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Lateral visual field stimulation reveals extrastriate cortical activation in the contralateral hemisphere: an fMRI study

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Abstract

We examined whether lateral visual field stimulation (LSTM) could activate contralateral extrastriate cortical areas as predicted by a large experimental literature. We asked seven unscreened, control subjects to wear glasses designed to allow vision out of either the left (LVF) or right lateral visual field (RVF) depending upon which side the subject looked toward. Each subject participated in a block design functional magnetic resonance imaging (fMRI) study with alternating 30-s epochs in which he was asked to look to one side and then the other for a total of five epochs. On each side of the bore of the scanner, we taped a photograph for the subject to view in the LVF and RVF. The data were analyzed with SPM99 using a fixed effect, box-car design with contrasts for the LVF and the RVF conditions. Both LVF and RVF conditions produced the strongest fMRI activation in the contralateral occipitotemporal and posterior parietal areas as well as the contralateral dorsolateral prefrontal cortex. LSTM appears to increase contralateral fMRI activation in striate and extrastriate cortical areas as predicted by earlier studies reporting differential cognitive and/or emotional effects from unilateral sensory or motor stimulation.

Keywords: Lateral visual fields; Cerebral laterality; Unilateral stimulation; Induced emotions; Altered cognitions; Statistical parametric mapping

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1. Introduction

Unilateral sensory or motor stimulation appears to produce a lateralized activation of the contralateral hemisphere and enhancement of certain cognitive abilities (Lempert and Kinsbourne, 1982; Walker et al., 1982; Drake and Bingham, 1985; Levick et al., 1993; Wittling and Schweiger, 1993; Schiff et al., 1998), as well as the modulation of affect (Dimond et al., 1976; Schiff and Lamon, 1989; Wittling and Roschmann, 1993; Schiff and Lamon, 1994; Schiffer, 1997; Schiffer et al., 1999). One form of unilateral stimulation, lateral visual field stimulation (LSTM), has been used to evaluate subjects' physiological and/or psychological responses when vision is limited primarily to one lateral visual field (left or right) compared to stimulation of the other field. LSTM has been reported to induce clinically relevant changes in the psychological state of patients with psychological disorders (Wittling and Schweiger, 1993; Schiffer, 1997, 2000; Schiffer et al., 2002), as well as alterations, in control subjects, in heart rate, blood pressure, cortisol (Wittling and Pflüger, 1990; Wittling, 1995), autonomic nervous system control (Wittling et al., 1998a,b) and affect (Wittling and Roschmann, 1993; Wittling and Schweiger, 1993; Schiffer et al., 1999; Morton, 2003).

This extensive literature suggests that unilateral sensory or motor stimulation might alter the balance of hemispheric activity. However, questions remain as to whether unilateral stimulation can selectively enhance the relative activity of the contralateral hemisphere since the corpus callosum allows for rapid transfer of information between the hemispheres and since most lateralized stimulation techniques do not limit stimuli entirely to one hemisphere.

Although two studies (Levick et al., 1993; Schiffer et al., 1999) have reported lateralized frontal and temporal theta EEG shifts suggesting brain activation contralateral to LSTM, we use blood oxygen level dependent (BOLD (Ogawa et al., 1990) fMRI to provide further insights into the neurophysiological basis for the behavioral results outlined above.

2. Methods

2.1. Subjects

Of the seven volunteers studied, five worked in a research department at McLean Hospital. Six of the volunteers were right handed according to the Edinburgh Inventory (Oldfield, 1971); the left-hander was male as were three others. The mean age of the subjects was 47 years (range 27–59). All signed a consent form approved by the IRB at McLean Hospital.

2.2. Paradigm

Subjects underwent a block-design fMRI study with alternating conditions that varied the direction of gaze. Each subject had his or her head stabilized in the mid-line with padding and a forehead strap. Subjects wore safety glasses modified so as to allow vision out of either the LVF or the RVF depending on whether the subject's eyes were turned to the left or right. See Fig. 1A,B. An artistic photograph was taped on each side of the bore of the scanner so that the subjects could attend to it when they looked to the LVF or RVF.

The fMRI scans for each individual were performed in one acquisition in which the subject was asked to look to one side until an experimenter instructed him through a speaker to look in the opposite direction. Each subject began by being asked to look to the left for 30 s, then right for 30 s, then left, then right and then left, each also for a 30-s period. Thus, the scan run was for 150 s (Fig. 2).

The last three subjects in the study repeated this protocol a second time, in the exact same manner, except that the subjects were instructed to keep their eyes closed but to move them as if they were looking at the photograph. This paradigm was performed as a control for ocular motion-induced artifacts (in addition to the motion-correction algorithms described below). The absence of contralateral hemispheric activation in the eyes-closed replication would enhance confidence in the LSTM results.

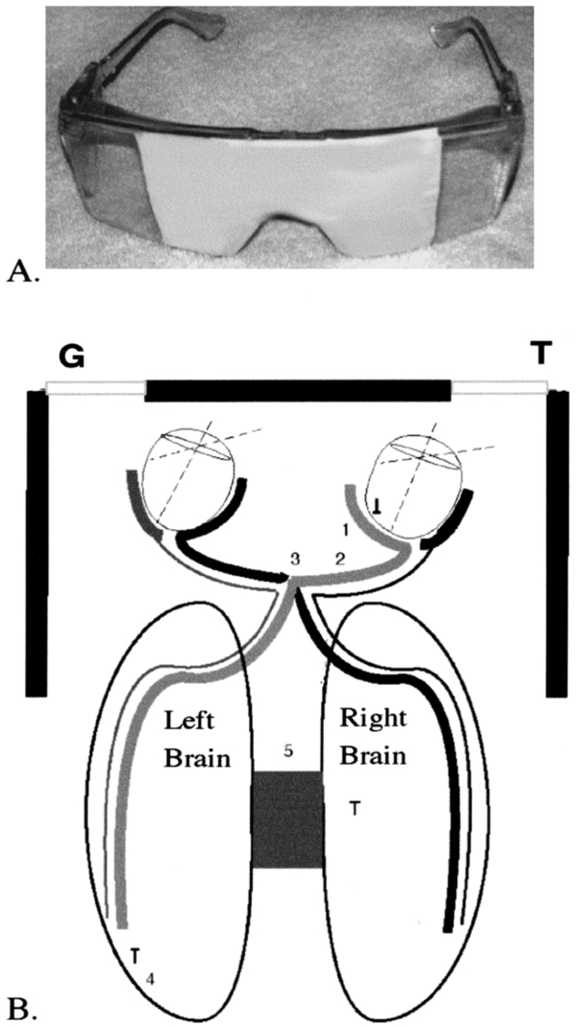

Fig. 1. (A) Taped safety glasses that were used in the experiment. (B) A diagram of how looking to the left allowed vision primarily out of the LVF and looking to the right allowed vision primarily out of the RVF. (1) Nasal retina; (2) optic nerve; (3) optic chiasm and (4) occipital cortex. When the subject looks to the right, he can see the '*T*,' which is primarily focused on the right nasal retina. At this time the left eye is occluded, and the '*G*' is not seen.

2.3. Imaging parameters

Images were collected on a 1.5 T General Electric Signa LX scanner (General Electric, Milwaukee, WI). Functional images were acquired with a single-shot gradient-echo echo-planar sequence: TE/TR = 40 ms/3 s; flip angle 90°; matrix = 64 × 64 on 20-cm field of view. We collected 28 axial slices, each with a thickness of 5.0 mm and a gap of 0. Each epoch consisted of 10 repetitions.

2.4. Data analysis

Data were analyzed and processed using SPM99 (Wellcome Department of Cognitive Neurology, London, Great Britain, http://www.fil.ion.bpmf.ac.uk). After realignment (no individual had motion greater than 0.8 mm in any of the three axes) and normalization (Montreal Neurological Institute template, size of the voxels = 2 × 2 × 2), data were smoothed (full width at half maximum = 8 mm^3). For the statistical analysis a fixed-effect (box car) design, convolved with the canonical hemodynamic response function was used. Low frequency confounds were removed with a high-pass filter specified at 120 s. The analysis combined all scans for the group of seven subjects. We applied a threshold with a *P* value of 0.05 corrected for whole brain multiple comparisons and a cluster size of 8 voxels. The LVF and RVF conditions served as contrasts. These same parameters were used to evaluate the group data from the three subjects who repeated the protocol with their eyes closed.

A hypothesis-driven statistical analysis, combining all eyes-open scans for the group of seven subjects, was also performed using the same par-

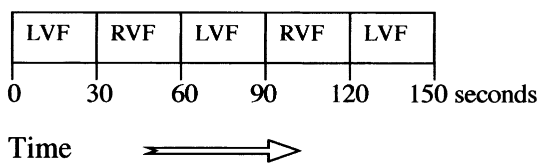

Fig. 2. This figure depicts the protocol of the study. At time zero, the experimenter asks the subject to look to the left, and the subject does so until the experimenter at time 30 s asks the patient to look to the right, and the subject does so until time 60 s when the experimenter again asks the subject to look to the left. This protocol is repeated until the end of the scan at 150 s.

Table 1
Statistics and coordinates for the largest clusters of activation

Anatomical area	Left lateral visual field								Right lateral visual field							
	Cluster-level		Voxel-level (maxima within cluster)			x,y,z MNI coordinates			Cluster-level		Voxel-level (maxima within cluster)			x,y,z MNI coordinates		
	P corrected	Cluster size	P corrected	t	z	x	y	z	P corrected	Cluster size	P corrected	t	z	x	y	z
OTP*	0.000	9536	0.000	15.3	Inf	20	−74	8	0.000	8252	0.000	15.9	Inf	−12	−92	30
			0.000	13.0	Inf	34	−74	−18			0.000	13.7	Inf	−30	−76	24
			0.000	12.4	Inf	50	−54	30			0.000	13.3	Inf	−42	−84	−2
DLPFC**	0.000	1964	0.000	12.5	Inf	46	38	−10	0.000	2764	0.000	10.8	Inf	40	40	0
			0.000	11.5	Inf	50	42	10			0.000	10.0	Inf	−46	4	2
			0.000	9.9	Inf	44	48	2			0.000	8.9	Inf	−50	12	14

Height threshold: $T=4.76$, $P=0.000$ (0.050 corrected); Extent threshold: $k=8$ voxels.
Degrees of freedom = [1.0, 315.0].
The x coordinate of the 3 MNI coordinates (x, y and z) indicates the hemisphere and positive numbers indicate the right hemisphere.
* OTP = Occipitotemporal and posterior parietal areas.
** DLPFC = dorsolateral prefrontal cortex.

ameters except for an uncorrected threshold of $P<0.05$. This was done in order to better test the hypothesis that LSTM would tend to activate extensive areas of the contralateral hemisphere but not the ipsilateral hemisphere.

3. Results

Statistics and coordinates for the largest clusters of activation under LVF and RVF are provided in Table 1. From the table, the LVF activation was strongest in the occipitotemporal and posterior parietal areas (OTP) and in the dorsolateral prefrontal cortex (DLPFC) in the right hemisphere. Conversely, the RVF activation was highest in the same anatomical areas in the left hemisphere. Fig. 3 presents the corrected data ($P<0.05$, $k=8$) for the seven subjects superimposed on a standard rendered brain. Fig. 4a. shows the corrected data ($P<0.05$, $k=8$) in an axial slice at $z=2$ (i.e. 2 mm above the level of the anterior and posterior commissure (AC/PC), indicating voxel t score intensities for the combined data from the three subjects performing the protocol with their eyes closed but moving them as if they were looking to the LVF and RVF. The figure illustrates that in the eyes-closed conditions, relatively few areas achieved the threshold criteria for activation. Fig. 4b shows the corrected data ($P<0.05$, $k=8$) in an axial slice at $z=2$ mm for the group of seven subjects when the subjects looked in the LVF and the RVF. By visual inspection of the statistical results displayed on the axial slices, the major areas of activation were in the contralateral OTP and DLPFC. The medial prefrontal cortex was activated bilaterally in the LVF condition. Fig. 4c shows the hypothesis-driven, uncorrected data ($P<0.05$, $k=8$) in an axial slice at $z=2$ mm indicating voxel t-score intensities for the group when the seven subjects looked in the LVF and the RVF. By inspection, at 2 mm above the AC/PC level, most of the contralateral hemisphere, but not the ipsilateral hemisphere, passed this lower threshold of activation in both the LVF and RVF conditions.

4. Discussion

Although there is a wealth of literature on vision and brain imaging (Paradiso, 2000; Miki et al., 2001), most studies involve lower level processing and/or full visual fields, and so are not directly

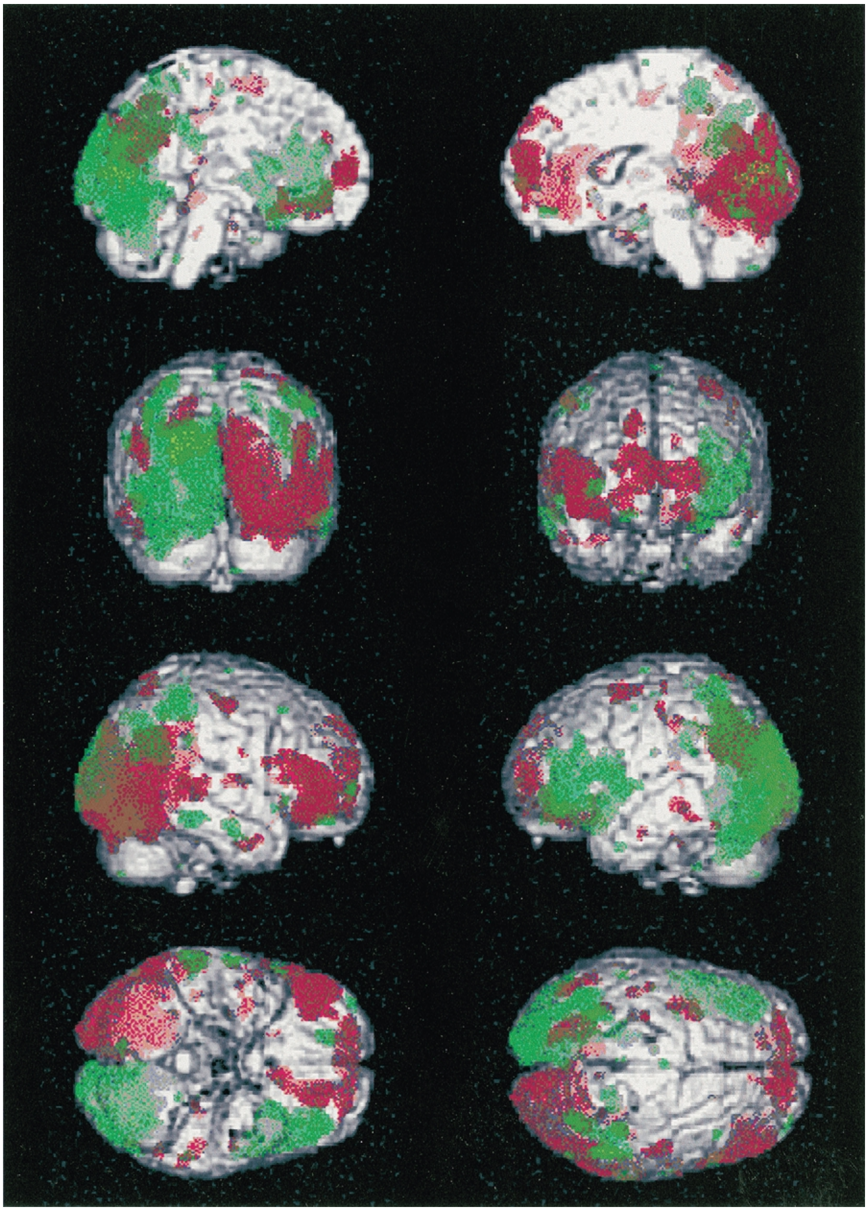

Fig. 3. The corrected data ($P<0.05$, $k=8$) for the seven subjects superimposed on a standard rendered brain. Red indicates clusters activated during LVF stimulation, and green indicates clusters activated during RVF stimulation.

comparable to the present study (Senior et al., 2000). A number of studies have used brain imaging in visual hemifield attention studies, and these have generally shown contralateral extrastriate cortical activation in the superior occipital gyrus and the occipitotemporal junction (Mangun et al., 1998; Macaluso and Frith, 2000), and the posterior lingual gyrus (Heinze et al., 1994; Vandenberghe et al., 1997). Vandenberghe and associates also found ipsilateral frontal activation

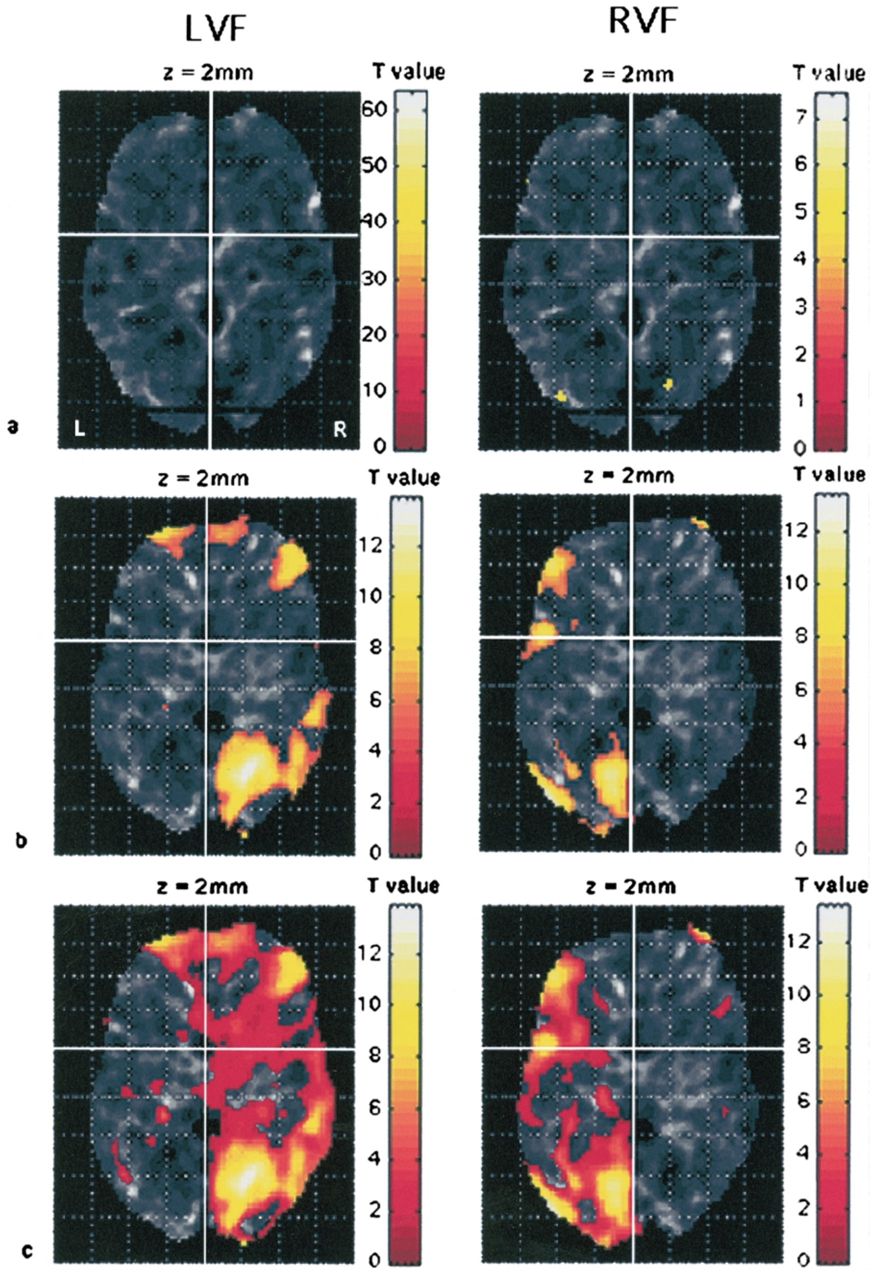

Fig. 4. (a) The corrected data ($P<0.05$, $k=8$) in an axial slice at $z=2$ mm (approximately 2 mm above the level of the anterior commissure) indicating voxel t score intensities for the three subjects performing the protocol with their eyes closed, but moving their eyes as if they were looking to the LVF and RVF. (b) The corrected data ($P<0.05$, $k=8$) in an axial slice at $z=2$ mm, indicating voxel t score intensities for the group of seven subjects when the subjects looked in the LVF and the RVF. (c) The hypothesis-driven, uncorrected data ($P<0.05$, $k=8$) in an axial slice at $z=2$ mm, indicating voxel t score intensities for the group when the seven subjects looked in the LVF and the RVF.

(Vandenberghe et al., 1997). Left and right eye monocular stimulation using alternating 40-s epochs revealed robust contralateral activation limited to the visual cortices (Toosy et al., 2001).

The present study, to our knowledge, is the first imaging study of LSTM. With hemifield attention studies, the subject fixates both eyes at a central point and is asked to attend to a task in either the left or right half of his full visual field, as images are presented to both fields of both eyes. Monocular stimulation could be expected to activate the contralateral visual cortex since each retina is connected to both hemispheres with about a 3:2 preference for the contralateral hemisphere (see Fig. 1b). With LSTM as used in this study, we believe the preference for the contralateral hemisphere is greater than with hemifield attention or with monocular stimulation because the image is presented primarily only to the nasal portion of one retina, the segment connected to the contralateral hemisphere. The taped safety glasses used in this study are not capable of limiting vision to only the nasal portion of the retina, but they can be expected to preferentially allow for stimulation of that section of the retina and therefore might be expected to generate a stronger stimulation of the contralateral hemisphere than hemifield attention or monocular stimulation. Each subject was instructed to look at the picture with half of his eye, fixating on the edge of the tape, but we did not monitor the eye's position, and it is possible that some subjects might have been able to move their eyes so that the fixation point was lateral to the tape's edge. To the extent to which that occurred, the condition would have changed from LSTM to monocular vision, and this would have lessened contralateral hemispheric activation.

We considered also that the corpus callosum allows the transfer of information between the hemispheres. Nevertheless, an accumulating body of evidence, as discussed in the introduction and reviewed in detail elsewhere (Schiffer, 1998, 2000), has suggested that unsophisticated, unilateral sensory or motor stimulation can influence cognition and affect. All of these studies were predicated on the hypothesis that unilateral sensory or motor stimulation produced contralateral hemispheric activation that, in turn, influenced cognition or affect. The present results are consistent with this hypothesis.

4.1. Theoretical implications

Even though the above literature had suggested that unilateral sensory or motor stimulation could activate the contralateral hemisphere, it is, given the fact of the corpus callosum, unexpected that such stimulation would not eventually activate the entire brain more uniformly. Of course, our findings do not indicate that only one hemisphere is functioning; rather they suggest that, on average, one hemisphere, the contralateral hemisphere, is relatively more active than the ipsilateral. We must address how it could be possible that unilateral stimulation could relatively activate one hemisphere more than the other.

The first possibility is that the results are due to an undetected systematic error or are due to a small population that may not, for some unknown reason, be typical of the larger population. These possibilities exist for all studies and cannot be ruled out in this one, but our findings are consistent with the hemifield attention and monocular stimulation studies cited above. These studies generally found striate and often extrastriate activation in the contralateral hemisphere, although none found activation to the extent that we did. After we saw that the results of the first few subjects indicated a large degree of lateralization, we felt we needed even more stringently to rule out motion artifact, gaze, or eye movements as a significant contribution to our findings. We decided to study the last three subjects with an additional condition: eyes closed, but an otherwise identical protocol. That condition did not produce comparable lateralized activation (as indicated in Fig. 4a), and we believe this suggests that our findings are neither the result largely of motion artifact, gaze, nor eye movements.

Our findings are consistent with Wittling's (Wittling and Pflüger, 1990; Wittling and Roschmann, 1993; Wittling and Schweiger, 1993; Wittling, 1995; Wittling et al., 1998a,b) work, showing that videos presented to one lateral visual field or the other in individuals with an intact corpus callosum, could consistently evoke differential physiological and emotional responses. The results in this report are also consistent with an earlier finding from our laboratory that LSTM could predict which of 37 patients with profound, refractory depression would respond to a 2-week course of rapid transcranial magnetic stimulation (rTMS) (Schiffer et al., 2002). It is interesting that rTMS is applied over the dorsolateral prefrontal cortex, the same frontal area that showed the most activation to each visual field in the present study. These observations could be coincidence, but they deserve further study, especially with patients suffering depression.

One possible explanation for the findings reported here is that the corpus callosum, in some individuals, limits or inhibits the transfer of interhemispheric information (Doty et al., 1994; Ringo et al., 1994; Leavengood and Weekes, 2000; Reggia et al., 2001). Another factor could be that LSTM might induce a high order (hemispheric) response in some subjects. For example, a split-brain study (Schiffer et al., 1998), reported a patient bullied in childhood who appeared to still be distressed about those events as an adult in his right hemisphere but not his left.

Thus, this study raises questions about the mechanisms and significance of the observed contralateral activation, and we hope it will stimulate further work from this perspective into the neurophysiological underpinnings of psychological processes.

Acknowledgments

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