Brain Activity Associated With Stimulation Therapy of the Visual Borderzone in Hemianopic Stroke Patients

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Background and objective. Visual restoration therapy is a home-based treatment program intended to expand visual fields of hemianopic patients through repetitive stimulation of the borderzone adjacent to the blind field. We hypothesized that the training itself would induce visual field location-specific changes in the brain's response to stimuli, a phenomenon demonstrated in animal experiments but never in humans with brain injury. *Methods.* Six chronic right hemianopic patients underwent functional magnetic resonance imaging (fMRI)—responding to stimuli in the trained visual borderzone versus the nontrained seeing field before and after 1 month of visual restoration therapy. Spatially normalized fMRI time-series data were analyzed in a fixed-effects group analysis comparing blood oxygen level dependent (BOLD) activity in the borderzone versus seeing location at baseline and at 1 month. Percent BOLD change was measured to determine each condition's contribution to the time-by-condition interaction. *Results.* There was a significant time by condition interaction manifested as increased BOLD activity for borderzone detection relative to seeing detection after the first month of therapy, which correlated with a relative improvement in response times in the borderzone location out-of-scanner. The right inferior and lateral temporal, right dorsolateral frontal, bilateral anterior cingulate, and bilateral basal ganglia showed the greatest response. *Conclusion.* Visual restoration therapy appears to induce an alteration in brain activity associated with a shift of attention from the nontrained seeing field to the trained borderzone. The effect appears to be mediated by the anterior cingulate and dorsolateral frontal cortex in conjunction with other higher order visual areas in the occipi-totemporal and middle temporal regions. Demonstration of a visual field–specific training effect on brain activity provides an important starting point for understanding the potential for visual therapy in hemianopia.

Key Words: *Visual restoration therapy—Hemianopia—fMRI—Visual training—Brain plasticity.*

INTRODUCTION

Visual restoration therapy (VRT, Novavision, Boca Raton, FL) is a home-based, computerized, visual stimulation treatment protocol for brain-injured patients with partial visual field loss. The therapy is reported to induce a functional expansion of visual fields as the patient engages in a targeted, repetitive stimulation of the visual borderzone next to the blind field over a 6-month treatment period.[1-3] We hypothesized that if the therapy is to work, brain activity associated with detection of stimuli in the trained portion of the visual field must necessarily change as part of the training process, as has been shown in animal models and human studies of visual learning in non–brain-injured subjects. To test this hypothesis, we examined the functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) activity associated with stimulus detection in the target borderzone portion of the visual field before and after the first month of therapy. We chose to assess changes during the early therapy period because patients are most compliant with the treatment during the first month. Furthermore, we wanted to have a stable visual field location in which to investigate training-induced alterations in brain activity. Once the border of the visual field defect begins to move as is the overall intent of the therapy, a new borderzone is defined in the therapy program and becomes the new target of training. Our specific goal in this study was to determine whether therapy would produce a unique

alteration in the brain's response to detection of stimuli in the trained borderzone location compared with the nontrained portion of the seeing field. Whereas animal models have demonstrated visual training–induced plasticity adjacent to and somewhat remote from a lesion, whole brain functional imaging permitted us to investigate for the first time in humans the pattern of regions throughout the brain that may be involved in a visual training process after stroke.

METHODS

Subjects

Patients were eligible for the study if they had occipital-temporal ischemic or hemorrhagic strokes at least 3 months prior to the start of training. They were considered candidates for VRT if they had a homonymous field defect with spared foveal vision on Humphrey or comparable perimetry assessment, and at least 20/50 central acuity on near vision exam. Patients were required to have adequate sustained attention to engage in 20 to 30-minute periods of therapy at a time, sufficient motor dexterity to operate a computer mouse and a 3-button finger response pad with one hand, and have no contraindication to MRI. All subjects signed informed consent for the protocol, approved by the Columbia University Institutional Review Board.

Six right-handed stroke patients aged 35 to 77 years were included, 4 men, 2 women. Each had a right homonymous field defect from a left temporal or occipital lesion. None had prior stroke. Patients 1 and 6 had mild aphasia at the time of the study. None had motor deficits. All had central visual acuity of at least 20/40 on the Snellen chart. Two patients had hematomas in the temporal lobe which were surgically evacuated (patients 1 and 6); the others had left occipital infarcts, treated according to standard stroke protocols. All patients' subjective visual field deficits had remained stable without change for at least 1 month prior to beginning the study. The high resolution perimetry (HRP) maps of the 6 patients remained unchanged through the first month of VRT. Central fixation accuracy remained greater than 95% for all patients during this period.

Visual Field Assessment

Assessment of visual fields at baseline and at 1 month was done with HRP. A fixation point (yellow to green color change) as well as 384 randomly appearing, eccentrically placed dots, were presented in the central portion of the visual fields (±21.5° vertical, ±27° horizontal), similar to a standard Humphrey perimetry test. Three

sequential HRP maps were performed to generate an average HRP visual field map. A gray scale was used such that white represented locations detected on 3 of 3 presentations, light gray for detections on 2 of 3 presentations, dark gray for 1 of 3, and black for locations never detected. The eccentric stimuli were presented as suprathreshold white dots, size = 0.15°, luminence = 95 cd/m^2 on a dark background <1 cd/m^2. Responses to fixation point color change and to the appearance of eccentric stimuli made within 1000 milliseconds generated a "correct" feedback tone; an "error" tone was generated if the response was made too late or before a stimulus appeared. Patient responses were recorded automatically. Each patient's initial therapy program was generated from his or her own baseline HRP map. For the purposes of this study, the "borderzone" was defined as the part of the seeing field within 4° of visual angle from the edge of the blind field in each patient. A nonborderzone location was defined in the seeing left visual field 8° to 12° from the vertical midline. The seeing field location was thus standardized for all patients at a consistent eccentricity from the vertical midpoint; the borderzone location was standardized across all patients as the ribbon of visual field next to the blind area, which was the target of the first month's stimulation therapy. A third field location was defined as a right visual field location 8° to 12° from the edge of the seeing field. Figure 1 shows an axial MRI of the lesion for each patient along with the "borderzone," "seeing," and "blind" field locations for each patient mapped onto their baseline HRP maps. T2-weighted fluid attenuation inversion recovery scans are shown for all patients except for patient 5 who only had a T2-weighted image available, in which the cerebrospinal fluid spaces appear white.

In addition to signal detection (yes or no), response times were recorded at each stimulus location during visual field assessments at baseline and 1 month, allowing specific measurements of average response times in the trained "borderzone" and nontrained "seeing" visual field locations. No overt instructions were given about responding as quickly as possible.

Intervention

Therapy was done at home twice daily for 20 to 30 minutes, 6 days a week. The VRT device is designed to enable stimulation of a specific, targeted region of the visual field while the patient maintains central fixation. With the chin supported on a frame 15 inches from an LCD screen, the patient fixates on a central stimulus and presses a mouse button when either the central fixation stimulus changes color or an eccentric stimulus appears in the peripheral field. The color change (yellow to green) is subtle enough to require foveal vision for
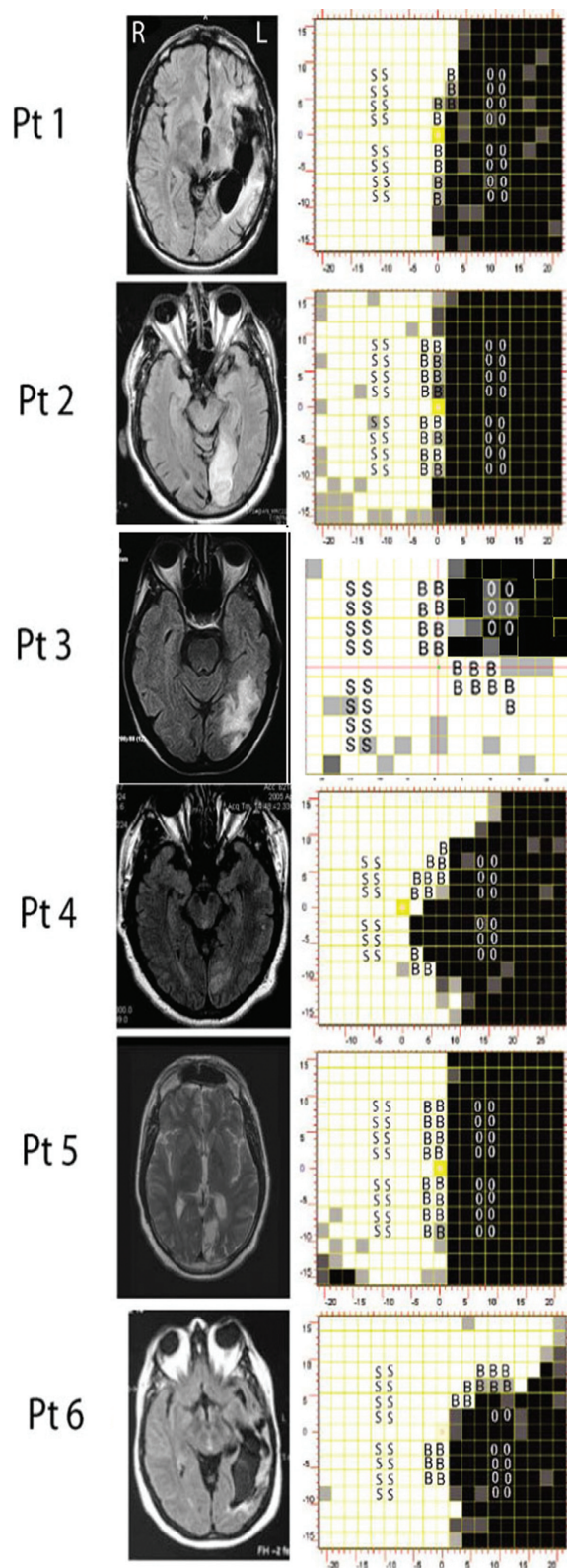
Figure 1. Axial MRI and baseline high resolution perimetry (HRP) visual field maps for the 6 study patients. Imbedded letters on the HRP maps indicate the location of the fMRI stimulus presentation locations for the Seeing field (S), Borderzone field (B), and Blind field (0) for each patient.

discrimination, thus maximizing central fixation. During therapy, stimuli consisted of suprathreshold white squares 2° in width which appeared sequentially along a horizontal path moving from a position in the seeing field 6° from the border of the blind field, into the blind field approximately 6°, and then back into the seeing field. The interstimulus interval was variable between 1000 and 1800 milliseconds. The horizontal paths traversed the visual borderzone at random locations along its vertical extent. For the therapy, 80% of eccentric stimuli appeared in the visual borderzone; the remaining 20% appeared at random locations in the seeing and blind fields to reduce the predictability of the next target location. A single mouse button was used for all responses.

Imaging

Task. Patients underwent fMRI at baseline and 1 month after beginning therapy, using a task that simulated the VRT. In the scanner, patients fixated on a central "X." Flashing 4-square checkerboard stimuli (size = 4.5° visual angle, stimulus duration = 200 milliseconds, interstimulus interval = 1.5 seconds) were presented in the borderzone (within 4° of the edge of the blind field—"borderzone" condition), in the nonborderzone (8° to 12° to the left of midline—"seeing" condition) or in the blind field (8° to 12° right of midline —"blind" condition) in 20-second blocks. Specific instructions to the patients were to respond with the index finger if the checkerboard appeared in the upper field, the middle finger if it appeared in the lower field, or the third finger if the central X changed in size. Patients were not aware of where stimuli would appear next or of the presence of the different categories of borderzone, seeing, or blind field conditions. The patient blinding to the experimental design was intended to minimize inadvertent bias in responding to particular stimuli. A "fixation only" condition was also included which consisted of the central X stimulus change only presented at the same frequency as it appeared in the other conditions. The fixation only and blind conditions served as controls for visual attention and response to visual stimuli and were used in the analysis as the baseline against which BOLD activity associated with the other conditions was assessed. For each patient, the location of the borderzone, nonborderzone, and blind field stimulus presentation was set using a computer program that incorporated the patient's baseline visual field (HRP) map (see Figure 1). The location of stimuli presented to each patient was identical for their baseline and 1 month scan. Patients were trained to ≥90% task accuracy prior to entering the scanner (correctly responding that the stimuli were in the upper or lower field of the border or seeing location ≥90% of the time). The 4 stim-

Table 1. Location and Significance of Maximally Activated Voxel Within a Cluster for the Time-by-Condition Contrast, Thresholded at $t = 3.0$

| Anatomical Region (Broadman Area)	Talairach Coordinates			t_{max}	Number of P Value	Voxels
	x	y	z			
Right occipitotemporal (18/19)	23	−76	−8	3.96	1.0×10^{-4}	520
Right middle temporal (21)	61	−19	−1	4.74	2×10^{-6}	555
Bilateral basal ganglia	−28	8	2	5.07	4.03×10^{-3}	1835
Right inferior parietal lobule (39/40)	45	−62	19	4.35	1.4×10^{-5}	597
Right/left anterior cingulate, medial frontal (24/6)	7	27	34	4.32	1.2×10^{-5}	2796
Right dorsolateral prefrontal (9/46)	42	4	27	3.729	2×10^{-4}	839

ulus conditions (seeing, border, blind, and fixation only) were presented in pseudorandom blocks of 20 seconds, with each condition being presented 4 times during a run. Each borderzone or seeing condition block was preceded by either fixation-only or blind condition block. Subjects were given 2 runs at baseline and 2 runs at the 1-month time point after 1 month of VRT. Responses to stimuli were recorded during the fMRI task to determine in-scanner performance accuracy. An eye camera was used to assess eye movements during the task, with qualitative assessment of whether excessive eye movements were occurring or whether eye movements occurred more during one condition than another.

Image Acquisition and Preprocessing. Imaging was performed on a GE 1.5 T magnet, imaged at 64×64 matrix, 19 cm² field of view, slice thickness = 4.5 mm/0 skip, TR = 2000, TE = 52, flip = 60°, 21 total slices, functional voxel dimensions $3.0 \times 3.0 \times 4.5$ mm. Patient image volumes were motion-corrected and slice timing–corrected, subjected to high pass filter = 3, coregistered to a high resolution (SPGR, T1-weighted) single subject template, transformed to the Talairach template, and smoothed with a 6-mm Gaussian kernel. The first 3 volumes of each run were excluded for signal stabilization. For all patients, motion correction (3 transposition planes, 3 directions of rotation) was well within the functional voxel dimensions.

Analysis. Voxel-wise time series analyses using the general linear model were performed on each subject's echo-planar imaging data to generate spatial maps of task-related activity for each condition at baseline and 1 month. (Brain Voyager QX, CRS, Ltd. UK, running on windows XP, Pentium 4 Intel processor, 1 GB RAM). A fixed-effects group analysis compared the BOLD activity in the borderzone condition at time 1 (baseline) and time 2 (after 1 month of VRT) with the seeing condition

BOLD activity at time 1 and time 2, evaluating for a condition-by-time interaction. The interaction contrast was therefore represented as (B2-B1)–(S2-S1) where B1 and B2 represented the borderzone condition at time 1 and time 2, respectively, and S1 and S2 represented the seeing condition at time 1 and time 2, respectively. A 2×2 factorial ANOVA was performed to test for an interaction of time with condition. All contrasts were assessed at a threshold of $t = 3.0$, corresponding to $P = .0027$ uncorrected for multiple voxel-wise comparisons. In a post hoc analysis to assess the relative contribution of each condition in the interaction and to determine the direction of the interaction we measured the percent BOLD signal change for each condition (borderzone time 1, borderzone time 2, seeing time 1, seeing time 2) in the Brodman areas containing the 5 largest clusters that emerged from the voxel-wise interaction analysis. Brain Voyager assesses BOLD % signal change by obtaining from the time series data the BOLD signal values found in the volumes corresponding to each condition during the run and creating an average plot for each condition with respect to one baseline applied to all conditions. The baseline used for this calculation was an average of the two volumes preceding each of the seeing or border conditions (these volumes would have been contained in a blind or fixation-only condition block).

Finally, out-of-scanner behavioral data (response times) were analyzed from the HRP maps at baseline and 1 month, comparing the response times for borderzone locations versus nonborderzone seeing locations across all patients. A paired t test was used to compare average change in borderzone versus seeing response times from before to after 1 month of VRT, representing a time by location interaction. Linear correlations were also sought between response time change and BOLD signal amplitude of the time by condition interaction in individual regions of interest (ROIs). All post hoc statistics were analyzed with SPSS v12.0.
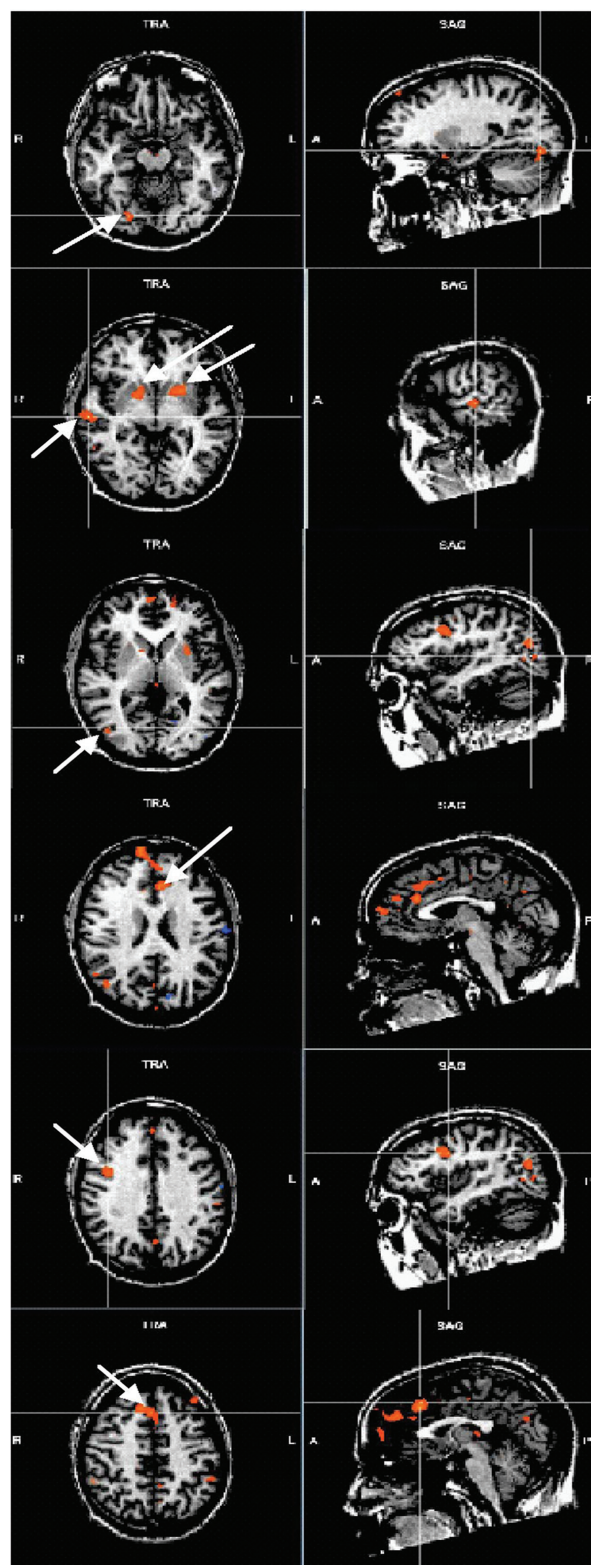
Figure 2. Axial and sagittal fMRI image of the time by condition interaction thresholded at t = 3.0, P =. 0027, uncorrected. Significant clusters are seen in right occipito-temporal and middle temporal, right dorsolateral pre-frontal, right posterior parietal, bilateral medial frontal regions and bilateral basal ganglia (arrows).

Table 2. Response Times in Milliseconds

| Patient	B1	B2	S1	S2
1	466.5	389.3	558.6	524.2
2	440.6	426.8	362.2	368.3
3	475.7	468.6	452.2	454.7
4	358.3	345.5	342.2	335.5
5	387	377.8	433.8	448.2
6	412.3	375.1	393.2	365.4

B1 = borderzone location at baseline; B2 = borderzone location after 1 month of visual restoration therapy; S1 = seeing location at baseline; S2 = seeing location after 1 month of visual restoration therapy.

RESULTS

In the scanner all 6 patients performed at >90% accuracy on the stimulus localization task in the seeing and borderzone conditions at both time points. The voxel-wise statistical analysis of BOLD activity revealed a significant interaction between time and condition as shown in Figure 2. Compared with the baseline time point and relative to the seeing condition, the borderzone condition after 1 month of VRT was associated with increases in BOLD activity in the right occipitotemporal and middle temporal regions, right dorsolateral prefrontal cortex, bilateral medial frontal cortex, bilateral basal ganglia, and right posterior parietal cortex. Table 1 lists the location, t value, and corresponding P value of the maximally activated voxel of the these clusters thresholded at $t = 3.0$. No responses to stimuli were made during the blind condition in any patient, and no significant BOLD activity was seen (data not shown).

The contribution of each condition to the interaction pattern is illustrated in Figure 3. The regional activity from the interaction demonstrated in Figure 2 was because of increases (red color) in the borderzone condition over time in the medial frontal, right dorsolateral prefrontal, and right middle temporal regions and to relative decreases (blue color) in the seeing condition in the medial frontal, right inferior temporal, and bilateral basal ganglia. The quantitative representation of BOLD % signal change in the Brodman area ROIs containing the 5 largest clusters is shown graphically adjacent to the images. Although there was some minor variability in the BOLD pattern from patient to patient, each patient had a similar regional pattern of activity, and no one patient dominated the main effect in the group analysis.

Out-of-scanner response time measurements taken from the 6 patients during the baseline and 1 month HRP mapping showed that at baseline all patients were faster at responding to stimuli presented in the nonborderzone seeing field than the borderzone field (394 vs 423 milliseconds, $P = .04$, 95% CI for difference = 1.5 to
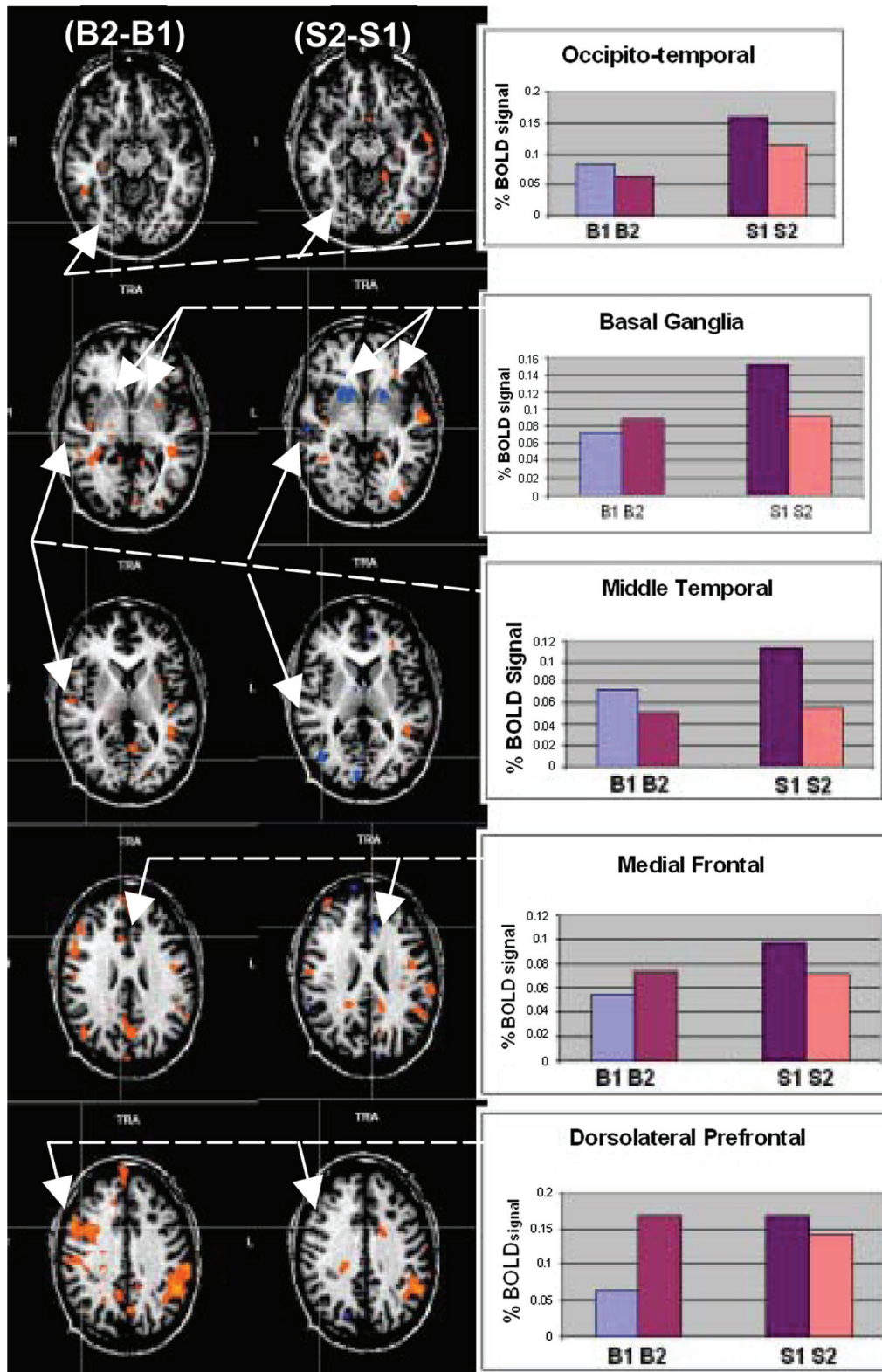
Figure 3. Components of the interaction. Arrows indicate locations of the clusters from the interaction analysis shown in Figure 2. (B2-B1)=Change in BOLD signal for the Borderzone condition over time. (S2-S1)=change in BOLD signal for the Seeing condition over time. Images thresholded at t = 3.0, P = .0027, uncorrected for multiple voxel-wise comparisons overlayed on the single subject T1 template. Red denotes increases, blue denotes decreases. Graphs depict contributions to the interaction of each condition at each time point. Inf Temp=inferior temporal (BA19/37), Lat temp=lateral temporal (BA21), Med Front = medial frontal (BA24), DLPFC = dorsolateral prefrontal cortex (BA46) and basal ganglia shown.

55.7 milliseconds). Over the first month of therapy, the average response times became 18.6 milliseconds faster in the borderzone location compared with the seeing location (paired *t* test for change in response time by condition, *P* = .02; 95% CI = 4.2 to 32.9 milliseconds), representing a time by location interaction (see Table 2). Among the Brodmann area ROIs examined there was no linear correlation between the BOLD signal increases for the posttraining borderzone location on fMRI and the degree of response time gain for the borderzone location behaviorally.

DISCUSSION

This is the first human study to our knowledge to demonstrate a change in brain activity in response to visual field–specific training after brain injury. We showed that 1 month of training by hemianopic stroke patients on the VRT program resulted in anatomically distributed increases in the BOLD signal associated with response to stimuli in the trained (borderzone) field versus the untrained field. Our experimental design allowed us to use the patients as their own controls and thereby identify the effect of the variable of interest—the location-specific training effect—while controlling for other host variables such as lesion size and location, time since stroke, cognitive strategy, and global attention.

Although any spatially distributed pattern resulting from the interaction between time and condition would support the hypothesis that a training-specific change in brain activity occurred, the fact that several identified regions are involved with visual processing (BA 19, 21, and 46)[4,5] and visual attention (BA 24)[6,7] lends support to the neurological specificity of the findings. Basal ganglia activation has been reported to occur as result of extended practice becoming more automatic.[8,9] In other imaging studies of visual training, both increases[10] and decreases[11] have been reported in primary visual cortex after training. Activity in brain regions outside of primary visual areas has been ascribed to more broadly distributed visual learning or attentional networks feeding back on primary visual cortex,[12,13] although some investigators have found little contribution from other brain regions when the training occurs only in a short time frame.[14]

As shown in Figure 3, the borderzone condition was associated with BOLD signal increases over time in the right inferior and middle temporal gyri, right dorsolateral prefrontal, and bilateral medial frontal regions. The time by condition interaction was thus driven by increases in the borderzone condition in these regions over time along with decreases in the right inferior and middle temporal, medial frontal, and bilateral basal ganglia for the seeing condition. Although a reduction in BOLD signal over time has been attributed to a habit-

uation or practice effect,[15-17] preservation or increase of BOLD signal for the borderzone condition in our data suggests that the regions we identified in our time by condition interaction were specific to enhanced visual processing in the borderzone location over time. One possible explanation for our findings, therefore, is that the therapy engaged the anterior cingulate and dorsolateral prefrontal cortex to mediate a shift away from the seeing location, where patients prior to therapy would tend to acquire more visual information, toward the borderzone location, where they were being trained to detect stimuli with VRT. A relative increase of BOLD activity in other higher order visual regions such as BA 19, 21, and 46 resulted from the upregulated directed attention. One might hypothesize that without the increase in cingulate-mediated activity, the occipital-temporal and lateral temporal activity would not be maintained. Our behavioral data of a relative gain in response time for detection of stimuli in the borderzone location after 1 month of therapy supports the imaging results. Although we failed to find a linear relationship between the relative gain in borderzone response times and the degree of increase in BOLD signal across subjects for the borderzone condition, both the imaging results and the behavioral results support a visual field location-specific effect of training.

Sensory systems in general are amenable to training,[18-23] and improvements often appear to be specific for task and location. Huxlin and Pasternak,[24] for example, showed that cats with extrastriate lesions that impaired their ability to discriminate motion could be retrained on a motion detection task to near baseline performance, and the behavioral improvement was restricted to the trained visual field location. Yang and Maunsell[23] showed that adult macaques undergoing extensive training on an orientation discrimination task also showed that performance improvement occurred only in the location that was trained. They further demonstrated that the neuronal activation associated with the improved performance was seen in V4 neurons with receptive fields overlapping the trained visual field location.[23] Thus both the performance improvement and the neuronal activation were specific to the trained location in the visual field. Kobatake et al[25] showed that visual training for shape discrimination in primates altered neuronal responsiveness in the inferotemporal region, concordant with our findings of training-associated activity in BA 19/37. Although our patients were responding to location without a requirement for shape, orientation, or motion discrimination, even rapid and rudimentary stimulus presentations involve brain regions outside primary visual cortex. Foxe and Simpson,[26] for example, showed that visual presentation of bilateral red disks at 4° eccentricity resulted in electrical evoked responses that spread from occipital to temporal and parietal lobes within the first 80 milliseconds of

presentation, before any sensory discrimination, let alone overt motor response, could be generated. Over longer time courses involvement of extrastriate brain regions during visual training may be because of feedback or "top-down" influences related to perceptual learning,[27-29] concordant with human imaging studies discussed above.

We interpreted our imaging results as being attributable to training alone. From this perspective, one would hypothesize that if patients were trained with stimuli in the seeing field location rather than the borderzone field location the findings would have been the same but with the seeing field showing relative increases in the right inferior temporal, dorsolateral frontal, and anterior cingulate regions. In addition to having training as a variable, however, the borderzone location differed from the seeing location with respect to its close proximity in visual space to the blind field. It is possible that the difference in the activation pattern over time was attributable not merely to the effect of repetitive stimulation in the trained location, but to the fact that the training was taking place adjacent to a part of the visual field with dysfunctional sensory processing. Animal studies of functional reorganization after injury generally attribute behavioral recovery to alterations in cortical areas adjacent to the cortex representing the dysfunctional sensory input. In the visual system, Eysel and Schweigart[30] showed spontaneous expansion of neuronal receptive fields in visual cortex adjacent to an induced V1 lesion. Zepeda et al[31] showed similar reorganization of orientation maps after V1 injury. In the somatosensory system, Xerri et al[32] showed that retraining on a manual dexterity task after a lesion in primary somatosensory cortex area 3b resulted in behavioral recovery that correlated with expansion of receptive fields in adjacent areas 3a and 1. Interestingly, these investigators found that such training-dependent remapping did not occur in intact animals, suggesting that there were factors unique to the injury such as local disinhibition[33] that promoted or permitted the cortical reorganization. It is possible that the visual borderzone in hemianopic stroke patients has a cortical representation with properties that make it uniquely amenable to training. Although our methods did not permit specific assessment of brain tissue immediately adjacent to the stroke, the findings do suggest that if reorganization is going to occur as a result of training after injury, widely distributed, functionally specific brain activity will occur throughout the brain.

Although the goal of VRT is to reduce the size of the blind field, none of our patients had an expansion of visual fields in the first month of training; improvements with VRT often occur after this time point. Our intention was to look at brain activity related to the training process which we reasoned was a necessary prerequisite to any subsequent change in visual field. Once spontaneous improvement in visual fields has plateaued in patients with brain injury, further visual field expansion generally does not occur.[34] In future investigation, a correlation of imaging changes with degree of visual field expansion will be needed to differentiate a location-specific stimulation effect that corresponds to visual attention and training itself, from brain activity that correlates with expansion of the visual borderzone into the previously blind field. An additional limitation of the study was the small number of subjects, necessitating a fixed-effects analysis, which prevents extrapolation to a larger population. Nonetheless, our current findings of a location-specific training effect on brain activity in the visual borderzone of human hemianopics are consistent with animal models of training-induced brain plasticity and provide an important starting point for the investigation of mechanisms of visual recovery in patients with brain injury.

ACKNOWLEDGMENTS

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