategies.

6.1. CS

We matched four additional patients from the TAPAT-visual study (DS, RL, JF, IS) based on age, time since lesion, and pre-training CS deficits with the four patients from the current study that completed both training conditions to enable a group-level comparison. A repeated-measures Time (pre/post) × Training Type (TAPAT-visual/TAPAT-auditory) ANOVA on the TPT difference score (left TPT − right TPT) revealed a significant main effect of time (pre/post; $F(1,7) = 61.92$, $p < .001$), but no significant interaction of time × training type [$F(1,7) = .16$, $p = .70$]. Thus, the results showed no difference in the magnitude of change in search scores following training (magnitude change in CS score: auditory TAPAT = 339 msec; visual TAPAT = 281 msec), suggesting that auditory TAPAT was as effective as visual TAPAT in reducing visual search bias.

6.2. LM

A repeated-measures Time (pre/post) × Training Type (TAPAT-visual/TAPAT-auditory) ANOVA comparing the magnitude of change in pixel deviation from objective center revealed a main effect of Time [$F(1,7) = 14.63$, $p < .01$], but no significant interaction of time × training type [$F(1,7) = .01$, $p = .91$]. Thus, the results showed no difference in training type in the magnitude of change in pixel deviation following training (average change in pixel deviation from objective center: auditory TAPAT = 6.85 pixels; visual TAPAT = 6.52 pixels).

6.3. AB

Similarly, we found no differences between auditory versus visual TAPAT training on AB outcomes at lag 2 [main effect of time, $F(1,7) = 18.59$, $p < .01$; no significant interaction, $F(1,7) = 3.16$, $p = .12$] or lag 6 [no significant interaction, $F(1,7) = .39$, $p = .55$]. Average percent post-training improvement at lag 2 (auditory TAPAT = 28%, visual TAPAT = 13%) and at lag 6 (auditory TAPAT = 16%, visual TAPAT = 13%).

7. Discussion

In the current study, we examined the effectiveness of an auditory sustained attention training task, in which patients with neglect were required to continuously engage in the rapid discrimination of a limited number of auditory tones, on visuo-spatial aspects of the neglect syndrome. As all sounds

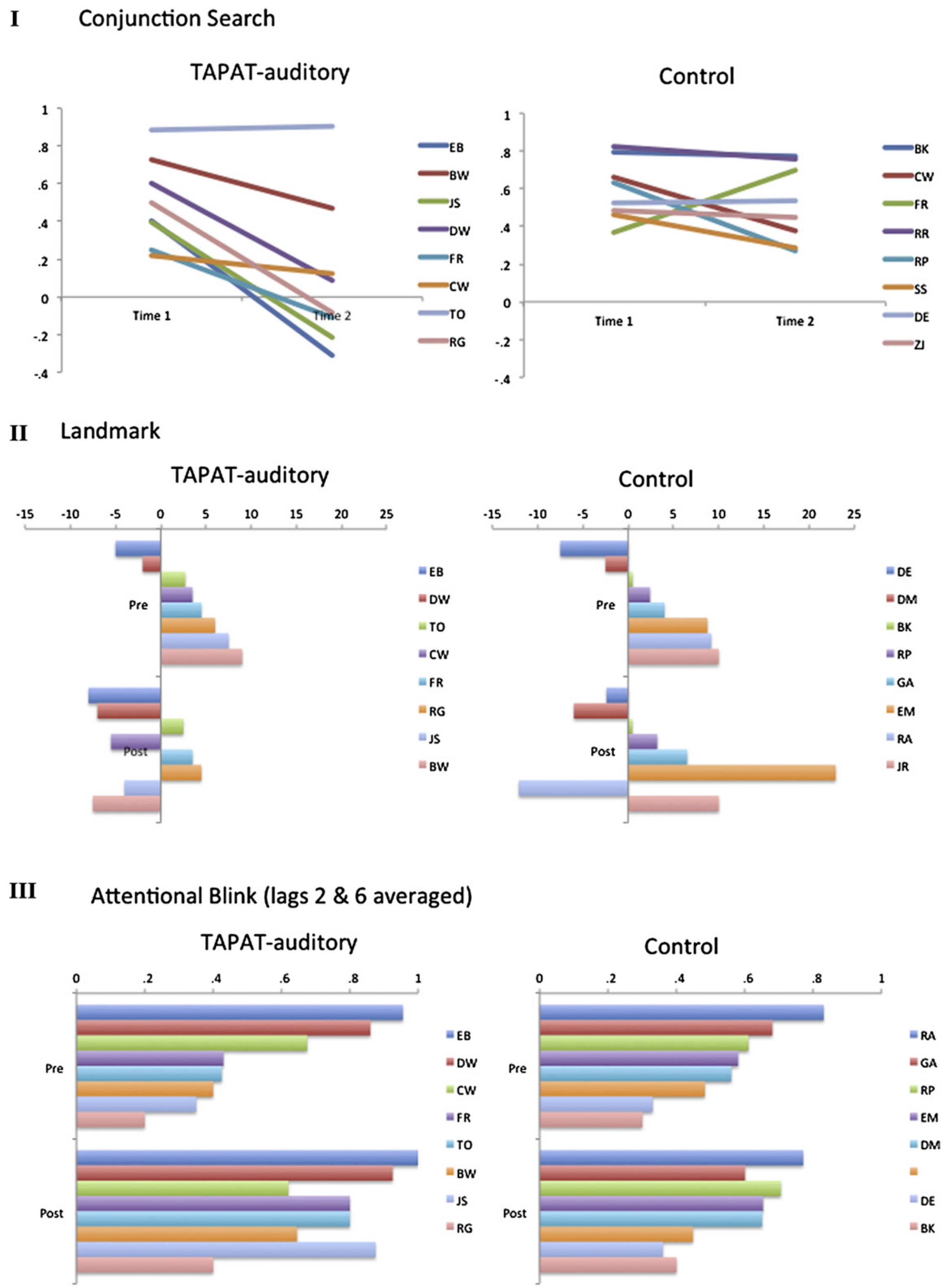

Fig. 6 – Single participant data: pre- versus post-training for the TAPAT-auditory group, and assessment I versus assessment II for the test/retest control group. For the CS, a search bias score of zero represents no bias or symmetrical search; search bias scores > 0 represent a rightward search bias, < 0 represent a leftward search bias. For the AB, T2 accuracy at both lags 2 & 6 were averaged to provide a single score.

were presented centrally, with infrequent and randomly presented target tones, patients were not required to deploy spatial attention. While it is possible that participants did not perceive the sound at objective center, the training task did not require judgment of its location. Following only 9 days of training, all patients showed significant improvement in speeded visual selective attention, greater visual search efficiency, and as a group failed to show a rightward attention bias. Together, the results show a novel effect of auditory-based training that generalizes across sensory modality and domain of attention trained. Further, the results are consistent with a recent study by DeGutis and Van Vleet (2010) that also failed to find evidence of a spatial bias at the group-level following training on a visual version of TAPAT, suggesting that improved endogenous activation of a supramodal alertness mechanism is capable of producing robust improvements in primary deficits common to neglect.

The pattern of training-related behavioral improvements reveals a malleable relationship between attentional domains (e.g., vigilance and spatial attention) that is influenced regardless of modality trained. These results suggest that the sensory modality stimulating the therapeutic mechanism is not crucial and that the effect is generalizable across domains of attention and over time (at least 24-h post-training and up to several weeks in some patients). Importantly, because patients in the current study simply had to make rapid auditory tone discriminations, and were not required to capture the *gist* of a visual scene, its unlikely that recruitment of regions implicated in gist perception (e.g., occipito-temporal and posterior parietal regions; Epstein and Kanwisher, 1998; Xu and Chun, 2009) were required. Rather, enhanced endogenous regulation of a supramodal alertness mechanism possibly mediated by anterior cingulate and right lateral frontal regions appears likely (Pardo et al., 1991; Sturm et al., 2006).

Due to the limited number of stimuli used in the current version of TAPAT (five tones) compared to the visual version in which subjects discriminated hundreds of images (DeGutis and Van Vleet, 2010) the results suggest that training-related improvements are due to improvements in intrinsic, task-related alertness rather than extrinsic alertness driven by stimulus novelty (Downar et al., 2002). Electrophysiological studies show that bottom–up and top–down phasic modulations of attention may engage similar mechanisms (Singh-Curry and Husain, 2009), though bottom–up modulations (e.g., when presented with an oddball stimulus) typically elicit a P300a component that is more related to stimulus novelty and may have a frontal source (Hermann and Knight, 2001), whereas top–down modulations (e.g., when presented with a pre-determined target) are more related to behavioral relevance of a stimulus and typically elicit a slightly later P300b component that may have a parietal source (Comerchero adn Polich, 1999). Due to the limited number of stimuli used in the current training procedure, it is more likely that training enhances mechanisms related to the P300b than the P300a (Nieuwenhuis et al., 2005).

The longevity of the training effect relative to prior studies using extrinsic alerting techniques (Robertson et al., 1998; Van Vleet and Robertson, 2006) suggests that the current approach (fostering endogenous regulation of alertness) is perhaps similar to current studies that improve alertness via 'focused attention meditation' (Lutz et al., 2009). Similar to TAPAT, this type of training involves attending to one object or sensation for a prolonged period of time, requires vigilance, the ability to disengage from distractions, and the ability to redirect focus promptly to the chosen object. After several months of meditation training, researchers have found improved sustained attention and increased attentional stability (Lutz et al., 2009). Thus, the mechanisms of TAPAT training may be somewhat overlapping with focused meditation training. One potential advantage of TAPAT training is the rapidity of therapeutic effects (4.5 h) compared to focused meditation training (typically weeks to months).

Unlike short-lived improvements in spatial and selective attention in patients with neglect subsequent to the presentation of task-irrelevant alerting tones (Robertson et al., 1998; Van Vleet and Robertson, 2006), the current study clearly shows a prolonged benefit (24 h+) of systematically discriminating tones that generalizes to untrained, demanding tasks of visual attention. While alerting tones may briefly activate a frontal control network via *bottom–up*, ascending thalamic–mesencephalic projections (Robertson et al., 1998), an important question raised by the current study is whether or not it is also possible to target *top–down* control processes directly and achieve more lasting effects. Recently, DeGutis and Van Vleet (2010) showed that training on a simple response monitoring task can induce greater self-sustained attention, as patients became significantly faster at finding targets in neglected space without any cost to search latencies for right targets. Patients in the DeGutis and Van Vleet study, as in the current study, increased their capacity to quickly update working memory as evidenced by significant improvement in discriminating rapidly presented targets in an AB task. Thus, TAPAT training, regardless of modality trained, may influence the cortical sustained attention network that monitors and modulates firing rates in subcortical arousal/alertness structures (i.e., locus coeruleus) and hence calibrates the state of alertness according to current goals and task demands (Foucher et al., 2004; Kinomura et al., 1996; Singh-Curry and Husain, 2009). The prefrontal cortices appear to be particularly important in exercising this top–down control of alertness as evidenced by the prevalence of sustained attention difficulties in patients with frontal dysfunction (e.g., Wilkins et al., 1987). Furthermore, recent imaging evidence shows that brief lapses of attention are preceded by momentary reductions of activity in the anterior cingulate and right prefrontal cortex (Weissman et al., 2006). Together, this suggests that TAPAT's therapeutic effects may result from exercising and re-invigorating mechanisms involved in sustained attention and the maintenance of optimal levels of alertness.

Although several other studies have examined techniques to boost endogenous alertness (Robertson et al., 1995; Thimm et al., 2006), consistent effects across patients may be best achieved by training *both* tonic and phasic alertness as in the current study (see also DeGutis and Van Vleet, 2010). This type of experience can foster an *exploitative* or *phasic mode* of attention (Kaelbling et al., 1996) characterized by increased phasic responses in the locus coeruleus (LC; Aston-Jones and Cohen, 2005). The efficiency of the *phasic mode* of alertness is thought to be reflected in performance on the AB task, a measure that requires patients to rapidly discriminate targets from distractors and recall the identity of two embedded targets (Husain et al., 1997; Shapiro et al., 1994; Van Vleet and Robertson, 2006). To push the limits of perceptual resolution and working memory, all characters in the AB are presented rapidly at the same location. In the current study, prior to training patients demonstrated significantly impaired discrimination accuracy for the second target, consistent with earlier reports (DeGutis and Van Vleet, 2010; Husain et al., 1997; Nieuwenhuis et al., 2006; Van Vleet and Robertson, 2006). This poor second target accuracy has been attributed to the refractory period that follows a phasic burst in LC activity tied to the correct discrimination of the first target (normally 300 msec; Usher et al., 1999). Following TAPAT-visual but not an active control task (see DeGutis and Van Vleet, 2010), and in the current study, T2 discrimination accuracy significantly increased post-training, indicating that TAPAT training may regulate the LC refractory period enabling phasic activation to the second target.

In addition to promoting better regulation of endogenous alertness, the current training task may have also fostered improved behavioral flexibility and response control. For example, patients were required to make unexpected changes in motor response based on the appearance of infrequent and unpredicted target presentation. In primate studies, maximal phasic LC responses have been shown during tasks in which the monkey waits for an unpredicted stimulus that signals a cognitive or response-related shift (Bouret and Sara, 2005). This is very similar to the TAPAT training task, with the shift requiring an inhibition of prepotent response (i.e., rapid responding *vs* effectively withholding response). Also, the moderate ISI jitter in TAPAT may challenge patients to engage in a more deliberate and controlled fashion (see Wodka et al., 2009). For example, children with ADHD are more variable than controls on a go/no-go test with fixed ISI, whereas their performance with jittered ISI is equivalent to that of controls (Ryan et al., 2010). Thus, jittering stimulus presentation may provide a nonpharmacologic mechanism for improving response control, mediated by increases in noradrenergic circuits that facilitate maintenance of frontal circuits critical to response control.

In the current study we have shown that a simple auditory sustained attention training task can improve neglect patients' ability to find visual targets in neglected space and more efficiently update visual representations in working memory. Given the robust effects, this method of training patients to endogenously regulate their alertness and practice greater response control has potentially far-reaching application given the widespread incidence of attention regulation deficits in neurologic and psychiatric populations. The results of the current study thus provide a compelling direction for the development of new and more effective attention rehabilitation programs for a broad range of clinical populations.

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