Behavioral/Cognitive

Ameliorating Hemianopia with Multisensory Training

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Hemianopia (unilateral blindness), a common consequence of stroke and trauma to visual cortex, is a debilitating disorder for which there are few treatments. Research in an animal model has suggested that visual-auditory stimulation therapy, which exploits the multisensory architecture of the brain, may be effective in restoring visual sensitivity in hemianopia. It was tested in two male human patients who were hemianopic for at least 8 months following a stroke. The patients were repeatedly exposed to congruent visual-auditory stimuli within their blinded hemifield during 2 h sessions over several weeks. The results were dramatic. Both recovered the ability to detect and describe visual stimuli throughout their formerly blind field within a few weeks. They could also localize these stimuli, identify some of their features, and perceive multiple visual stimuli simultaneously in both fields. These results indicate that the multisensory therapy is a rapid and effective method for restoring visual function in hemianopia.

Key words: **cortical blindness; cross-modal; hemianopsia; superior colliculus; training; visual-auditory**

Significance Statement

Hemianopia (blindness on one side of space) is widely considered to be a permanent disorder. Here, we show that a simple multisensory training paradigm can ameliorate this disorder in human patients.

Introduction

Hemianopia is a severely debilitating disorder and a common consequence of a unilateral injury to visual cortex (Zhang et al., 2006; Goodwin, 2014), affecting up to 49% of patients on stroke wards and 0.8% of adults over the age of 49. Although some patients experience spontaneous resolution of some deficits within 6 months, others are permanently blind in all or part(s) of the hemifield opposite the damaged cortex (contralesional). There is great interest in identifying the mechanisms underlying hemianopia and potential therapies to ameliorate it (Saionz et al., 2021).

Recently, we developed a novel multisensory rehabilitation paradigm that rehabilitates hemianopia in an animal model (cat). This noninvasive technique is rapid, easy to implement, effective even under anesthesia (Jiang et al., 2020), and requires neither overt behavioral responses nor any of the cognitive factors known to be critical in other neuro-rehabilitative paradigms (Taub, 2004; Danzl et al., 2012; Brett et al., 2017). Rather, it relies on the inherent capabilities of the brain for multisensory plasticity (Woods and Recanzone, 2004; Yu et al., 2009, 2013, 2014; Bolognini et al., 2013; Hakon et al., 2018). Presumably, because this plasticity does not require active engagement in a task, or even alertness (Bi and Poo, 2001; Yu et al., 2010, 2013; Cuppini et al., 2012), rehabilitation can rapidly be achieved in their absence.

The paradigm involves presenting spatiotemporally aligned visual-auditory stimulus pairs within the blind hemifield of animals rendered hemianopic by unilateral lesions of visual cortex. Within weeks of training, the multisensory output layers of the ipsilesional superior colliculus (SC), which were indirectly rendered visually refractory by the lesion (Sprague and Meikle, 1965; Sprague, 1966; Sherman, 1977; Wallace et al., 1989, 1990), regained visual responsiveness. Concomitant with this neural recovery was recovery of the ability to detect and orient toward contralesional visual stimuli. The restored vision was even more robust than what might have been expected (Dakos et al., 2019); it was competitive with vision in the opposite hemifield and extended well beyond the simple stimulus detection and localization capabilities generally ascribed to the SC (Jiang et al., 2015, 2020; Dakos et al., 2019, 2020). The regularity and precision with which the visual-auditory stimuli are presented appear to be crucial to successful rehabilitative outcomes (Dakos et al., 2020). A similar paradigm using only visual or auditory stimulation was not effective (Jiang et al., 2015).

This paradigm seemed to be ideal for rehabilitating human hemianopic patients. The cat and human visual systems have fundamental similarities (Blake, 1979, 1988; Crawford et al., 1990); the cortices and subcortical structures of both are sensitive

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to auditory and visual stimuli, and both show evidence of multisensory plasticity (Giard and Peronnet, 1999; Foxe et al., 2000; Calvert, 2001; Calvert et al., 2001). Thus, we examined the possibility that this multisensory rehabilitation paradigm would be effective in human stroke-induced hemianopic patients.

Materials and Methods

All methods were conducted in compliance with an approved protocol by the Institutional Review Board of the Wake Forest University School of Medicine (IRB00074687) and a registered clinical trial on the clinicaltrials.gov website (NCT04963075).

Patients. The inclusion criteria for this study were patients with (1) homonymous hemianopia in the absence of hemineglect and as a result of an ischemic or hemorrhagic stroke, who had been stable for at least 6 months to avoid confounding by spontaneous recovery soon after the insult; (2) a lesion encompassing at least primary visual cortex but sparing parietal cortex; (3) normal auditory and cognitive function (the paradigm required hearing and the ability to follow commands); (4) the willingness to participate in the program; and the (5) ability to perform visual discriminations in their intact field.

Two patients who met these criteria were referred from the Department of Neurology by C.B., a vascular neurologist at Atrium Health Wake Forest Baptist. Both patients had undergone formal visual field testing with the Humphrey visual field test (Goldmann size 3) at least 3 months before providing their consent.

JM is a 64-year-old dextral male who suffered an earlier right posterior cerebral artery (PCA) infarct (August 2020) followed by a left PCA infarct 2 d later. A magnetic resonance imaging (MRI) scan without gadolinium (October 2020) confirmed bilateral occipital lobe infarct with hemorrhagic conversion with subsequent reduction in vasogenic edema on the left. JM was referred for rehabilitation with physical therapy (PT) and occupational therapy (OT). He underwent outpatient follow-up of visual fields with Humphrey visual field test (Goldmann size 3) in August 2021, which showed persistent left homonymous hemianopia with a small right inferior quadrantanopia. The patient consented and was enrolled in the study in October 2021, 14 months after the initial stroke.

On an initial examination by the research team, patient navigation into the room was highly compromised, and he required assistance in being guided into the chair because of his visual impairment. He reported complete absence of stationary visual perception on the left side of space starting at midline and also in the far-right periphery, with significant impacts on quality of life, particularly with navigating complex environments because of what he described as "tunnel vision." He also reported subjective difficulty in thinking clearly and with short-term memory, which he attributed to the effort required to process visual scenes.

The results of initial research testing matched the results of the earlier clinical examination; the patient could not detect 500 ms flashes of light (~1000 lm) anywhere to the left of fixation (flash test). He could, however, detect such flashes everywhere to the right of fixation, although detectability was not perfect beyond 45° of eccentricity. There was a total lack of visual perception for stationary or moving stimuli to the left of fixation and compromised visual perception in the far-right periphery. In right space at eccentricities <45°, detection, localization, and identification of visual stimuli were fully intact. Based on these findings, the left hemifield was identified as the targeted blind field.

CW is a 72-year-old dextral male who suffered a right PCA infarct along with multiple scattered foci of infarction involving the cerebellum and bilateral supratentorial cerebral hemispheres following ST-segment elevation myocardial infarction and cardiac arrest in February 2021. Cardiology diagnostic evaluation revealed severe diffuse coronary disease without an obvious culprit lesion. CT surgery was consulted to echodensity within the pericardium adjacent to the right ventricle, and CW underwent subxiphoid pericardial window and evacuation of pericardial hematoma. At the time of discharge from the hospital to inpatient rehabilitation, he was noted to have impaired mobility and activities in daily living, and cognitive deficits from the multifocal strokes. While undergoing rehabilitation with PT and OT, he was noted to have visual impairment on the left. The patient was referred for a visual field test in August 2021, when a Humphrey visual field test (Goldmann size 3) showed homonymous hemianopia on the left with sparing of the bottom-left quadrant below −10°. He was seen in the neurology clinic for follow-up, recruited to participate in the study, and consented.

The results of the initial research testing at study onset, 8 months after the insult, matched the results of the earlier visual examination. CW could not detect 500 ms flashes of light (~1000 lm) anywhere in the upper-left quadrant of space (flash test) but could detect flashes in the left inferior space below −10° of eye level and everywhere in right space. Tests with stationary and moving objects produced similar results, total lack of any visual perception in the upper-left quadrant but intact detection, localization, and identification of visual stimuli everywhere else in space. Based on these findings, the upper-left quadrant was identified as the targeted blind field.

Scheduling. The patients committed to 10 sessions of training and testing, each lasting a maximum of 2 h. A session was terminated before the 2 h limit when the patient reported eye strain or continued difficulty in maintaining fixation. Sessions began near the beginning of October 2021 and continued on an approximately weekly basis until January 2022 (14 weeks). In each session, the patient was led into the experimental room at the Wake Forest University School of Medicine Clinical Research Unit (CRU) and seated in a comfortable chair facing the apparatus. The patients were briefly interviewed and briefed by the investigator (B.A.R.) before interleaved blocks of visual testing and multisensory training. Each session concluded with a debriefing.

Training/testing room. Three rooms of similar size and layout within the CRU were used (selection dependent on availability). Each was ~8 × 20 meters and contained a patient bed, chairs, and tables, with ample room for the apparatus described below. Shades over the windows in each room produced a dimly lit environment (~10 lm), and each had low ambient background noise (~41 dB).

Apparatus. The apparatus (Fig. 1) consists of visual-auditory stimulation devices affixed to the top of movable towers. Each tower was a height-adjustable desktop stand (YIFU B07KX29CB7) with a 5.9 × 5.11 inch base placed on a table as shown in Figure 1. The stimulation device on top of each tower consisted of a wide-frequency speaker (Panasonic 4D02C0) and a 3 × 6 array (~1 inch wide × 3 inches high) of white light emitting diode (LED) strips (Dephen DEP-SNW320F008W05-COB) attached to it. The assembly connected via a flexible adapter with a custom-printed circuit board (PCB; OSH Park) to an Arduino Mega 2560 Rev3 microcontroller modified to run at a clock frequency of ~31 kHz. The PCB routed output ports and grounds of the Arduino to connectors for each of the towers. The Arduino was connected to a laptop via a USB, with which it communicated via a virtual serial port. Custom firmware on the Arduino and software on the computer controlled stimulus delivery. The LED/speaker assembly atop a single (inactive) tower placed 2 m in front of the patient served as the fixation point. A camera (Zuodon) on tripod recorded each session. Data from the camera were used *post hoc* to confirm the real-time assessments of patient visual fixation that were made by the researcher. A movable LCD monitor (Acer S241HL) was used to present virtual visual stimuli. All stimuli were presented 2 m from the patient's head, at eccentricities between −90° (left) and +90° (right) of fixation, and at elevations −30° (below) and +30° (above) eye level.

Rehabilitation procedure. As in previous studies in animals (Jiang et al., 2015, 2020; Dakos et al., 2019, 2020), the rehabilitation procedure involved repeatedly presenting identical visual-auditory stimuli at a chosen location in the hemianopic field (initially at 45° of eccentricity) while the patient maintained fixation on the top of the central (0°, 0°) tower. Fixation was monitored by the researcher. The visual stimulus consisted of a brief (500 ms) and bright flash of an LED complex (1000 lm). The auditory stimulus was in spatial and temporal congruence with the LEDs and consisted of a brief (500 ms) broadband noise burst (68 dB SPL) emitted from the speaker. Most rehabilitative training sessions contained 600 of these cross-modal stimulus trials in blocks of 100–150 trials at

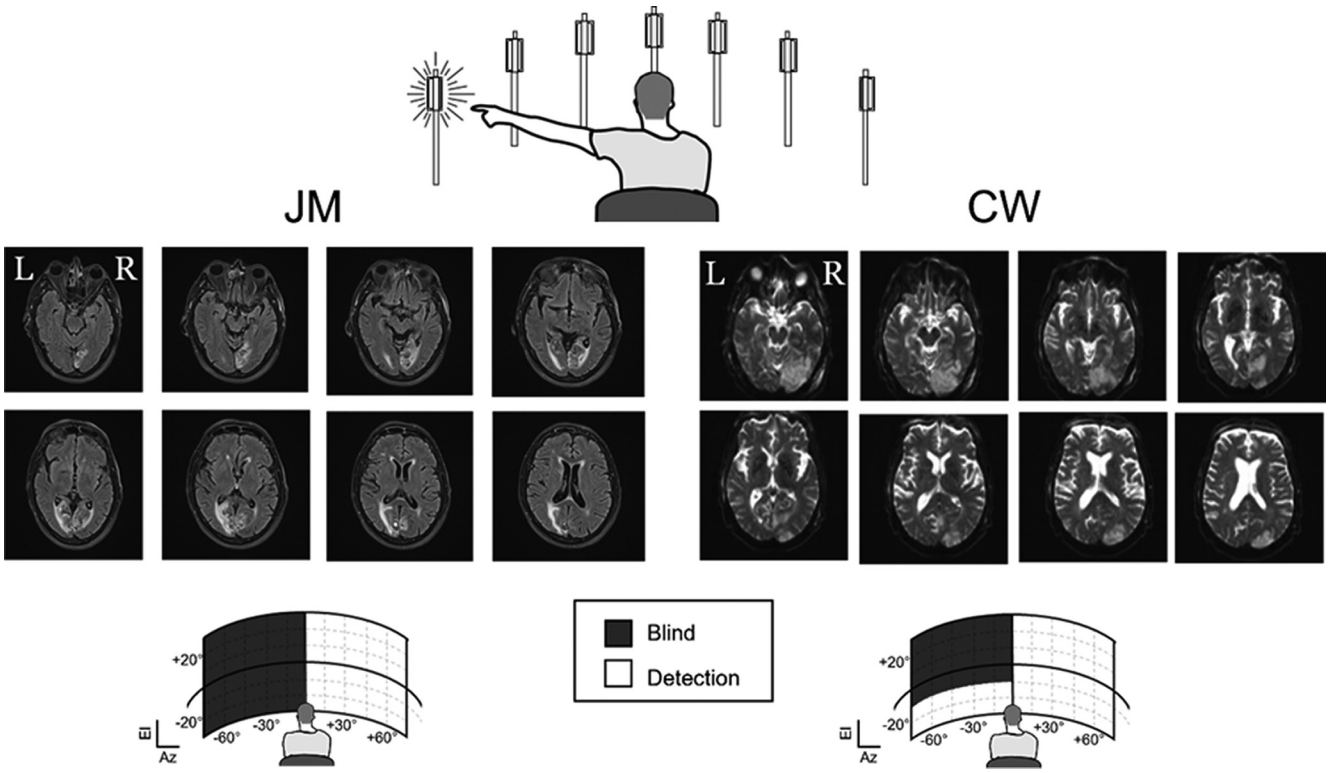

Figure 1. Top: The apparatus used in multisensory training and flash detection/localization. LED and speaker assemblies were mounted on top of a set of movable and height-adjustable towers (7 depicted). During training, visual-auditory stimuli were repeatedly presented at a location within the blind field. During testing, patients were asked to verbally report and/or point to the location of a flashed stimulus. Middle and Bottom: MRI scans and initial testing for both patients. In both patients, a right PCA infarct created blindness on the left side of space. Unshaded areas in the plots (Az = azimuth, El = elevation) indicate areas responsive to light flashes, black shaded regions indicate where those flashes could not be detected. Note that CW had vision spared in left space below −10° of elevation.

interstimulus intervals of 2–6 s. These rehabilitative training stimuli were interleaved with fixation breaks and visual probe tests.

Tests of visual function. All visual tests were performed binocularly while the patient maintained fixation, following as closely as possible the paradigm developed in the cat model (Jiang et al., 2015, 2020; Dakos et al., 2019, 2020). As in the animal model, testing here included multiple sites in both visual hemifields.

The principal quantitative visual test was a standard flash test in which the patient responded as fast as possible with a verbal report and pointing response to the onset of a brief (500 ms) and high-intensity (~1000 lm) flashed LED complex that was unpredictable in space and time (Fig. 1). In some tests patients were also asked to report the nature of the resultant visual percept (i.e., the perceived intensity, shape, and color of the stimulus). Interleaved with stimulus-containing trials were occassional trials in which no stimulus was presented, but patients were prompted for a response. Additional qualitative tests of visual capability were added as rehabilitation proceeded to determine whether capabilities beyond the simple detection and conscious perception of flashed lights had emerged. For example, to determine whether small discrepancies in stimulus location could be accurately detected in the rehabilitated hemifield, the patient was asked to discriminate which of three closely spaced (3° apart) identical LED complexes were flashed in central (centered at −18°) or peripheral (centered at −48°) space. Additional qualitative tests probed the patients' perception of real 3-D dimensional objects (e.g., cell phone, wallet, plastic toys, pliers, roll of tape, soap dispenser, water bottle, glasses, experimenter's hands/fingers) or virtual geometric shapes (triangle, square, rectangle, parallelogram, etc.) when they were stationary, moved, or (for virtual stimuli) flashed at different locations. Real objects were first introduced in regions in which flashed visual stimuli were ineffective and then moved to regions in which flashed stimuli were detected. Patients were asked to identify and describe the features of the object/shape and describe its motion if it was moving. To assess the ability to simultaneously perceive multiple lights, two bright (~2000 lm) nonflashing light sources were placed at different disparities from one another (from 0 to 30°) and at different positions in the left and right hemifields. These were activated individually or together, and patients were asked to report how many (and which) they perceived. In some testing sessions patients wore goggles in which the central half of the left eye and peripheral half of the right eye were occluded to effectively block all visual input from the right (intact) hemifield. These were used to eliminate the possibility that this input could contaminate tests in the left field; however, they did not appear to affect test results.

Experimental design and statistical analysis. The hypotheses guiding this study were qualitative; subjects would either regain the ability to detect and localize visual stimuli in the blinded hemifield, or they would not. Before the training paradigm, they could not in the identified areas of contralesional space. Binomial tests were used to evaluate the significance of the probabilities with which they could detect and localize stimuli after the training paradigm.

Results

Pre-rehabilitation visual detection capability

Baseline visual capabilities were established in the first session. The standard flashed visual stimulus was presented at multiple eccentricities and elevations in left (-) and right (+) visual space while central fixation was maintained. The patient was instructed to verbally acknowledge when he detected a stimulus and to point to its perceived location while maintaining fixation. The results were consistent with the visual defects evident in clinical examination, the lesions observed with MRI (Fig. 1), and the patients' own reports.

Both patients had left visual field defects. JM could not detect flashes anywhere left of fixation but could detect them

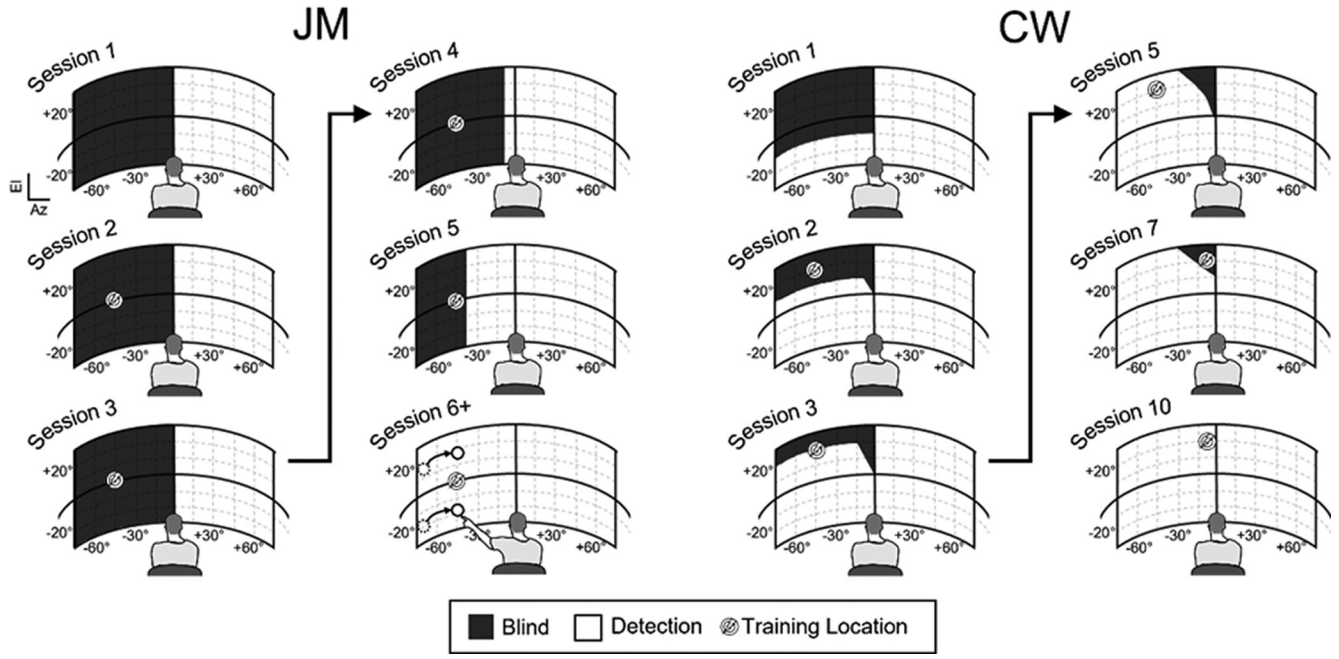

Figure 2. Recovery of visual detection and localization. Depicted are each patients' ability to detect the flashed stimulus at the beginning of select sessions in the experiment. Unshaded regions indicate areas where responses were elicited by the flash stimulus and black shaded regions indicate where they were not elicited. The icon (a flash in a circle) indicates the location of the visual-auditory training stimulus in the previous session. Dashed and solid circles (connected by arrows) in the last of JM's figures (see session 6) represent his translocation of visual stimuli in the far periphery of the rehabilitated field, which were systematically biased to a compressed, more central range.

everywhere to the right. CW could not detect flashes above −10° of elevation on the left but could detect them below this level and everywhere on the right (Fig. 1). Neither patient could detect stationary or moving stimuli where they could not detect flashes: They were totally blind to all presented visual stimuli in these regions.

JM had also had a visual defect in his intact (right) hemifield. He could not detect stationary or moving stimuli in the inferior (below 0°) periphery (greater than +60°), although flashes could be detected there. This region was not subjected to rehabilitative training and served as a within-subject control.

Rehabilitation of visual detection and localization

The primary assessment in tracking visual rehabilitation during weekly sessions was the ability to detect and localize flashed LEDs, a sensitive measure of visual recovery (Dakos et al., 2019, 2020). Using this measure, rapid training-induced visual improvements were observed in both patients. The most impressive changes occurred within the first 4–5 weekly sessions. This is in keeping with the timeline for rehabilitation in the animal model (Jiang et al., 2015, 2020; Dakos et al., 2020; Stein and Rowland, 2020). As in the animal model, both patients showed little tendency to lose gains made over the weekly interlude between training sessions.

In each rehabilitative training session, patients received 600 exposures to a spatiotemporally concordant visual-auditory stimulus presented well within the blind region (JM, −45, 0°; CW, −45, +20°). The higher elevation of CW's training stimulus ensured it did not encroach on regions of spared vision. Both patients were highly motivated and eagerly engaged in training and testing. Patients were noted to break fixation 3–4 times/session, typically toward the end of the 2 h period. In all such instances the trial was aborted, and training or testing began again when the patient had reacquired fixation. In each visual test trial, patients responded to detected stimuli with little delay and had no difficulty verbally reporting their occurrence and pointing to them while maintaining fixation. They never reported seeing a stimulus when one had not been presented and, when asked "Did you see anything?" they always answered no.

Rapid improvements in visual detection and localization were observed with training, initially for stimuli at the border of the sighted field, followed by a progressive expansion of the effective visual field that ultimately extended beyond the training stimulus location.

JM first showed visual improvement during the pretraining evaluation period of session 3 (Fig. 2). He could for the first time reliably (5/5) detect and point to a visual stimulus at −4° of eccentricity, but not to more eccentric stimuli. Post-training session tests revealed that his visual field expanded to −8° of eccentricity. He was aware that his detection capability had improved and commented on this. The expansion was retained at session 4 pretraining tests. At the midpoint of this session (after 300 visual-auditory exposures), visual probe tests revealed that he could now detect and point to a visual stimulus at −20° of eccentricity (5/5). Once again, this visual field expansion was confirmed in postsession tests. At this point, JM could also accurately discriminate which of three adjacent lights (3° separation) were flashed in central space (78/128 = 61% correct vs chance = 33%, binomial test, $p < 3E\text{-}11$). In pretraining tests at the beginning of session 5 it became apparent that his visible field had again expanded, in this case without additional training. He could now detect and point to flashes out to −40° at all tested elevations (±30°). During the midpoint break of this session, probe tests revealed that his visual field now extended to −90°. In post-training tests he correctly detected the visual stimulus at every location tested from 0 to −90° at all elevations tested (±30°) with 100% reliability.

However, his ability to accurately localize stimuli beyond −45° of eccentricity was significantly compromised and would remain so. Stimuli at eccentricities of −45 and −90° were all localized to

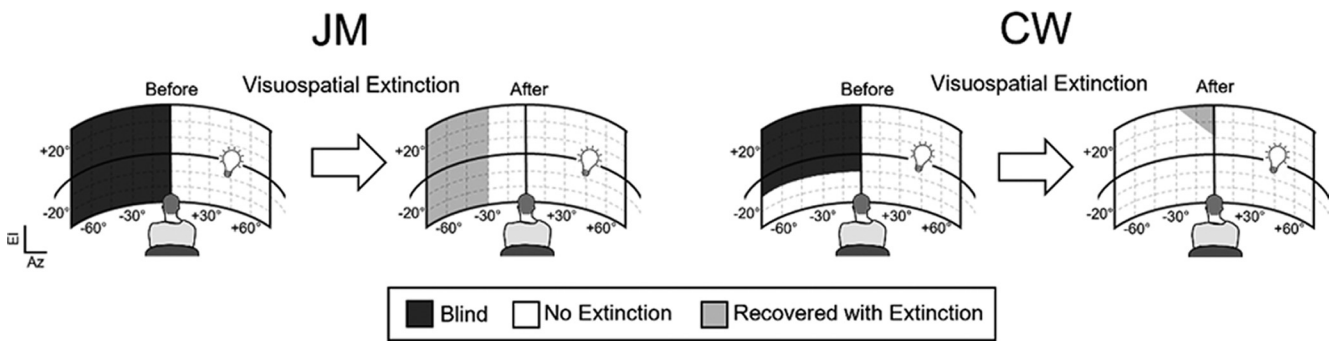

Figure 3. Visuospatial extinction: before and after. Visual extinction was evaluated by simultaneously presented two lights within the same hemifield or in different hemifields. Depicted above are the regions where a bright light could or could not be detected in the left hemifield when an equally-bright light was simultaneously presented in the right hemifield (depicted with a light bulb). Different plots illustrate the observations before (blind regions shown with black shading) and after rehabilitation. Areas of space in which both lights could be perceived are unshaded. Areas of space after rehabilitation in which individual lights could be detected, but where detection was suppressed by the simultaneous presence of a light in the right hemifield, are shaded in gray.

approximately −45°, indicating a compression of the perceptual field. Consistent with this observation, he never accurately discriminated the locations of the three adjacent lights (3° separation) when individually flashed in peripheral space (6/20 = 30% correct vs chance = 33%, binomial test, $p = 0.51$). He could, however, infer that their locations were different based on differences in their perceived intensity (see below). He was unaware that these percepts were anomalous, and these were not observed in the seeing portion of the opposite hemifield (his visual perception in the anomalous region on the right was unchanged).

CW showed even more rapid training-induced visual improvements. These were apparent at the end of session 1 when visual stimuli were detected on 50% (5/10) of the trials at (−45°, 0°). He was even more reliable (10/10 = 100%) at elevations below 0° (but was unable to detect stimuli (0/10 = 0%) at elevations above 0°). By the midpoint of session 2, after 300 visual-auditory exposures, visual stimuli were reliably detected and localized on 100% (10/10) of the trials at the training site (−45, +20°; Fig. 2). Post-training tests revealed that the visual field had expanded significantly, now extending from −30 to −70° of eccentricity at elevations of 0 to +20°. This improvement in contralesional visual performance was retained and evident at the beginning of session 3. He could now reliably (21/36 = 58%, chance = 33%, binomial test, $p < 5E\text{-}4$) discriminate the individual locations of three adjacent (3° separation) lights at −48, +20° in peripheral space. This localization accuracy was retained in the next session (40/69 = 58%, binomial test, $p < 7E\text{-}6$) and improved once again in session 5 (38/44 = 86%, binomial test, $p < 3E\text{-}14$). By session 6, visual detection and localization extended to −90° of eccentricity and to +30° of elevation (Fig. 2). But a blind region in upper central visual space remained and was described by him as a "blind spot." This region was roughly triangular, defined by three points: (0°, 0°), (0°, +30°), and (−30°, +30°; Fig. 2).

To examine whether training within this residual blind spot would ameliorate this residual deficit, an additional 450 training trials were conducted at (−5°, +10°) in session 6. The training stimulus was very near the border of the blind spot. The strategy was effective and raised the lower border of the blind area by 5°. With additional training in session 7, the lower border reached +10° of elevation. Although his localization of flashes in this area of restored vision were accurate in azimuth, they were systematically mislocalized in elevation, always appearing ∼10° above their actual location. The training stimulus was moved once again to an equivalent location within the contracted blind spot, in this case to (−10°, +10°). With additional training, the blind spot was eventually eliminated (session 10), as was the tendency for systematic mislocalizations in elevation; CW now accurately pointed to flashes everywhere in space. Whether additional training at the original stimulation site would have also resolved the blind spot is unknown; however, it had not changed in the six sessions preceding the change of the training location.

Additional observations

Visuospatial extinction

The ability to perceive multiple visual objects was assessed using two high-intensity (∼2000 lm) and continuously illuminated light sources. These light sources were either presented individually or together at different spatial separations and locations. Both patients easily detected and reported the presence of both lights in the right (normal) hemifield. However, the perception of a light in the recovered hemifield could be altered by the presence of a simultaneous competing light placed within either hemifield (Fig. 3).

This was evident in JM as soon as he detected lights on the left (previously blind) side of space during rehabilitative training. The light in the recovering hemifield would disappear and reappear when a second light was moved into and out of the intact hemifield (he reported that the first light appeared to be "turned off"). When two lights were presented in the left visual hemifield, even when separated by up to 30°, he only perceived the more central of them. This central stimulus appeared brighter when the second light was moved closer to it. These instances of competitive interactions were resolved over the central portion of the hemifield during the rehabilitative period so that by the final session, lights central of −30° were no longer extinguished by a simultaneous light in the right or left hemifield (i.e., two lights were perceived).

CW had no such problem. He could perceive two lights within his recovered visual hemifield (as it expanded) regardless of their spatial separation. The presence of a light in the intact hemifield diminished the apparent intensity of one in the rehabilitated hemifield but did not extinguish it. The exception to this was his previous blind spot, where perceived lights were extinguished by a light in the opposite hemifield. This defect did not resolve by the end of the testing period.

Perception of intensity, movement, and stationary objects

Interspersed with the above quantitative evaluations were requests for the patients to describe the intensity and color of the flashed lights and requests for them to report and describe

the features (e.g., color, shape, size, identity) of a variety of real objects, as well as virtual 2-D objects illuminated on an LCD monitor.

Within and across sessions, JM reported that the flash stimulus was becoming "brighter" and "sharper" and described a change in his perception of its color from yellow to white (which was correct). He accurately reported when the flashes changed intensity and could also detect large (>5°) and flashed or stationary illuminated gray 2-D shapes wherever he could detect flashes. This capability eventually extended over the entire left hemifield. However, all visual stimuli beyond −10° of eccentricity were perceived as large "blobs." In central space, moving and stationary real objects could be detected and identified at −4° in session 3 and −7° in session 6. Within these areas he was able to report the color, shape, and contour (often its identity) and general features of real and virtual objects. However, object perception was consistently described as "blurry" compared with that of identical stimuli in the intact hemifield.

CW's recovery was more impressive for both real and virtual stimuli. He accurately characterized the intensity and color of detected flashes. He also accurately described stationary and moving objects wherever he could detect flashes. This rapid improvement in his visual abilities was readily apparent to him, and he commented on it spontaneously. He could (after a few seconds) identify novel objects on the left by session 5. When queried about this delay, he reported making a conscious inference about the identity of the object based on its detected features such as angles and/or contours. In his intact field, reports of shapes were more immediate, and he was unaware of any inferential process preceding his report. The retention of a blind spot in upper-left central space provided an interesting discontinuity in his stationary visual perception. He noted that objects with straight lines (e.g., handrails) crossing the blind region were not perceived as continuous, although he knew they must be.

Quality of life changes

Both patients reported significant quality of life improvements that they attributed to the restoration of visual capabilities. Both reported that their perception of eye strain outside the session improved within the first 3–4 sessions. After four sessions both noted a new awareness of high contrast visual stimuli in their rehabilitated hemifield; for example, streetlights or lights in houses that were now perceptible. JM noted, as did his wife, that his navigation had markedly improved between the first and third sessions, and he had a decreased sense of "tunnel vision." At home he was able to detect illuminated lamps on his rehabilitated side and use them to navigate. CW reported improvements in reading in sessions 4 and 5 so that he no longer depending on using his finger to keep place. He also noted a renewed perception of leaves on trees to his left during walks and great improvement in navigating root-laden paths when hiking, a favorite hobby. He now hiked with greater confidence and at speeds equal to those before the stroke. These were twice his hiking speed at the beginning of the study.

Discussion

The present study demonstrated that a multisensory rehabilitative technique for hemianopia first developed in an animal model can be successfully applied to human patients. Both patients in this study initially failed to detect any visual test stimuli presented in the affected field (i.e., stationary or moving objects or lights, high intensity flashes, etc.). Over several 2 h weekly training/testing sessions they progressively regained the ability to perceive light flashes throughout their previously blind regions. They also regained some ability to detect and describe moving and stationary objects, and both reported significant improvements in their quality of life and activities of daily living.

The trajectory of visual recovery was similar to that observed in the cat model of hemianopia that guided the rehabilitative training paradigm used here (Jiang et al., 2015, 2020; Dakos et al., 2019, 2020; Stein and Rowland, 2020). In this model, a standard daily (five/week, 600 trials/session) multisensory training session was conducted with invariant and spatiotemporally congruent visual-auditory cues centered in the blind hemifield of the animal. This restored its ability to detect and localize visual stimuli throughout that hemifield in 2–4 weeks. Recovery was also obtained in anesthetized hemianopic animals given less frequent sessions (one/week) and between 100–2400 visual-auditory trials/session (10 min–4 h; Jiang et al., 2020). Greater numbers of trials were associated with more rapid recovery but with diminishing returns; 100 trials/session produced recovery in 8 weeks, whereas 600 and 2400 trials/session produced recovery in 4 weeks. The training paradigm for human patients was similarly sparse (one/week, 600 trials/session), and recovery (4–6 weeks) was similarly short.

An important earlier study also found salutary effects in hemianopic patients presented with interleaved visual, auditory, and visual-auditory stimuli varying in location and timing (Bolognini et al., 2005). In that study, patients became efficient at making saccades to visual stimuli in the blind hemifield, but when required to maintain central fixation, they had no visual awareness in that hemifield. Their recovery was therefore interpreted as strictly visuomotor in nature. This contrasts with the current findings, which yielded both motor and perceptual recovery. The difference likely exists in the stimulation paradigm adopted which, in the present case, strictly adhered to the paradigm developed in the animal model. During rehabilitative training, patients were presented only with visual-auditory pairs that were invariant in their congruent spatiotemporal relationship. It is possible that restoring visuomotor processing is dependent on looser constraints than those leading to visual awareness and may precede its emergence. If engaged in the present paradigm, it might have even speeded recovery. That would be consistent with findings that some visual recovery can be obtained in hemianopic patients trained to make progressively larger saccades into the hemianopic field (Zihl, 1995; Nelles et al., 2001) or to saccade to moving targets there (Dundon et al., 2015; Frolov et al., 2017; Sahraie et al., 2020; Szalados et al., 2021).

Other recent work has shown some recovery on visual responsiveness in hemianopic patients using visual-auditory training in a virtual reality (VR) headset (Daibert-Nido et al., 2021). VR devices can be convenient therapeutic tools, and the patients in these studies reported some improvements in the detectability of visual stimuli in formerly blind regions as well as improvements in quality of life. In another recent study, intensive visual discrimination training also proved to have some positive visual effects in the hemianopic field (Ajina et al., 2021). Other work in hemianopic nonhuman primates has also established some recovery after extensive visual training (Yoshida et al., 2008, 2017; Kato et al., 2011, 2021; Takakuwa et al., 2017; Kinoshita et al., 2019; Isa and Yoshida, 2021). However, it is notable that these different studies used different tests for visual function evaluation and subject populations with different lesions and different

preintervention visual capabilities. (Here, as in the cat model, they were totally blind to flashes in the affected field.)

It is clear from prior work in the animal model that not only is the multisensory nature of the stimuli presented necessary for the present rehabilitative paradigm to be effective (Jiang et al., 2015) but also their spatiotemporal congruence (Dakos et al., 2020). These are the same factors that govern the mechanisms of multisensory plasticity by which SC neurons are sensitized to their visual inputs (Yu et al., 2013) and may help explain how these neurons, which lose visual sensitivity after a hemianopia-inducing lesion, regain this sensitivity and do so in parallel with the restoration of overt visual behavior. The SC is believed to be the nexus of the residual neural circuit through which recovery is achieved, and its neurons are particularly well positioned for a role in controlling sensorimotor recovery (Stein and Rowland, 2020). They send efferents to both brainstem and spinal targets involved in visuomotor responses (Graham, 1977; Stein et al., 1982, 1984; Meredith and Stein, 1985; Moschovakis and Karabelas, 1985; Bruce and Stein, 1988; Sparks and Hartwich-Young, 1989; Paré et al., 1994; Burnett et al., 2004) and (via thalamic connections) to sensory processing cortical areas for visual perception (Graham, 1977; Benedek et al., 1997; McHaffie et al., 2005). The specific subtypes of tectopetal and tectofugal neurons engaged in this process and their neurobiological dynamics remain to be identified.

Their overlapping visual and auditory topographies also appear to be reflected in the pattern of visual recovery, which, in both animals and humans, expands progressively from the margin of the sighted hemifield to beyond the training location, ultimately encompassing the entire hemifield. Recovery does not begin at the stimulation location, which would be the naive expectation for a process that engaged a Hebbian mechanism. At present it is not known why recovery starts from the margin of the sighted field, and why it seems to expand in broad pattern. It is plausible that the pattern is dependent on cooperative dynamics between adjacent neurons in a topographic map; for example, along the anterior–posterior axis of the SC (representing central-peripheral visual space), but this is speculative at present. Furthermore, it is quite possible that other circuits in the midbrain, thalamus, and/or cortex contribute to this process (Baleydier, 1977; Benedek et al., 1997, 2019; Jiang et al., 2003; McHaffie et al., 2005; Nagy et al., 2011). These possibilities remain to be explored.

It is also important to note that the hemianopia in these patients were a consequence of stroke, rather than a direct lesion as in the referential animal studies. This makes possible the sparing of tissue within the damaged areas of visual cortex in which visual-auditory interactions may still take place (Foxe et al., 2000; Foxe and Schroeder, 2005; Schroeder and Foxe, 2005; Sperdin et al., 2009; Fiebelkorn et al., 2011). Results from the animal model have suggested that certain higher-order areas are crucial to recovery (Jiang et al., 2015) but that residual regions of visual cortex are not. However, they may facilitate the rehabilitative process and make possible far greater visual capabilities than could otherwise be achieved. Whether patients with more focal scotomas resulting from different lesions could be rehabilitated using a similar technique, whether the plasticity engaged here might degrade with time, and whether early interventions might yield a faster or more robust recovery are unknown at present. A larger, more comprehensive study is required to answer these questions.

By verbally reporting and describing their visual perception, the patients provided more detailed information about visual recovery than was previously available. Both regained conscious visual perception and the ability to describe the intensity and color of flashes and point to them without shifting gaze. Furthermore, neither could detect moving low-contrast stimuli or identify them at a given site without previously being able to detect flashes at that site. It could be that the ability to detect a light flash is a more rudimentary capability whose recovery necessarily precedes recovery of other abilities.

Despite these similarities between patients, there were also substantial individual differences, especially in the visual capabilities observed at the end of rehabilitative training. Whereas CW could accurately localize flashes and describe the shape and direction of motion of visual stimuli, JM perceived peripheral visual stimuli as diffuse light sources and had a persistent defect in localizing them. CW also had no difficulty in detecting multiple stimuli, whereas JM's peripheral visual perception was readily challenged when presenting a second visual stimulus elsewhere. It is notable, however, that JM's ability to perceive multiple simultaneous lights continued to improve, and the endpoint of this recovery is not clear. Ultimately, rehabilitated cats had no difficulty in making choices among multiple simultaneous lights (Dakos et al., 2019).

The specific factors accounting for the variability in the recovery of CW and JM are not easy to identify. Both patients were highly motivated, of similar age and time since their stroke, and underwent the same rehabilitative training paradigm. However, their lesions and the initial topography of their visual deficits differed. CW presented with a larger sighted visual field and a more impressive recovery, perhaps reflecting less extensive functional damage to critical components of the residual visual circuit (e.g., certain tectopetal afferents from association cortex must be spared for recovery to occur; Jiang et al., 2015). JM had a less impressive recovery and had suffered a second PCA affecting the opposite cortex. Although the visual defects associated with this left-side lesion appeared minor and restricted to the far periphery, it may have interfered with any facilitation of recovery it provided to CW. Relating lesions to the pattern of recovery is a general problem in assessing the effectiveness of any rehabilitative strategy in stroke patients, underscoring the importance of large population studies in which patients can be categorized properly into subgroups, and treatment paradigms can be varied. Of particular interest in the present context is how the specifics of the rehabilitative strategy (time, number, and patterns of multisensory exposures, etc.) affect recovery among different groups (see below).

Most significant to the present patients were improvements in their quality of life and activities of daily living. They noted a reduction in what they described as "eye strain" and improvements in reading, navigation, and detecting moving objects (e.g., falling leaves, streetlights, etc.). These benefits were noted as soon as visual detection was possible but continued to improve. The ability to detect visual events in the previously blind hemifield also allowed the patients to engage a variety of strategies to compensate for their impaired vision (e.g., orienting to bring visual events into the fully sighted field and/or depending on other senses for object identification) and to gain greater confidence in everyday tasks.

Given the present results, it may seem surprising that hemianopia is normally such a persistent disorder. Spontaneous recovery appears limited to a short window following a stroke (<6 months; Zhang et al., 2006) despite continued exposure to a host of cross-modal events whose number and frequency in the normal environment will ultimately far exceed those

provided in the training paradigm. Based on the current and prior studies, the answer is likely to involve the consistency, regularity, and simplicity of the training paradigm stimuli, as well as the absence of contravening sensory experience. Yet, despite the rapidity and extent of visual recovery induced by the current training paradigm, it is unlikely to have optimized all its features. Matching the types of stimuli presented, their iterative rate, the number of trials per session, the responses required, and/or a variety of other paradigm specifics to the lesion and visual defect will likely hasten the speed and extent of recovery. Thus, the present results may best be viewed as proof of concept that this paradigm is a highly effective therapeutic strategy.

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