Blindsight Mediated by an S-Cone-independent Collicular Pathway: An fMRI Study in Hemispherectomized Subjects

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Abstract

■ The purpose of our study was to investigate the ability to process achromatic and short-wavelength-sensitive cone (S-cone)-isolating (blue–yellow) stimuli in the blind visual field of hemispherectomized subjects and to demonstrate that blindsight is mediated by a collicular pathway that is independent of S-cone inputs. Blindsight has been described as the ability to respond to visual stimuli in the blind visual field without conscious awareness [Weiskrantz, L., Warrington, E. K., Sanders, M. D., & Marshall, J. Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain, 97,* 709–728, 1974]. The roles of the subcortical neural structures in blindsight, such as the pulvinar and the superior colliculus, have been debated and an underlying neural correlate has yet to be confirmed. Using fMRI, we tested the ability to process visual stimuli that isolated the achromatic and short-wavelength-sensitive (S-)-cone pathways in three subjects: one control subject, one hemispherectomized subject with blindsight, and one hemispherectomized subject without blindsight. We demonstrated that (1) achromatic and S-cone-isolating stimuli presented to the normal visual hemifield of hemispherectomized subjects and to both visual hemifields of the control subject activated contralateral visual areas (V1/V2), as expected; (2) achromatic stimulus presentation but not S-cone-isolating stimulus presentation to the blind hemifield of the subject with blindsight activated visual areas FEF/V5; (3) whereas the cortical activation of the control subject was enhanced by an additional stimulus (achromatic and S-cone isolating) presented in the contralateral visual field, activation pattern of the subject with blindsight was enhanced by achromatic stimuli only. We conclude that the human superior colliculus is blind to the S-cone-isolating stimuli, and blindsight is mediated by an S-cone-independent collicular pathway. ■

INTRODUCTION

The purpose of our study was to investigate the ability of hemispherectomized subjects to process achromatic and short-wavelength-sensitive (S-) cone-isolating (blue–yellow) stimuli in their blind visual field and to demonstrate that blindsight is mediated by a collicular pathway that is independent of S-cone inputs.

Blindsight has been described as the ability to respond to visual stimuli in the blind visual field without conscious awareness (Weiskrantz, Warrington, Sanders, & Marshall, 1974). Its correlate has yet to be confirmed and has been debated. Subcortical neural structures such as the pulvinar and the superior colliculus have been suggested as potential contributors, but a connection between functional activity in subcortical structures and blindsight has not been shown, probably due to the methodological limitations of the techniques used (Bittar, Ptito, Faubert, Dumoulin, & Ptito, 1999; Sahraie et al., 1997). In addition, the examination of subjects with small circumscribed lesions has been debated (Stoerig, Kleinschmidt, & Frahm, 1998; Kentridge, Heywood, & Weiskrantz, 1997; Fendrich, Wessinger, & Gazzaniga, 1992) as it leaves open the possibility that spared islands of visual cortex may contribute to residual visual abilities in the blind field and has fueled scepticism toward the existence of blindsight (Fendrich et al., 1992).

One approach has been to examine hemispherectomized subjects in whom an entire cerebral hemisphere has been removed or disconnected from the rest of the brain for the relief of intractable epilepsy. After hemispherectomy, the possibility that spared islands of visual cortex are responsible for any residual visual abilities in the blind field can be excluded. Hemispherectomy is a rare surgical intervention that involves massive removal or disconnection of an entire cerebral hemisphere, including the occipital lobe. These subjects are relevant to our research because any evidence of blindsight cannot be attributed to spared islands of occipital cortex either via a koniocellular pathway (Wessinger, Fendrich, Ptito, Villemure, & Gazzaniga, 1996) and/or through a direct geniculo-extrastriate projection (Sincich, Park, Wohlgemuth, & Horton, 2004).

Careful application of behavioral paradigms, in conjunction with advances in Diffusion Tensor Imaging (DTI) technologies, and the control of artifacts such as light scatter

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and control of central fixation have supported the existence of blindsight and have given new insights into the correlate of blindsight (Leh, 2008; Ptito & Leh, 2007; Leh, Johansen-Berg, & Ptito, 2006). In a previous behavioral study where light scatter and central fixation were closely monitored, we used the color processing properties of the different visual pathways to delineate the one most involved in blindsight (Leh, Mullen, & Ptito, 2006). Human vision involves three postreceptoral mechanisms, an achromatic one consisting of the summation of the long-wavelength-sensitive (L-) cone and the medium-wavelength-sensitive (M-) cone and two cone opponent mechanisms consisting of an antagonistic comparison of signals from the L/M-cones (loosely called the red–green mechanism) and the S/(L+M) cones (loosely called the blue–yellow system; Sankeralli & Mullen, 1996, 1997; Cole, Hine, & McIlhagga, 1993; Noorlander, Heuts, & Koenderink, 1981; Sperling & Harwerth, 1971).

Previous studies in nonhuman primates have indicated that the superior colliculus does not receive retinal input from S-cones, consequently rendering them blind to blue–yellow stimuli (Savazzi & Marzi, 2004; Sumner, Adamjee, & Mollon, 2002; Marrocco & Li, 1977; Schiller & Malpeli, 1977). In contrast, the pulvinar is known to receive input from all classes of color opponent ganglion cells (L/M- as well as S-cone opponent; Cowey, Stoerig, & Bannister, 1994; Felsten, Benevento, & Burman, 1983) and to be involved in color processing in humans (Barrett et al., 2001). We used the knowledge from these studies of collicular properties (Savazzi & Marzi, 2004; Sumner et al., 2002; Marrocco & Li, 1977; Schiller & Malpeli, 1977) to design a "spatial summation effect" paradigm using achromatic and S-cone-isolating stimuli to test the color processing abilities in the blind visual field of hemispherectomized subjects. In a spatial summation effect paradigm, control subjects obtain significantly faster RTs to two simultaneously presented stimuli across the vertical meridian compared to a single stimulus (Marzi, Tassinari, Agliotti, & Lutzemberger, 1986), and they do so for both achromatic and S-cone-isolating stimuli (Leh, Mullen, et al., 2006). From our prior behavioral results, we were able to demonstrate the presence of a spatial summation effect in three hemispherectomized subjects (subject SE, DR, and LF). RTs to a stimulus presented in the sighted visual field were decreased when an unseen achromatic stimulus was simultaneously presented in their blind visual field. No such effect was observed when S-cone-isolating stimuli were used in the blind visual field (Leh, Mullen, et al., 2006), although these stimuli generated an effect in normal subjects. These results demonstrated the absence of S-cone input in the blind visual field of blindsight subjects and suggest involvement of the superior colliculi in blindsight. Here we present an fMRI study to ascertain the involvement of the superior colliculi in the blindsight phenomenon.

We recruited one healthy control subject (CC) with no history of neurological or ophthalmological disease and two postoperative hemispherectomy patients (average intelligence) with a well-documented hemianopia without macular sparing (SE and JB; for further information, see Leh, Mullen, et al., 2006). Both subjects SE and JB had previously participated in visual research projects and had been tested for blindsight (Leh, 2008; Leh, Mullen, et al., 2006). We modified the psychophysical spatial summation effect paradigm (as described above; Leh, Mullen, et al., 2006) to test processing abilities in the blind visual field of hemispherectomized subjects in an fMRI study using two stimulus types to isolate either the achromatic or the S-cone pathway, respectively.

In the first part of our study, we investigated the color properties of the human superior colliculus by comparing effect sizes in the superior colliculi to S-cone-isolating and achromatic stimuli. In the second part, we investigated BOLD activation to achromatic and S-cone-isolating stimuli in the blind visual field of a hemispherectomized subject (SE) who has reliably shown blindsight in the past. These results were compared with those of the healthy subject (CC) and to those of a hemispherectomized subject (JB) who has not shown blindsight in previous studies. From our previous behavioral results, we expected an absence of cortical activation to S-cone-isolating stimuli presented in the blind visual field of hemispherectomized subjects. This would confirm our behavioral results and allow us to draw conclusions on the neuronal correlate underlying blindsight.

In the third part of our study, we investigated whether an additional stimulus in the blind visual field of the blindsight subject (SE) can enhance the cortical activation pattern to a seen stimulus presented in the normal visual field. This tests whether an enhancement in the BOLD activation can be found consistent with the behavioral enhancements of RTs observed in our previous report (Leh, Mullen, et al., 2006). fMRI results were compared to a healthy subject (CC) as well as to the subject without blindsight (JB). To date, such an "enhancement paradigm" using stimuli that isolate different visual pathways has not been implemented in an fMRI study to test blindsight in hemispherectomized subjects.

METHODS

Hemispherectomized Subjects

Subject SE (with Blindsight)

At birth, a left hemiparesis was noted followed by seizure onset at the age of 7 years. At the age of 25 years, a hemispherectomy (temporo-parieto-occipital removal) was performed to alleviate intractable seizures due to a congenital cyst. In 1991, a neuropsychological evaluation demonstrated a full-scale IQ rating in the average range (93), with the performance scale (99) and the verbal scale (90) in the same classification using the seven-subtest short form of the Wechsler Adult Intelligence Scale–Revised. Subject SE was tested in several studies and

has consistently shown blindsight (e.g., Leh, Mullen, et al., 2006; Tomaiuolo, Ptito, Marzi, Paus, & Ptito, 1997).

Subject JB (without Blindsight)

At birth, a congenital right hemiparesis was noted followed by seizure onset at the age of 5 years. A left functional hemispherectomy was performed in two steps (1983 and 1985) to remove a congenital porencephalic cyst. The frontal and occipital poles were left in place to prevent superficial hemosiderosis and to reduce hydrocephalus but were disconnected from the rest of the brain. A neuropsychological evaluation demonstrated a full-scale IQ rating in the low average range (88), with the performance scale (88) and the verbal scale (90) in the same classification using the seven-subtest short form of the Wechsler Adult Intelligence Scale–Revised. Subject JB has consistently never shown blindsight (e.g., Leh, Mullen, et al., 2006; Tomaiuolo et al., 1997).

fMRI Task

Head movements were restrained with a head coil. During our fMRI paradigm, central fixation was assured by a fixation computer task (for further details, see Fixation and Attention Control). We used a block design in that each experimental condition was presented in blocks of 10 trials followed by three null events. Blocks were presented in a randomized order and included three additional blocks consisting of null events (baseline condition). Stimuli used were either S-cone-isolating (blue–yellow) or achromatic and were presented either to the right and/or left of the central fixation point at three positions: +8° unilaterally, −8° unilaterally, or ±8° bilaterally (see also Figure 1). Each stimulus was presented for 800 msec with an ISI of 2000 msec. Cardiac gating (Guimaraes et al., 1998) was used to minimize motion artifacts in the brain stem signal resulting from pulsation of the basilar artery. The functional images were triggered 300 msec after the R-wave in the electrocardiogram, when the cardiac cycle is in its diastolic phase.

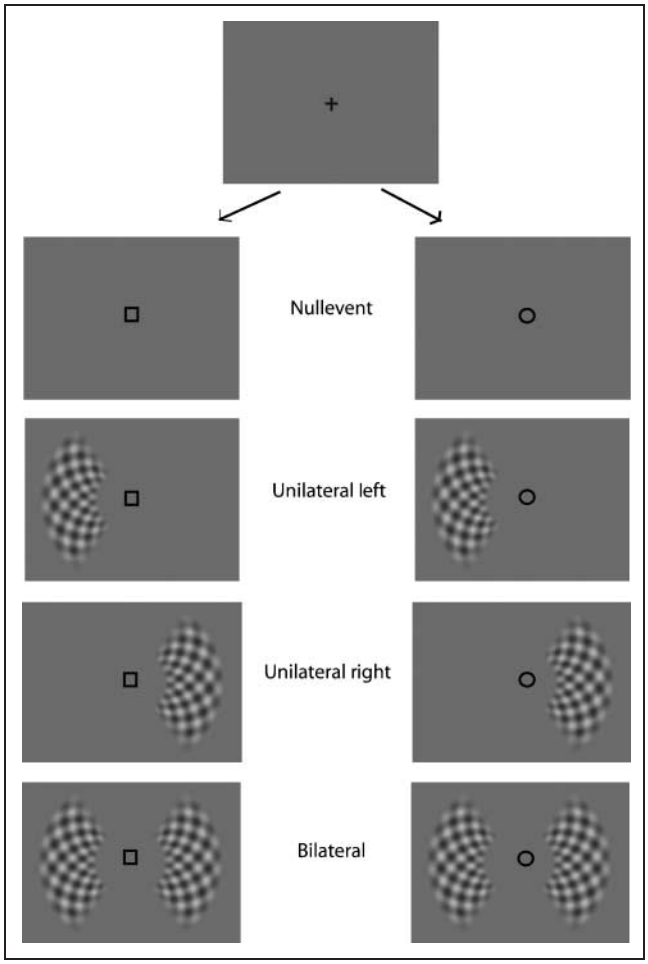

Figure 1. Stimulus conditions. The subject fixated a cross in the middle of a screen. This fixation cross changed to a circle or a square while test stimuli appeared on the left and/or right side simultaneously. The subject indicated by pressing the right or left mouse button whether a circle (left mouse button) or a square (right mouse button) appeared. We used a block design in which each experimental condition was presented in blocks of 10 trials followed by three null events. Blocks were presented in a randomized order and included three additional blocks consisting of null events (baseline condition). Stimuli used were either S-cone-isolating (blue–yellow) or achromatic and were presented either to the right and/or to the left of the central fixation point at three positions: +8° unilaterally, −8° unilaterally, or ±8° bilaterally. For simplicity, this figure only shows achromatic stimuli.

Stimuli and Color Space

Stimuli consisted of radially modulated sine wave checks defined in polar coordinates and set in a uniform background of the same mean luminance and chromaticity (see Figure 1). The stimulus patch was annular (5.4° radius to internal stimulus edge, 11° radius to external stimulus edge), presented in a raised cosine envelope modulating contrast in both angular and radial directions to remove sharp edges from the stimulus display window. For further details of the stimulus, see Mullen, Sakurai, and Chu (2005). An annular stimulus was used to avoid stimulations of central vision and to assure stimulus presentation within the blind visual field. The use of peripheral stimuli does not disadvantage S-cone over achromatic sensitivity or vice versa because both have a similar distribution across the human visual field (Mullen & Kingdom, 2002). The spatial frequency was 0.5 cycles per degree. This relatively low spatial frequency was used to optimize the sensitivity of color vision, which has a low-pass contrast sensitivity function (Mullen, 1985). Stimuli were presented in a temporal Gaussian contrast envelope with a σ = 250 msec. The display screen was 20° high × 27° across. Display mean luminance was 566 cd/m^2 measured with a UDT S370 photometer (Graseby Optronics, Orlando, FL).

Stimuli were either achromatic or isolated the S-cones and were represented in a three-dimensional cone-contrast space (Sankeralli & Mullen, 1996, 1997) in which each axis is defined by the incremental stimulus intensity for each cone type to a given stimulus normalized by the respective intensity of the fixed adapting white background. Achromatic stimuli modulate all cone types equally (L+M+S), and the S-cone-isolating stimuli activate only the S-cone axis. The cone contrast of the stimuli was close to the maximum that could be obtained at 90% cone modulation for achromatic stimuli and 50% for S-cone-isolating stimuli.

Apparatus and Calibration

For all fMRI experiments, the visual stimuli were generated using the freely available PsychToolbox software (Brainard, 1997; Pelli, 1997) on a Macintosh G3 iBook and displayed on a white screen using an LCD projector (InFocus LP840, InFocus Corp., Wilsonville, OR; resolution 1024 × 768, frame rate 80 Hz). The red, green, and blue spectral emissions were measured using a PhotoResearch PR-650-PC SpectraScan (Chatsworth, CA), and the Smith and Pokorny (1975) fundamentals were used for the spectral absorptions of the L-, M-, and S-cones. From these data, a linear transform was calculated to specify the phosphor contrasts required for given cone contrasts (Cole & Hine, 1992). The projector was gamma corrected in software with look-up tables.

Fixation and Attention Control

During our fMRI paradigm, central fixation and attention was assured by a central fixation computer task (see also Figure 1): The subject had to fixate a cross in the middle of a screen. This fixation cross changed to a circle or a square while stimuli appeared on the left and/or right side simultaneously and the subject had to indicate by pressing the right or left mouse button whether a circle (left mouse button) or a square (right mouse button) appeared. All of the subjects were able to maintain accurate fixation as demonstrated by their fixation scores. Their correct response rates were 87% or higher (CC = 98%, SE = 97%, JB = 87%).

Data Acquisition

Scanning was performed on a 3-T Siemens TIM Trio scanner using EPI with an eight-channel head coil. All subjects underwent a high-resolution anatomical MRI scan (1 × 1 × 1 mm voxel size) for anatomical localization of the functional data. Slices of the functional scans were oriented along the line connecting the anterior and the posterior commissures in an ascending order and positioned so that the fifth slice covered the superior colliculus. Brain activation was then measured using BOLD fMRI by means of a T2*-weighted gradient EPI sequence (repetition time = 2540 msec, echo time = 30 msec, flip angle = 90°, 30 slices). A total of 822 acquisitions were collected in three runs from each participant.

Data Analysis

The functional volumes of each run were realigned to the third volume of that run to correct transient head movements caused by breathing and swallowing during data acquisition. The images were then spatially smoothed with a 3-mm FWHM Gaussian kernel to increase signal-to-noise ratio and tolerance of the analysis to residual motion. Statistical analysis was performed in Matlab (The MathWorks, Natick, MA) using the FMRIstat toolbox (Worsley et al., 2002). The preprocessed image series were analyzed with fixed-effects general linear models. Experimental conditions were modeled as boxcar functions convolved with a generic hemodynamic response function.

In the first study, effect sizes were determined at local *t* score maxima within the right and the left superior colliculus (Figure 2). This strategy is based on the matched filter theorem, which implies in this case that the activity in an anatomical structure is best represented by the center voxel if the size of the smoothing kernel matches the size of the anatomical structure in question. Because of slight spatial distortions between anatomical and functional images, we used the voxel at a local *t* score maximum closest to the center point of the left or right inferior colliculus identified on the structural images in place of the central voxel. In Studies 2 and 3, ROIs were defined to examine activation patterns in V1, V2, V5, and FEF. Significant BOLD changes were determined after defining ROIs. ROIs included visual areas of the right and left hemisphere and were separately defined, including the occipital pole, the superior occipital gyrus, the middle occipital gyrus, the inferior occipital gyrus, the cuneus, the lingual gyrus, and the occipital lobe. These lobes were identified using a two-step technique known as ANIMAL + INSECT (Collins, Zijdenbos, Baaré, & Evans, 1999). The structural volumes were registered into the Montreal Neurological Institute space (Collins, Neelin, Peters, & Evans, 1994) followed by tissue classification (CSF; Zijdenbos et al., 1996). The volumes are then nonlinearly transformed onto the ICBM-152 nonlinear average upon which a probabilistic macroanatomical atlas has been defined. The atlas is warped back to the native space of the individual structural volumes, and the identification of cortical structures is refined using the tissue classification data. The local *t* score maxima within the ROIs are shown in Figures 4 and 5, and the effect sizes are shown in Figures 3 and 4. The resulting *t* statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory to correct for multiple comparisons given the size of the ROI. Please note that the term "effect sizes" is used for the beta coefficients of the linear model. This value divided by its standard deviation is the *t* value.

RESULTS

Study 1: Is the Human Superior Colliculus Color Blind to S-Cone-isolating (Blue–Yellow) Stimuli?

In Study 1, we investigated the color properties of the human superior colliculus by comparing effect sizes in the superior colliculi to S-cone-isolating versus achromatic stimuli in our control subject and two hemispherectomized subjects. Previous research in nonhuman primates has shown that the superior colliculus does not receive retinal input from S-cones involved in color vision, but this has yet to be confirmed in humans. To do this, we determined the effect sizes at the local *t* maxima (at the peak voxel for each contrast) for the following contrast: (a) all achromatic (black/white) stimuli conditions minus all S-cone-isolating (blue–yellow) stimuli conditions and (b) all S-cone-isolating stimuli conditions minus all achromatic (black/white) stimuli conditions. Effect sizes can be seen in Figure 2. We decided to combine the achromatic conditions and the S-cone-isolating conditions to optimize and to increase potential activation in the superior colliculi. All three subjects demonstrated significant effect sizes in both superior colliculi when achromatic stimuli were presented (contrast a). In contrast, this effect was not seen for S-cone-isolating stimuli (contrast b), consistent with previous electrophysical studies in nonhuman primates.

Study 2: Cortical Activation Patterns to Unilaterally Presented Stimuli

Healthy Visual Fields

In the second study, we compared cortical activation patterns in V1, V2, FEF, and V5 associated with stimuli presented in the right visual field to stimuli presented in the left visual field. Significant BOLD changes were determined after defining an ROI. ROIs included visual areas of the right and left hemisphere and were separately defined (see Methods). To do this, we separately determined *t* maps for S-cone-isolating and for achromatic stimuli by subtracting the baseline condition from unilateral conditions (Figures 3 and 4; Table 1).

All subjects showed contralateral activation in visual cortical areas to stimuli presented in their healthy visual field (see Figures 3 and 4; Table 1). Activation patterns observed in hemispherectomized subjects are consistent with activation patterns in a healthy subject, who

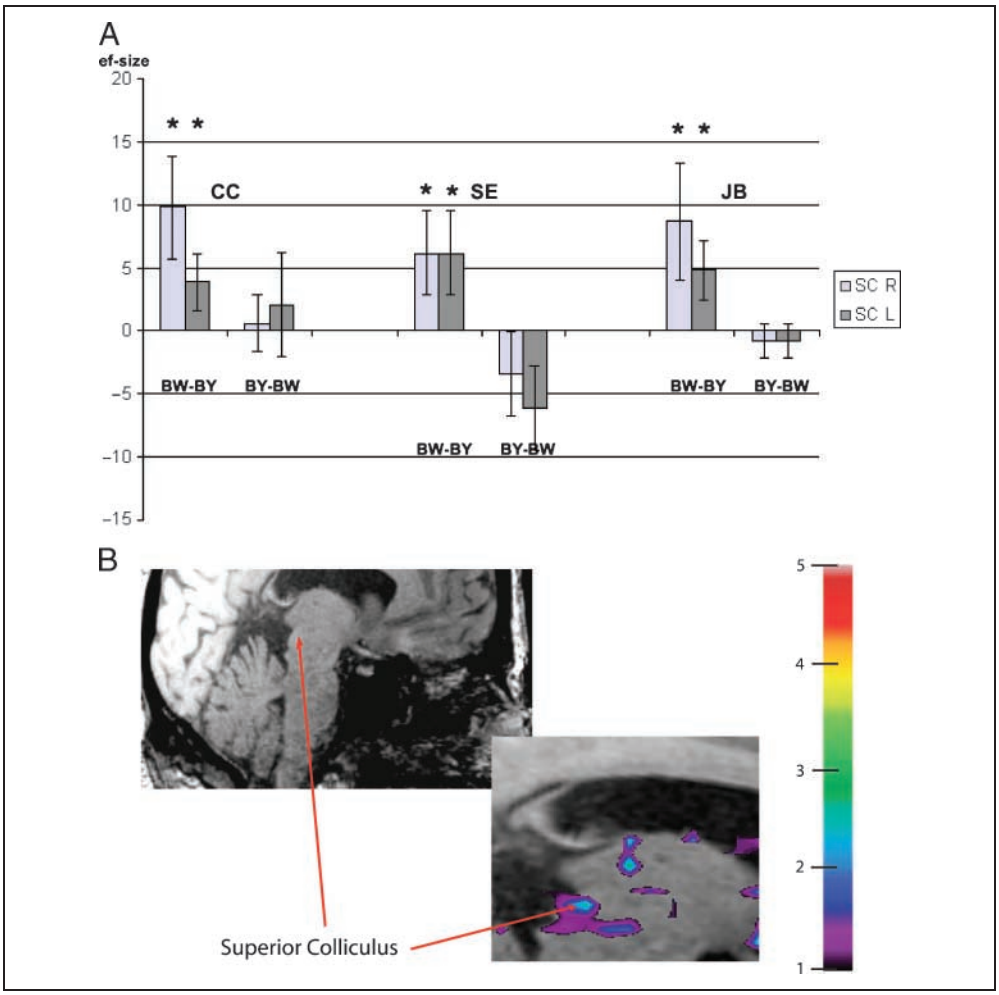

Figure 2. Effect sizes in the superior colliculi. (A) Effect sizes and standard deviations (error bar) in the right (light gray) and left (dark gray) superior colliculus of all three subjects (CC, JB, and SE) for the following contrasts: achromatic black/white minus S-cone-isolating stimuli (BW-BY) and S-cone-isolating minus achromatic black/white stimuli (BY-BW). *Significant activation. (B) Example (subject SE) of a *t* map within the left superior colliculi for the contrast achromatic (black/white) minus S-cone-isolating stimuli (BW-BY). ef-size = effect size.

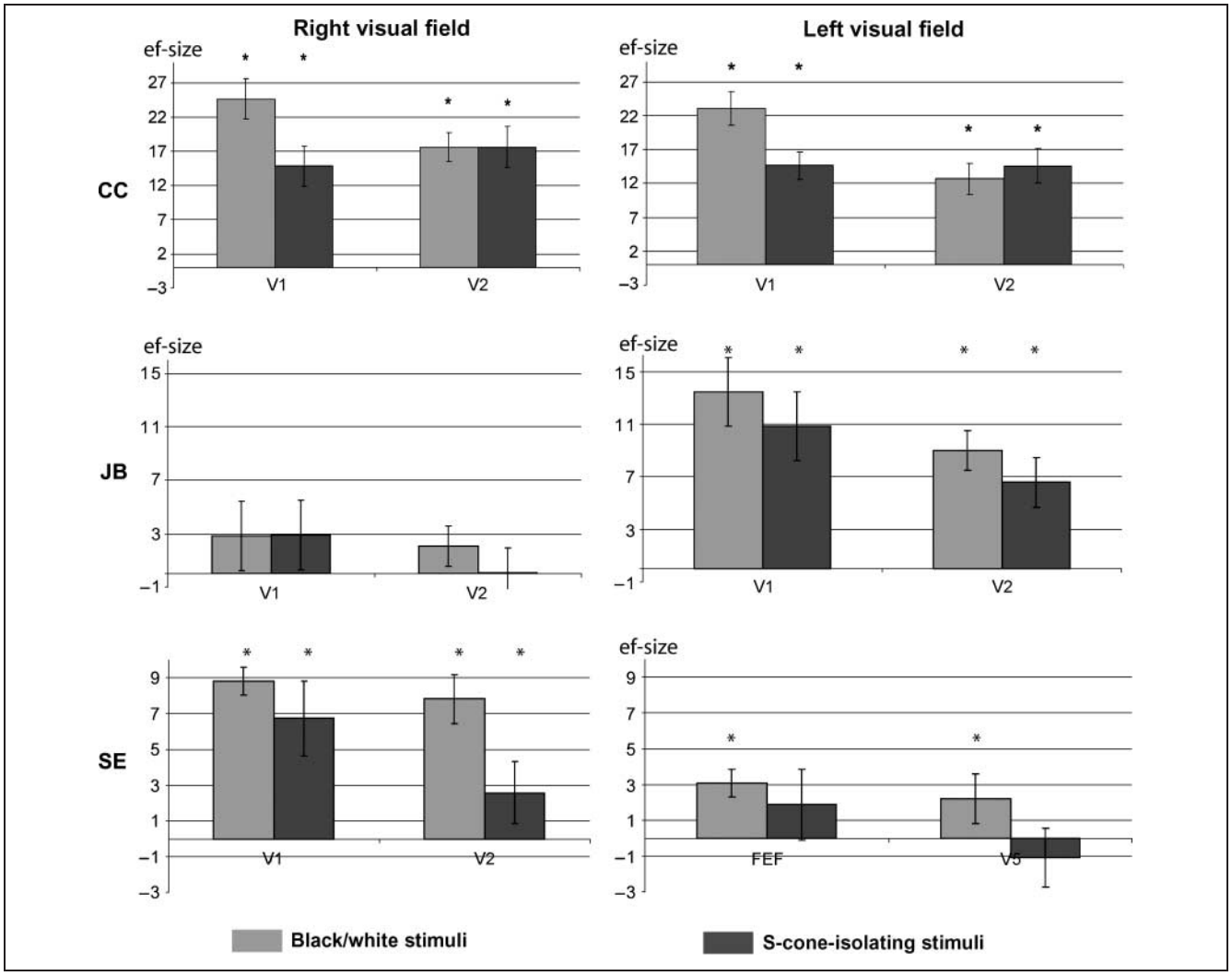

Figure 3. Effect sizes to unilaterally presented achromatic and S-cone-isolating stimuli. Achromatic and S-cone-isolating stimuli were presented to the left or right visual field. Effect sizes to achromatic stimuli are presented in light gray and to S-cone-isolating stimuli in dark gray. Effect sizes with standard deviations are displayed for areas V1 and V2 for subjects CC, JB (hemispherectomized subject without blindsight), and SE (hemispherectomized subject with blindsight). Please note that effect sizes with standard deviations for area V5 and FEF are only displayed in subject SE (where applicable) because we did not see any activation in these areas in subjects CC and JB. Significant effect sizes are denoted with an asterisk (*). ef-size = effect size.

showed contralateral activation in areas V1 and V2 to S-cone-isolating stimuli and to achromatic stimuli (Figures 3 and 4; Table 1) for achromatic stimuli.

Blind Visual Field in Hemispherectomized Subjects

As expected, JB did not show any activation patterns to stimuli presented in his blind field (Figures 3 and 4; Table 1). This is consistent with previous studies, in which he has never shown blindsight. In contrast, SE showed significant activation in area V5 and FEF when achromatic stimuli were presented in his blind visual field and an absence of activation if S-cone-isolating stimuli were presented, consistent with previous behavioral studies in which he reliably demonstrated blindsight (Figures 3 and 4; Table 1).

Study 3: Does Presentation of an Additional Stimulus Enhance the Cortical Activation Pattern?

We determined whether the presence of the additional stimulus in the contralateral visual field increases cortical activation patterns in V1, V2, and V5 compared with unilateral conditions. To do this, we used the same ROIs as in Study 2 and determined *t* maps for S-cone-isolating and achromatic stimuli separately and subtracted the unilateral condition from bilateral conditions (Figures 5 and 6; Table 2).

Subtraction of a Unilaterally Presented Stimulus in the Normal Visual Field of All Subjects from the Bilaterally Presented Stimulus

Control subject CC showed an enhanced cortical activation patterns in visual areas to bilaterally presented stimuli

compared with unilaterally presented achromatic and S-cone-isolating stimuli. Activated areas included V1 and V2 for both achromatic stimuli and for S-cone-isolating stimuli (see Figures 5 and 6; Table 2), demonstrating the presence of this effect in normal vision.

Subject JB did not show any enhanced cortical activation patterns in visual areas to bilaterally presented stimuli compared with unilaterally presented achromatic and S-cone-isolating stimuli in the normal visual field. This was expected because this subject does not have blindsight, and a stimulus presented to the blind visual field does not enhance the cortical activation pattern to stimuli presented in the normal visual field (Figures 5 and 6; Table 2).

In contrast, subject SE showed enhanced cortical activation patterns in remaining visual areas to bilaterally presented stimuli compared with unilaterally presented achromatic stimuli in the healthy visual field. Activated areas included V5 (right visual field subtraction). Whereas activation of areas V1 and V2 appear to be sufficient for an activation enhancement in healthy subjects, hemispherectomized subjects seem to use different pathways and mechanisms when this enhancement occurs. This result is consistent with previous studies that already suggested an involvement of area V5 in blindsight (e.g., Bridge, Thomas, Jbabdi, & Cowey, 2008; Bittar et al., 1999).

However, this enhancement was not seen to S-cone-isolating stimuli (Figures 5 and 6; Table 2), consistent with

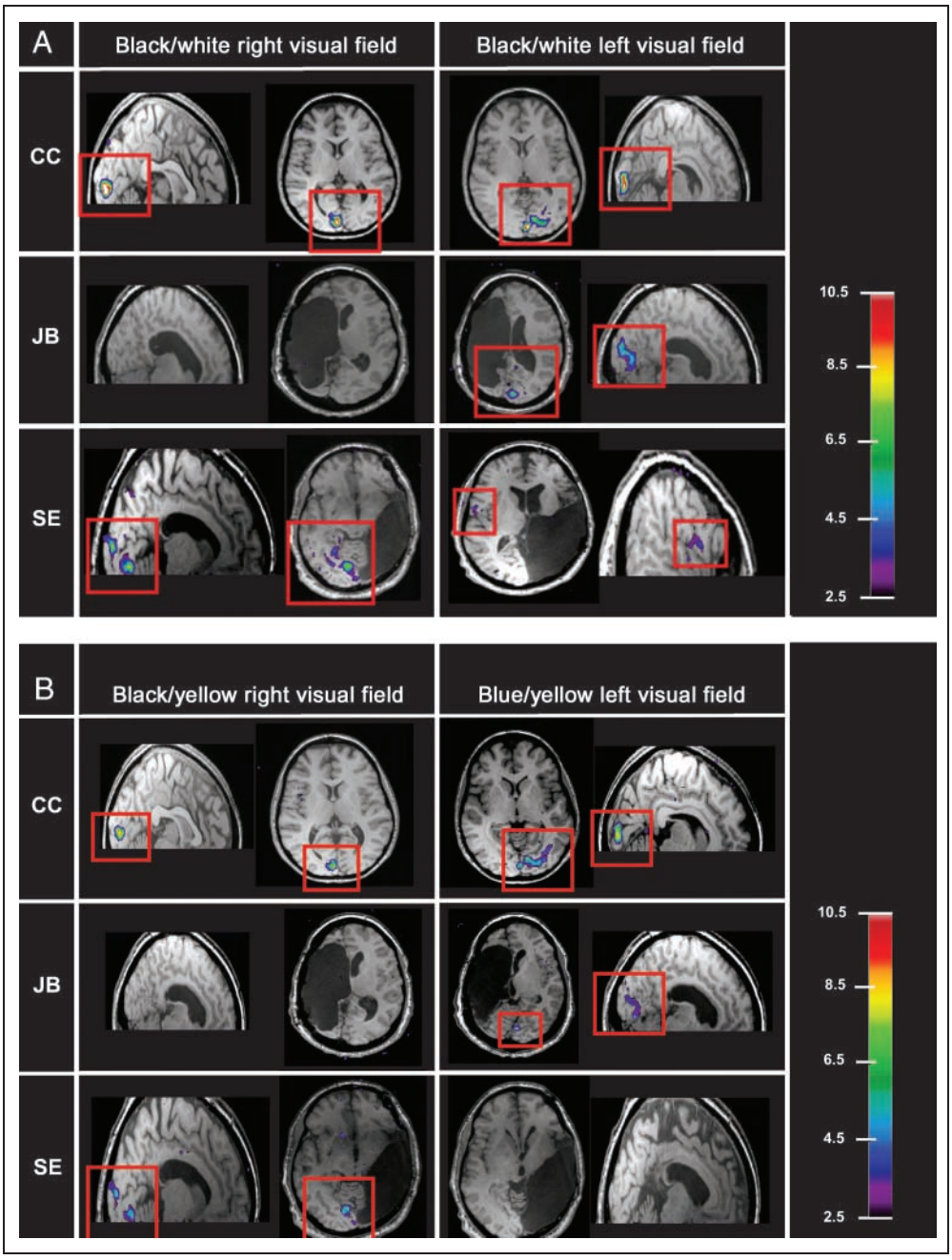

Figure 4. Study 2: *t* statistical maps for unilateral stimulus presentation. *t* maps for unilateral achromatic (black/white) (A) and S-cone-isolating (B) stimuli are displayed for all subjects (CC, JB, and SE). Examples of activation patterns to stimuli presented to the right visual field can be seen in the left column and to the left visual field in the right column. All subjects showed contralateral activation in visual cortical areas to stimuli presented in their healthy visual field. JB did not show any activation pattern when stimuli were presented in the blind visual field (right visual field). SE showed activation in V5 and FEF if achromatic (black/white) stimuli were presented to his blind visual field but not to S-cone-isolating stimuli (see also fMRI results—Study 2).

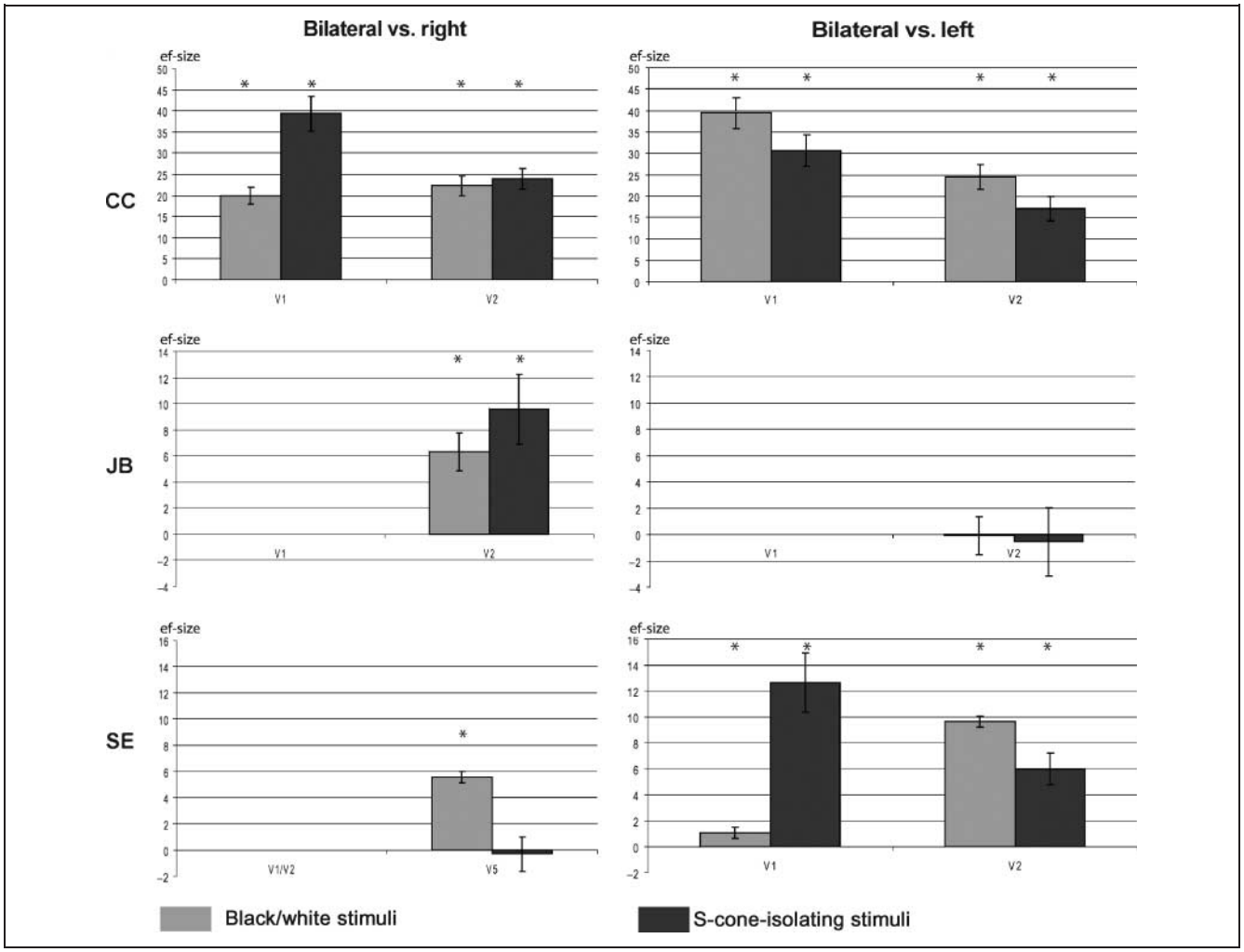

Figure 5. Enhancement measured in effect sizes to bilateral stimuli compared with unilateral stimuli. Achromatic and S-cone-isolating stimuli were presented to the left, right, or both visual fields. An enhancement effect was calculated by subtracting unilateral conditions (right or left) from the bilateral conditions. Effect sizes were calculated for achromatic stimuli, which are presented in light gray, and for S-cone-isolating stimuli, which are presented in dark gray. Effect sizes with standard deviations are displayed for areas V1 and V2 for subjects CC, JB (hemispherectomized subject without blindsight), and SE (hemispherectomized subject with blindsight). Note that effect sizes with standard deviations for area V5 are only displayed in subject SE (where applicable) because we did not see any activation in these areas in subjects CC and JB. Significant effect sizes are denoted with an asterisk (*). ef-size = effect size.

the results of Study 1 in which SE did not show activation in response to S-cone-isolating stimuli in the blind visual field and with our previous behavioral study (Leh, Mullen, et al., 2006). Taken together, these results demonstrate that blindsight in subject SE is color blind to S-cone-isolating stimuli.

Subtraction of a Unilaterally Presented Stimulus in the Blind Visual Field of Hemispherectomized Subjects from the Bilateral Presented Stimulus

Subject JB showed "enhanced" cortical activation patterns in visual areas to bilaterally presented stimuli compared with unilaterally presented achromatic and S-cone-isolating stimuli (right visual field subtraction). Achromatic and S-cone-isolating stimuli activated area V2. This subject has consistently never shown blindsight in previous studies; therefore, we did not expect a contribution from the blind visual field. We note that the activation shown here is the activation from stimulus presentation within the sighted visual field. Stimulus presentation within the blind visual field did not yield any additional activation (Figures 5 and 6; Table 2).

Subject SE, who has consistently shown evidence of blindsight, showed enhanced cortical activation patterns in visual areas to bilaterally presented stimuli compared with unilaterally presented achromatic and S-cone-isolating stimuli (left visual field subtraction). Activated areas included V1 and V2 for achromatic stimuli and for S-cone-isolating stimuli, as expected (Figures 5 and 6; Table 2).

DISCUSSION

We designed an fMRI paradigm using achromatic and S-cone-isolating stimuli to address the following: (1) absence

Table 1. Unilateral Stimulus Presentation (Study 2)

		Achromatic Stimuli		*S-Cone-isolating Stimuli*	
Subjects		*Right Visual Field Presentation*	*Left Visual Field Presentation*	*Right Visual Field Presentation*	*Left Visual Field Presentation*
CC	V1	5, −90, 2	−5, −90, 2	2, −91, −1	−5, −91, 2
	V2	11, −90, 6	−11, −90, 6	6, −90, 1	−6, −90, 1
	FEF	No activation	No activation	No activation	No activation
	V5	No activation	No activation	No activation	No activation
SE	V1	No activation	−1, −86, −4.5	No activation	−6, −96, −1
	V2	No activation	−25, −90, −4.5	No activation	−6, −90, 0
	FEF	−22.5, 31, 27	No activation	No activation	No activation
	V5	−61, −11, 10	No activation	No activation	No activation
JB	V1	−2, −94, 2	No activation	2, −91, −1	No activation
	V2	−0.5, −81, −1.5	No activation	2, −81, −12	No activation
	FEF	No activation	No activation	No activation	No activation
	V5	No activation	No activation	No activation	No activation

Displayed are local maxima of *t* maps in standard space using the Montreal Neurological Institute coordinates (*x*, *y*, *z*).

or presence of S-cone activation within the superior colliculi; (2) processing abilities in the blind visual field of hemispherectomized subject with blindsight; and (3) presence or absence of enhanced activation to two simultaneously presented stimuli.

We first investigated the chromatic and achromatic sensitivity of the superior colliculi by designing stimuli that isolated either the achromatic or the S-cone color pathway and measuring the activation of the human superior colliculus by these stimuli. All three subjects (CC, JB, and SE) showed significant effect sizes within the superior colliculi to achromatic but not to S-cone-isolating stimuli. Our results were consistent with previous studies in nonhuman primates showing that the superior colliculus is color blind to S-cone-isolating stimuli (Savazzi & Marzi, 2004; Sumner et al., 2002; Marrocco & Li, 1977; Schiller & Malpeli, 1977). It is to be noted that comparative anatomical analyses between humans and nonhuman primates (old world monkeys) have suggested similarities between different species but do not exclude differences in color vision systems between species (see e.g., Wade, Augath, Logothetis, & Wandell, 2008; Solomon & Lennie, 2007). Our fMRI results, however, seem to confirm achromatic collicular properties in humans.

In the second part of the study, we investigated the processing abilities of the blind visual field in two hemispherectomized subjects (JB and SE) to achromatic and S-cone-isolating stimuli that were presented to the left, right, or both visual fields. Activation patterns in visual cortical areas to unilaterally presented stimuli in the healthy visual field of hemispherectomized subjects (SE and JB) were very similar compared with those of a healthy control subject (CC). Robust contralateral V1 and V2 activation by S-cone-isolating stimuli and achromatic stimuli has previously been demonstrated in healthy subjects (Mullen, Dumoulin, & Hess, 2008; Mullen, Dumoulin, McMahon, de Zubicaray, & Hess, 2007). Activation was absent if achromatic or S-cone-isolating stimuli were presented to the blind visual field of hemispherectomized subject JB, which is consistent with our previous studies in which JB has never demonstrated evidence of blindsight (Leh, Johansen-Berg, et al., 2006; Leh, Mullen, et al., 2006; Bittar et al., 1999; Tomaiuolo et al., 1997).

Hemispherectomized subject SE, who has consistently demonstrated evidence of blindsight (Leh, Johansen-Berg, et al., 2006; Leh, Mullen, et al., 2006; Bittar et al., 1999; Tomaiuolo et al., 1997), demonstrated activation patterns in V5 and FEF, but not in V1 and V2, if achromatic stimuli were presented. This activation cannot be attributed to light scatter as stimuli were modulated about a uniform white background of the same mean luminance. We were also able to exclude the possibility that light scatter was entering the other visual hemifield by demonstrating that activation to unilateral presented stimuli in the healthy subject CC occurred only in the contralateral hemisphere, whereas no activation was observed ipsilaterally (see also Figure 5). Spared islands of visual cortex and all direct geniculo-extrastriate projections to explain activation patterns obtained to stimuli presented in the blind visual field of subject SE were also ruled out because surgery involved removal or disconnection of an entire cerebral hemisphere, including the occipital lobe, leaving the patient with a contralateral hemianopia without macular sparing.

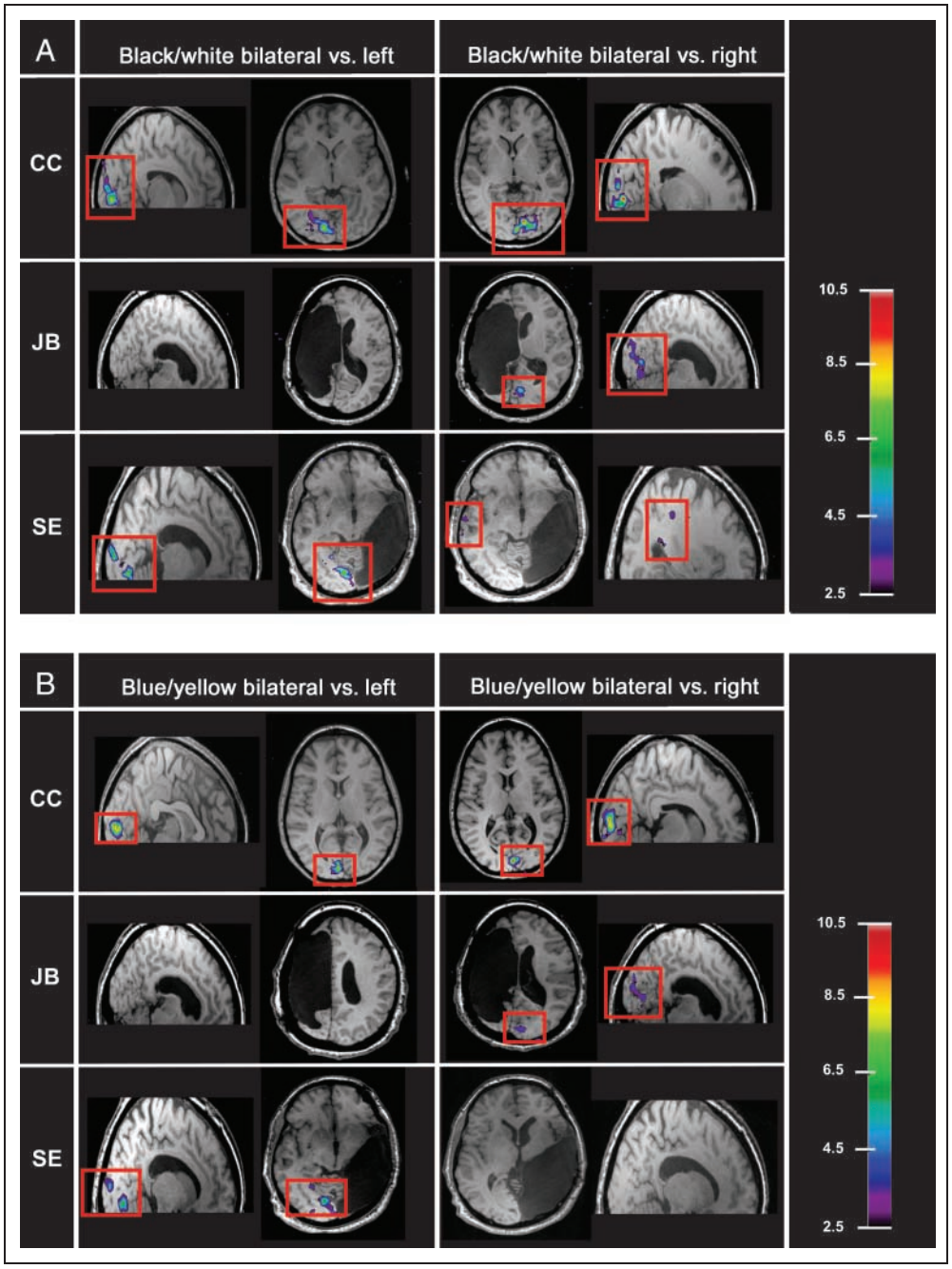

Figure 6. *t* statistical maps for enhanced activation patterns to two stimuli. Examples of enhanced activation pattern to two stimuli compared with a single stimulus in the right (left column) and left visual field (right column) are displayed as *t* maps for all subjects (CC, JB, and SE). Results for achromatic black/white stimuli are displayed in panel A, and results for S-cone-isolating stimuli are displayed in panel B. Whereas subject CC showed an enhancement to two achromatic black/white and to two S-cone-isolating stimuli compared to single conditions, JB did not show this enhancement when a second stimulus was presented in his blind visual field (see JB, left column). In contrast, SE showed enhanced activation patterns to two stimuli compared to a single stimulus if stimuli presented were achromatic black/white but not to S-cone-isolating stimuli (see SE column, right, and see fMRI results—Study 3).

These results confirm that subject SE is able to process achromatic visual information in his blind visual field, consistent with behavioral experiments in which he has shown blindsight to black/white stimuli (Leh, Mullen, et al., 2006). Subject SE did not, however, exhibit any activation to S-cone-isolating stimuli presented in his blind visual field.

Our results also excluded the possibility of a direct retino-pulvinar-cortical connection as the pulvinar nucleus is known to receive input from all types of color-opponent ganglion cells. In addition, our results also excluded all geniculo-extrastriate connections because they were removed by surgery. In view of the fact that previous electrophysiological studies have indicated that the primate superior is color blind to S-cone-isolating stimuli because it is not receiving retinal input from S-cones involved in color vision (Savazzi & Marzi, 2004; Sumner et al., 2002; Marrocco & Li, 1977; Schiller & Malpeli, 1977) and because similar results were observed in humans in part 1 of the present study, we conclude that a direct S-cone-independent retinal–tectal pathway is involved in blindsight.

In the third part of this study, we investigated the presence or the absence of an enhanced cortical activation if an additional stimulus was presented simultaneously to the contralateral visual field. We demonstrated that the simultaneous presentation of an additional achromatic stimulus to the blind visual field can enhance cortical activation patterns compared with a single presentation in the healthy visual field in a healthy subject as well as in a

Table 2. Enhancement of Activation Patterns to an Additional Stimulus Presentation (Study 3)

		Achromatic Stimuli		*S-Cone-isolating Stimuli*	
Subjects		*Enhancement of Additional Stimulus in Right Visual Field*	*Enhancement of Additional Stimulus in Left Visual Field*	*Enhancement of Additional Stimulus in Right Visual Field*	*Enhancement of Additional Stimulus in Left Visual Field*
CC	V1	−7, −90, 0	1, −90, 0	−7, −90, 0	1, −90, 0
	V2	−5, −91, −2	2, −88, −4	−5, −91, −2	2, −88, −4
	V5	No activation	No activation	No activation	No activation
SE	V1	−8, −95, −4	No activation	−7, −93, 3	No activation
	V2	−1, −90, −4	No activation	−9, −94, −1	No activation
	V5	No activation	−58, 5, −7	No activation	No activation
JB	V1	No activation	No activation	No activation	No activation
	V2	No activation	2, −81, −5	No activation	13, −96, 17
	V5	No activation	No activation	No activation	No activation

Displayed are local maxima of *t* maps in standard space using the Montreal Neurological Institute coordinates (*x*, *y*, *z*).

hemispherectomized subject (SE) with blindsight and is consistent with our previous behavioral study using RTs (Leh, Mullen, et al., 2006). Cortical areas that were involved in enhanced activation included V1 and V2 in control subject CC and V2 and V5 in blindsight subject SE. This enhancement was not seen in the hemispherectomized subject without blindsight (JB).

A behavioral enhancement in which the mean RTs to two bilaterally presented stimuli are significantly faster than to a single stimulus has previously been described as a spatial summation effect. This effect is reliably present in healthy subjects and was also used to demonstrate blindsight in hemispherectomized subjects previously (Leh, Mullen, et al., 2006; Tomaiuolo et al., 1997). We interpret this result as a form of implicit processing or "attention blindsight" whereby the simultaneous presentation of a second stimulus in the blind field alters the mean RT to the consciously perceived stimulus in the intact field. In our previous behavioral study, we were able to demonstrate a spatial summation effect to achromatic stimuli but not to S-cone-isolating stimuli. Our present fMRI study supports these results by demonstrating a correlation between our fMRI and behavioral results, namely, that there was an enhancement of cortical activation to achromatic stimuli but not to S-cone-isolating stimuli in the subject with blindsight.

In a previous study (Leh, Johansen-Berg, et al., 2006; Leh, Mullen, et al., 2006), we used diffusion tensor imaging tractography to investigate the pathways of the superior colliculi and we addressed the question of why subject JB does not show blindsight but subject SE does. We compared hemispherectomized subjects with blindsight to hemispherectomized subjects without blindsight, including the two subjects of the present study. Hemispherectomized subjects with blindsight showed ipsilateral and contralateral connections from the superior colliculus to visual association areas, primary visual areas, parietal areas, prefrontal areas, and posterior part of the internal capsule. In contrast, no projections from the superior colliculi on the hemispherectomized side were observed in hemispherectomized subjects without blindsight, suggesting considerable degeneration of both superior colliculi.

These results suggest that in hemispherectomized subjects with blindsight (e.g., subject SE), visual information within the blind visual field is processed via the ipsilesional superior colliculus and from there passed on to the contralesional superior colliculus and hemisphere. Interhemispheric interactions seem to be critical for blindsight to be observed in hemispherectomized subjects and this view is consistent with the present findings as well as with our previous studies showing contralesional cortical activation in hemispherectomized subjects (e.g., Bittar et al., 1999). These results, however, contrast with the hypothesis posed by Perenin and Jeannerod (1978), namely that blindsight can be mediated by the superior colliculi alone without any cortical processing and that it may differ between subjects with V1 lesions.

In addition, we did not find any correlation between the presence or the absence of blindsight and seizure onset, age at surgery, and so forth, and therefore can only speculate that the surgery involving subcortical areas may have affected the outcomes differentially. Further studies are planned with future hemispherectomy candidates using detailed neurosurgery reports to investigate whether blindsight is present before or only after the intervention.

Conclusion

We confirmed the existence of blindsight to superior colliculus visible (achromatic) stimuli. Our results also strongly suggest that the human superior colliculus is

color blind to S-cone-isolating stimuli and that hemispherectomized subjects show blindsight only to stimuli visible to the superior colliculi. Stimuli invisible to the superior colliculi such as S-cone-isolating stimuli do not mediate blindsight. Further studies are necessary to examine the neuronal correlates of blindsight in subjects other than hemispherectomized patients.

The existence of several types of unconscious vision has been demonstrated in numerous studies, and their neuronal correlates have been suggested according to the nature of the residual vision observed (Danckert & Rossetti, 2005; Weiskrantz, 1989).

The classification system of Danckert and Rossetti (2005) assumes that blindsight is mediated by subcortical neural structures that were not affected by the cortical damage and the ensuing degeneration. They classify perceptual processing such as form and wavelength discrimination as "agnosopsia," presumably mediated by interlaminar layers of the dorsal LGN, and "action blindsight" and "attention blindsight" as implicating the retinofugal pathway from the eye to the superior colliculi but differing in the regions of extrastriate cortex involved.

Studies are needed to investigate the neuronal correlate and the color opponent mechanisms in blindsight subjects with smaller lesions. At this point, it is difficult to speculate on their color opponent abilities in their blind visual field as there are important anatomical differences and pathways underlying blindsight may vary between hemispherectomized subjects and subjects with small clinical lesions. The combination of carefully designed experiments, such as those using the spatial summation effect, and imaging techniques, such as fMRI, offers an opportunity to investigate the contribution of other subcortical structures, such as the interlaminar layers of the dorsal LGN and the pulvinar, to the residual visual abilities of hemianopic patients with smaller lesions.

Acknowledgments

We would like to thank the subjects for their time and participation. This study was supported by a doctoral scholarship from CRIR to S. E. L., a doctoral and postdoctoral scholarship from FRSQ to S. E. L., an NSERC research grant to A. P. (RGPIN 37354-02), and a CIHR grant to K. T. M. (MOP-10819).

Competing Interests Statement

The authors declare that they have no competing financial interests.

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