fMRI evidence for individual differences in premotor modulation of extrastriatal visual–perceptual processing of redundant targets

T. Schulte,^a S.H.A. Chen,^{b,d} E.M. Müller-Oehring,^c E. Adalsteinsson,^b
A. Pfefferbaum,^{a,c} and E.V. Sullivan^{c,*}

^aNeuroscience Program, SRI International, Menlo Park, CA 94025, USA

^bDepartment of Radiology, Stanford University School of Medicine, Stanford, CA 94305, USA

^cDepartment of Psychiatry and Behavioral Sciences (MC 5723), Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5723, USA

^dDepartment of Psychology, National Taiwan University, Taipei, Taiwan

Received 23 April 2005; revised 17 August 2005; accepted 14 October 2005

Available online 13 December 2005

To perceive the vast array of stimuli in the world around us, the visual system employs parallel processing mechanisms that ensure efficiency in perceiving multiple objects in a scene. A way to test this efficiency is to measure reaction time (RT) to pairs of identical stimuli, presented singly or as doublets; typically, the resulting phenomenon is the redundant targets effect (RTE), which manifests as faster RTs to paired than singly presented stimuli. It is controversial, however, whether the neural locus of the parallel processing mechanisms invoked to produce the RTE is perceptual or motor and why some studies observe a substantial RTE and others do not. To resolve these two issues, we measured the RTE in young adults while undergoing functional MRI. Regarding the question of a perceptual or motor basis for the RTE, we observed that bilateral activation of extrastriate cortex was prominent in paired vs. the sum of the two single stimulus conditions, indicating that the RTE invoked perceptual mechanisms; by contrast, the motor cortex was not disproportionately activated in this comparison. Regarding the magnitude of the RTE, we compared activation patterns in individuals with small vs. large RTEs and observed that frontal and premotor areas were activated with small RTEs. These data indicate that the primary processing level of response facilitation, observed as the RTE, is perceptual, but the modulation of the RTE magnitude is premotor and associated with basic aspects of response selection and preparation.

© 2005 Elsevier Inc. All rights reserved.

Introduction

To perceive the vast array of stimuli in the world around us, the visual system employs parallel processing mechanisms that ensure efficiency in perceiving multiple objects in a scene (Kastner et al., 1998). Previous behavioral studies have asked how information

from multiple sources produces a single response and have implemented paradigms to test parallel stimulus processing and the integration of information with displays containing two targets compared with single targets (Miller, 1991; Mordkoff and Yantis, 1991, 1993). Typically, multiple targets presented simultaneously result in faster responses than those to single targets, a manifestation of the redundant targets effect (RTE) (Miller, 1986; Reuter-Lorenz et al., 1995; Corballis, 1998; Iacoboni et al., 2000; Reuter-Lorenz and Stanczak, 2000).

The response facilitation of redundant targets can be explained with two models: probability or coactivation. The probability or race model assumes that the processing of the two stimuli is transmitted along separate channels and the response is triggered as soon as a decision is made by either one of the two channels (Raab, 1962; Mordkoff and Yantis, 1991). However, when RTE is large and the gain exceeds probability measures, processing of simultaneous stimuli may be combined at some stage between the two channels, increasing the signal strength of redundant targets. The coactivation model (Miller, 1982) assumes some kind of multiplier of the activation created by paired stimulus presentation. Although Miller's use of the term coactivation was theoretical and not founded on measured brain activity, recent studies associated coactivation with neural correlates, e.g., the corpus callosum and interhemispheric processing in studies on split-brain patients (Reuter-Lorenz et al., 1995; Corballis, 1998; Iacoboni et al., 2000; Corballis et al., 2002; Roser and Corballis, 2002; Barr and Corballis, 2003) and extrastriate and premotor areas in neuroimaging studies on healthy subjects (Miniussi et al., 1998; Savazzi and Marzi, 2002; Iacoboni and Zaidel, 2003). Some studies have reported small RTEs in healthy subjects (Reuter-Lorenz et al., 1995; Corballis, 1998; Roser and Corballis, 2002), indicating that processing of each stimulus is stochastically independent (race model), whereas others report a large RTE, indicating that the processing of each of the two stimuli is not stochastically independent, but rather interactive (Miniussi et al., 1998; Savazzi and Marzi, 2002; Turatto et al., 2004). Variables

* Corresponding author. Fax: +1 650 859 2743.

E-mail address: edie@stanford.edu (E.V. Sullivan).

Available online on ScienceDirect (www.sciencedirect.com).

that may contribute to this range in RTE include stimulus quality (luminance vs. equiluminance or stimuli of two modalities) (Corballis, 1998; Gondan et al., 2004; Turatto et al., 2004), task demands (simple RT or go/no-go) (Miller, 1986), modality (unimodal or bimodal, e.g., auditory and visual) (Giray and Ulrich, 1993; Gondan et al., 2004), and subject strategy in task execution. Within a group of healthy subjects participating in the same study, Corballis (2002) reported a considerable intersubject variability, where nearly half the subjects exhibited violation of the race model and the other half did not. A possible explanation for the reported variability between normal subjects is that the RTE may operate by activating different neural loci (extrastriate or frontal cortical areas) depending on strategy selection, task demands, and stimulus characteristics.

Split-brain studies have consistently reported enhanced redundancy gains with luminance contrast stimuli and small gains with equiluminant stimuli, suggesting that the corpus callosum, the superior colliculus, and cortico–subcortical interactions are involved in interhemispheric redundant targets processing (e.g., Roser and Corballis, 2002, 2003; Corballis et al., 2004). Recently, we reported how interhemispheric processing can be affected by aging and alcoholism (Schulte et al., 2004) and found that healthy subjects of all ages exhibited enhanced RTE, implicating interaction of stimuli or neural summation, whereas older alcoholics did not, suggesting probability summation. Potential abnormality in neural structures contributing to the RTE (Miller and Reynolds, 2003), such as degradation of the corpus callosum, may have led to parallel hemispheric processing of redundant targets in alcoholics when processing is restricted to the parvocellular system using equiluminant stimuli. What remains unanswered is which brain structures are involved in the RTE under each potential behavioral outcome, i.e., supporting or violating the race model predictions, and at what level of neural processing does the RTE take place. Previous studies have investigated whether the RTE occurs at a perceptual (Miniussi et al., 1998; Murray et al., 2001), motor (Diederich and Colonius, 1987; Giray and Ulrich, 1993), or decisional stage (Miller, 1991) of processing. Evidence that the RTE appears at early stages in extrastriate cortical processing rather than at late decisional or premotor stages comes from several physiological studies. An electrophysiological study reported divergence between the ‘pair’ and the ‘sum of two single’ visual-evoked potentials, indicating a neural response interaction over parieto-occipital regions that occurred within 72–86 ms after stimulation (Murray et al., 2001). Another study measured event-related potentials to visual stimulation in the same, opposite, or both visual fields and revealed earlier peak N1 and P1 latencies for the ‘pair’ versus ‘sum of two single’ comparison in healthy subjects (Miniussi et al., 1998), suggesting that neural summation occurs at a level of early visual processing, possibly in extrastriate cortices. Furthermore, in a functional magnetic resonance imaging (fMRI) study using the RTE paradigm, activations were reported in the right medial and lateral occipital areas (extrastriate cortex) in a patient with callosal agenesis, supporting the neural summation model and suggesting a subcortical route for interhemispheric information exchange (Iacoboni et al., 2000). By contrast, in an event-related fMRI study of normal subjects, the same authors reported that the functional locus of the RTE occurred at premotor level bilaterally (Iacoboni and Zaidel, 2003), thereby raising the possibility that higher level interhemispheric information exchange occurs and cortical systems become involved when the

corpus callosum is intact. These authors suggest that neural summation probably occurs at premotor stages but is influenced by input from the extrastriate cortex.

In the present study, we investigated the neural correlates of interhemispheric processing with fMRI using a simple detection task to test the RTE in healthy subjects. First, we asked whether greater activation for bilateral than for unilateral stimuli occurs in extrastriate cortex or motor areas. Second, we tested the hypothesis that the neural correlates of RTE would differ between subjects who violate the race model by showing an enhanced RTE versus those who do not. Here, we predicted that enhanced RTE would be associated with activations of sensory visual areas, whereas smaller RTE would invoke neural systems involved in cognitive and sensorimotor aspects of response inhibition.

Materials and methods

Subjects

We studied ten healthy right-handed subjects, five women and five men, mean age = 28.1 ± 4.6 years. All subjects were neurologically healthy, highly educated (17.2 ± 1.7 years), and had no substance abuse or dependence according to DSM-IV Axis I. Subjects gave written informed consent to participate in this study, which was approved by the Institutional Review Boards at Stanford University School of Medicine and SRI International.

Task

Stimuli were created and presented with PsyScope software (Cohen et al., 1993). Subjects viewed interleaved blocks of single targets presented in one quadrant of the visual field and paired targets presented within one hemifield (unilateral paired stimulation) or in two hemifields, one to each cerebral hemisphere (bilateral paired stimulation). Subjects were instructed at each imaging run to press with their index finger a response button upon target detection as quickly and as accurately as possible. Two runs were performed, one with the left and the other with the right hand. Instructions on which hand to use were given at the beginning of each run, which consisted of 10 blocks, i.e., all five conditions (Fig. 1A), were presented twice within one run in a pseudorandom fashion, avoiding two similar consecutive conditions.

Subjects were asked to fixate on a cross in the center of the screen to prevent saccadic eye movement. To ensure fixation, subjects were required to press a response button when the color of the fixation cross changed from white to green, which occurred randomly throughout the experiment. Three interstimulus intervals were used (600, 800, and 1000 ms) and were pseudorandomly varied, so that each interval was equally represented in each condition. Stimuli consisted of white flashes on a black background and were displayed for 150 ms. Each trial had a total duration of 3000 ms and was presented in a block of 10, that is, one fixation trial was followed by nine stimulus presentations. The redundant targets paradigm was tested under two conditions.

(1) When interhemispheric processing was required, paired stimuli were presented simultaneously in the left and right hemifield and were contrasted with the sum of two single stimuli presented to each hemifield. (2) When intrahemispheric process-

Fig. 1. (A) Redundant targets paradigm: stimulus parameters timing. (B) SPM contrasts for inter- and intrahemispheric processing.

ing was required, paired stimuli were presented simultaneously in both the upper and lower hemifield and were contrasted with the sum of two single stimuli presented in the upper or lower hemifield. For intrahemispheric processing, stimuli were presented in the hemifield ipsilateral to the responding hand (see Fig. 1B). Thus, the amount of visual stimulation was equal across conditions.

Race model analysis for redundancy gains

We analyzed the shortening of RTs to paired stimuli relative to single stimuli according to the race measure $R(t)$ (Miller, 1982). The race model assumes two stochastically independent processes; RT is initiated when information processing of either one of two or more stimuli is completed. If the shorter response to paired targets depends on the winner of a race between two independent processes initiated by either of two stimuli (S1 or S2), then the race model predicts that the cumulative probability of observing a response to redundant targets (S1 and S2) by time t would be less than or equal to the sum of the cumulative probabilities for detecting each component by time t :

$$P(RT_{S1 \text{ and } S2} \leq t) = P(RT_{S1} \leq t) + P(RT_{S2} \leq t). \quad (1)$$

Eq. (1) provides an upper limit of the gain achieved by the detection of redundant targets. By transforming Eq. (1) into Eq. (2), we can test whether the shortening of RTs under double stimulation conditions violates the predictions of the race model by

comparing the cumulative distribution function for redundant targets $P(RT_{S1S2})$ with the sum of cumulative distribution functions for single targets, $P(RT_{S1}) + P(RT_{S2})$:

$$R(t) = P(RT_{S1S2}) - [P(RT_{S1}) + P(RT_{S2})]. \quad (2)$$

In Eq. (2), the race measure $R(t)$ can only be evaluated when $P(RT_{S1}) + P(RT_{S2}) \leq 1$. Thus, the range of possible values of $R(t)$ is -1.0 to 1.0 . To evaluate whether the shortening of RTs with redundant targets violates the predictions of the race model, we used this race measure $R(t)$. The graph $R(t)$ was calculated for each subject by ranking the RTs for the three stimulus conditions (S1, S2, and S1S2). We defined a bin consisting of 10 RTs and computed a cumulative distribution function, counting the number of stimuli in each condition in the first bin containing the 10 shortest RTs, in the second bin containing the 20 shortest RTs, and so on, cumulatively. Positive values indicate a higher number of fast responses elicited by bilateral than by unilateral trials within one bin, i.e., the amount of violation of the race model (Corballis, 1998; Corballis, 2002).

For statistical analysis, the maximum violation was defined by amplitude, which quantifies the maximum number of fast responses to paired in relation to single targets within the cumulative distribution function. By contrast, the latency of violation describes that more than twice as many responses to paired than to single targets are within the 10, 20, 30, or even 60 fastest responses (Schulte et al., 2004, 2005b).

Data acquisition and analysis

Imaging was performed with a 3.0-T whole body MRI scanner (General Electric Medical Systems, Signa, Waukesha, WI, USA) using a standard GE 3 T quadrature head coil. Structural MRI protocols consisted of a SpinEcho localizer scan and a T2-weighted Fast SpinEcho anatomical scan (axial acquisition; TE = 85 ms; TR = 3000 ms; FOV = 24 cm; 256 × 192 matrix; NEX = 1.0; slice thickness = 5 mm; 35 slices) used for spatially registering the fMRI data. For display purposes, group activations were superimposed onto an averaged normalized T2-weighted image across the 10 subjects. Whole-brain fMRI data were acquired with a T2*-weighted gradient echo spiral pulse sequence (TE = 30 ms; TR = 3000 ms; flip = 83°; in plane resolution = 3.75 mm; slice thickness = 5 mm with 0 mm gap; 35 axial slices; FOV = 24 cm; 1 NEX) (Glover and Lai, 1998). The start of the scan was triggered automatically from PsyScope software. Test instructions were reviewed with the subject by the examiner via the scanner's intercom system before the onset of each task.

Image preprocessing and statistical analyses were performed using the SPM2 software package (Wellcome Department of Cognitive Neurology). The fMRI analysis focused on the whole brain. The functional images were subjected to motion correction, and the T2-weighted FSE structural image was coregistered to the mean motion-corrected functional image for each subject. The images were then normalized to Montreal Neurological Institute (MNI) space, and the volumes were smoothed with a Gaussian kernel of 5 mm (FWHM). Individual statistics were computed using a general linear model approach (Friston et al., 1995) as implemented in SPM2. Statistical preprocessing consisted of high pass filtering at 60 s, low pass filtering through convolution with the SPM2 canonical hemodynamic response function, and global scaling.

A random effects analysis was conducted for group averaging and population inference. To perform this, one image per contrast was computed for each subject, and these images were subjected to *t* tests. The contrasts of interest were 'paired' vs. 'sum of two single' stimulation conditions for bilateral and

Table 1
Activation foci of the bilateral redundant targets effect (RTE) in 10 healthy subjects

Brain structures	BA	Hemisphere	N Vox	SPM	Talairach coordinates		
			k_E	Z_{max}	<i>x</i>	<i>y</i>	<i>z</i>
Lingual gyrus	18	Left	286	5.38	−20	−74	−1
	17			4.84	−18	−82	1
Cuneus	18			3.71	−12	−85	15
Lingual gyrus	19	Right	223	4.93	31	−72	−1
	18			4.17	14	−72	0
	19			4.06	16	−64	0
Posterior cingulate	30	Right	34	4.43	6	−58	12
Cuneus	18	Right	68	4.43	20	−81	21
	18			4.29	18	−90	17
Precuneus	31	Left	67	4.35	−24	−71	18

Contrast: pair > sum of two single. *Z* score values are depicted representing an FDR corrected *P* value threshold of 0.05 ($P_{\text{uncorrected}} > 0.0001$). Abbreviations: BA = Brodmann area, N Vox = number of voxels in a cluster of contiguous 2 × 2 × 2 mm voxels.

Table 2

Activation foci of the RTE amplitude in 7 healthy subjects (*n* = 4 no violation; *n* = 3 violation of the race model prediction)

Brain structures	BA	Hemisphere	N Vox	SPM	Talairach coordinates		
			k_E	Z_{max}	<i>x</i>	<i>y</i>	<i>z</i>
Precentral gyrus	6	Left	353	4.43	−32	−12	63
Postcentral gyrus	1			3.66	−34	−32	64
				3.37	−42	−15	56
Middle frontal gyrus	46	Left	65	4.37	−40	43	5
Inferior parietal lobe	40	Right	101	4.07	51	−36	50
				3.86	57	−29	47
				3.05	42	−39	41
Inferior frontal gyrus	47	Left	82	3.92	−40	19	−3
				3.13	−42	25	−8
Insula	13			2.77	−38	12	−2
Postcentral gyrus	3	Right	24	3.56	34	−34	59
Precentral gyrus	4			2.88	36	−26	64
Postcentral gyrus	1			2.75	32	−34	66
Postcentral gyrus	3	Left	24	3.50	−24	−30	70
Precentral gyrus	6	Right	20	2.94	38	−9	56

Contrast: no violation > violation. *Z* score values are depicted representing an uncorrected *P* value threshold of 0.003. Abbreviations: BA = Brodmann area, N Vox = number of voxels in a cluster of contiguous 2 × 2 × 2 mm voxels.

unilateral visual field presentations. We used random effects analysis to compare group images. Analyses were carried out with all subjects with an FDR-corrected *P* value of 0.05. However, to explore individual activation patterns associated with small and enhanced redundancy gains (one between subjects experiment and one within subject experiment), we chose an uncorrected *P* value threshold of 0.005 because of the small sample sizes in the subgroups and the exploratory character of this analysis. Coordinates in tables were transformed into the coordinate system of the Talairach and Tournoux (1988) stereotaxic atlas using the transformation from Matthew Brett (<http://www.mrc.cbu.cam.ac.uk/Imaging/mnispace.html>).

Results

The redundant targets effect: interhemispheric processing

Atlas locations and significance levels for key contrasts for interhemispheric redundant targets processing are presented in Tables 1, 2 and Figs. 2 and 4A, B. We calculated the RTE for each subject by subtracting the mean RT of two single events from the mean of paired events. Each subject had faster RTs to paired (273 ± 26 ms) than single stimuli (290 ± 24 ms), evidence for the RTE (difference = 17 ± 8 ms) ($Z = -2.805$, $P < 0.005$).

Contrasting paired stimulation to the average of the two single stimulations, all subjects showed significant ($P < 0.05$) activations bilaterally in extrastriate cortices, the lingual gyri and cuneus corresponding to Brodmann areas 17, 18, and 19, the precuneus in the left hemisphere corresponding to Brodmann area 31, and the

Fig. 2. Bilateral redundant targets effects: activation of extra-striate areas in the paired > single stimulation contrast in 10 healthy subjects. SPM2, height threshold $T = 4.30$ ($P = 0.001$), extend threshold $k = 20$ voxel.

posterior cingulate corresponding to Brodmann area 30 (Table 1 and Fig. 2). Additional activations, which were marginally significant with an FDR corrected P value of 0.07, were found in the left frontal cortex, specifically in the precentral gyrus corresponding to Brodmann area 44 and insula corresponding to Brodmann area 13.

We also examined whether trial repetition using a block design invoked learning or spatial attention differentially influencing the processing of single and paired events (e.g., a diffuse spotlight of attention in paired trials and a focused spotlight of attention in single trials). Accordingly, we created a scatter plot of the RTs to repeated trials for each of the three conditions (pair bilateral, single right, and single left) and estimated the curve of the regression model for each subject. A nonlinear relationship fit best the data with an inverse regression model with the equation $Y = b_0 + (b_1 / t)$. Beta values indicative for a general trend of RT change with stimulus repetition in each subject were averaged for single trials and compared to beta values of paired trials. Differences between beta values for single and paired events were not statistically significant (pair: mean beta = 53.7 ± 50.7 ; single: mean beta = 45.9 ± 35 ; $t = 0.43$, n.s.).

The redundant targets effect: intrahemispheric processing

As a control condition to bilateral stimulation, we tested unilateral redundant targets processing. Each subject had faster RTs to unilateral paired (293 ± 33 ms) than single stimuli (303 ± 26 ms), evidence for an intrahemispheric RTE (difference = 10.32 ± 10.82 ms) ($Z = -2.09$, $P < 0.04$). There was a trend of a smaller RTE in the unilateral task than in the bilateral task ($Z = -1.68$, $P = 0.09$; Wilcoxon test). Accordingly, when comparing BOLD responses to unilateral ‘paired’ versus ‘sum of two single’ stimulation, subjects showed no significant activations at either cluster or voxel levels ($FDR_{corrected}$).

Neural or probability summation?

We tested whether the shortening of RTs to bilateral paired stimuli relative to single stimuli for each subject could be explained by the probability summation model by calculating the function $R(t)$. Four subjects showed a small RTE ($R(t) \leq 0$), regardless of hand used for responding, supporting the probability model,

Fig. 3. Cumulative plot of mean (SEM) probabilities over response bins. $R(t)$ is a function describing the probability of an RT at time t with paired stimuli in relation to the summed probabilities of single stimulus events at time t . If the curve values are exactly zero or below zero for all bins, the race model can be accepted (probability summation), whereas positive values indicate that RTs to redundant targets are faster than the race model would predict and the race model is violated.

whereas three subjects showed enhanced RTEs ($R(t) > 0$), irrespective of response hand, supporting the neural summation model. The remaining three subjects showed ambiguous results, supporting one or the other model, depending on which hand responded. We further tested for statistical differences in response facilitation in the behaviorally extreme groups, i.e., testing the mean cumulative distribution functions revealed by the race measure $R(t)$, where the graph $R(t)$ can be described by the amplitude (maximum of violation) and the latency (the number of response bins with positive $R(t)$ values) (Schulte et al., 2004). Subjects supporting the neural coactivation model showed a significantly enhanced *amplitude* ($Z = -2.36$, $P = 0.018$) and prolonged *latency* ($Z = -2.36$, $P = 0.018$) relative to those supporting the probability model (Mann–Whitney U test) (Fig. 3).

We contrasted activations invoked by redundant targets (RTE) in subjects with small versus enhanced RTE and found activations primarily in left precentral gyrus (Brodmann area 6) and postcentral gyrus (Brodmann areas 1, 3) and in the left middle and inferior frontal gyri (Brodmann areas 46–47) (Table 2 and Fig. 4A). Activations were also found in the right precentral (Brodmann

areas 4, 6) and postcentral gyri (Brodmann areas 1, 3). Thus, subjects who did not show enhanced RTEs engaged motor and premotor areas bilaterally and the left middle and inferior frontal gyri, whereas subjects who showed enhanced RTEs did not exhibit this pattern of activation.

A within-subject comparison of the three subjects with ambiguous results (probability model support with one hand > neural summation support with the other hand) also showed activation in the precentral gyrus (Brodmann area 6; $x, y, z = 38, -2, 39$; $P_{\text{uncorrected}} < 0.0001$ at voxel level, $Z = 3.35$). These subjects also showed activation in the left cingulate gyrus corresponding to Brodmann area 31 ($x, y, z = -16, -27, 35$; $P_{\text{uncorrected}} < 0.001$ at voxel level, $Z = 3.22$) (Fig. 4B).

Discussion

This fMRI study provides evidence that the RT speed gained by the presence of redundant targets is associated with BOLD signal increases in the visual association cortex, especially the

Fig. 4. (A) Violation of the race model: activation of premotor, motor, and frontal brain areas in 4 subjects with no violation contrasted to 3 subjects with violation of the race model predictions. SPM2, height threshold $T = 4.03$, extend threshold $k = 20$ voxel. (B) A within-subject comparison of the three subjects with ambiguous results (probability model support with one hand > neural summation support with the other hand).

lingual gyri bilaterally (Brodmann's areas 18/19). This region is known to subserve size estimation, color perception, and motion processing (Servos et al., 2002), and our study expanded its purview to processing redundant stimuli. This result suggests that the shortening of RT by redundant targets presented bilaterally occurs at an early cortical visual processing stage. This effect cannot be accounted for by simple differences in the amount of visual stimulation present because, when pairs of stimuli were presented unilaterally, no significant activation patterns were observed. Thus, interhemispheric processing was a requirement for bilateral RTE showing extrastriate activity. However, when subjects with small bilateral RTE were compared to those with enhanced bilateral RTE, premotor and frontal areas were prominent with small RTEs. This activation pattern suggests individual differences in the responsiveness of frontal neurons to visual input that may reflect involvement of allocation of spatial attention, maintenance of central fixation, and inhibition of motor responses (Saron et al., 2001).

Extrastriate mechanisms of processing redundant stimuli

Redundant targets effects have been reported in patients with striate cortex lesions, suggesting that visual information can bypass lesions in the primary visual cortex and invoke extrastriate areas (Marzi et al., 1986; Wust et al., 2002). Moreover, studies using equiluminant stimuli that restrict visual input to the parvocellular system (Livingstone and Hubel, 1987) in split-brain (Corballis, 1998) and in healthy subjects (Turatto et al., 2004) suggested the locus of the RTE to occur at early visual processing stages in subcortical structures, especially the superior colliculus, or result from cortico-subcortical interactions (Roser and Corballis, 2002; Savazzi and Marzi, 2004; Schulte et al., 2004). The role of the superior colliculus in RTE in normal and acallosal subjects has been demonstrated by experiments using short-wavelength monochromatic or isoluminant stimuli (Corballis, 1998; Barr and Corballis, 2003; Savazzi and Marzi, 2004; Turatto et al., 2004). Because redundant stimuli equiluminant with the background (low contrast) restrict processing to the parvocellular system, they may necessitate interhemispheric exchange via the corpus callosum, whereas redundant stimuli that contrast with background (high contrast) processed via the superior colliculus suggesting that interhemispheric neural summation occurs in the bilateral superior colliculus through the intercollicular commissure (Savazzi and Marzi, 2004). However, brain imaging studies using simple stimulus detection tasks have repeatedly found activation in extrastriate visual areas (Marzi et al., 1999; Tettamanti et al., 2002; Omura et al., 2004). Given that the superior colliculus projects to extrastriate (Leichnetz, 1990) and motor areas (Lunenburg et al., 2001), a possible explanation may be that the extrastriate activation in the RTE is triggered by subcortical activation in the bilateral superior colliculus. These findings suggest a network involving the superior colliculus, extrastriate cortex, premotor, and motor areas without involvement of the geniculo-striate pathways (Savazzi and Marzi, 2004). Our results provide further evidence that extrastriate cortices are bilaterally engaged in response facilitation in healthy subjects and that the summation process here is primarily perceptual. However, BOLD responses in visual cortices are complex and depend on interactions between visual properties of the task, like stimulus complexity and stimulus size (Marcar et al., 2004; Marcar and Loenneker, 2000). The two conditions of interest 'paired' and 'sum

of two single' stimulation did not differ in complexity, stimulus size, stimulus luminance, or chromatic contrast, but in the number of presented stimuli presented at a given time. One possible explanation for the activation of visual cortices would be a change in the overall luminance of the display when two stimuli are present at a given time compared with one stimulus. But no significant extrastriate activations were found in the unilateral 'paired vs. sum of two single' contrast, i.e., when stimuli were presented unilaterally in either the left or the right hemifield. This pattern of activation suggests that interhemispheric connectedness of extrastriate areas via the bilateral superior colliculus or the corpus callosum (Van Essen et al., 1982) contributes to the RTE rather than stimulus characteristics in the task employed.

It is possible that attention played a role in our paradigm with a different distribution of spatial attention between the single and paired target blocks. An admittedly speculative account is that attention was focused at one restricted spatial position in the single target block, whereas attention in the paired target block was spread over the area subtended by the two stimuli and possibly resulting in extrastriate activation (Moran and Desimone, 1985; Treue and Maunsell, 1996). However, Theeuwes (1994) found no influence of spatial uncertainty or attention directed to one target location on redundancy gain. In addition, recent fMRI data have shown that spatial attention can be split between discrete regions of space, both intra- and interhemispherically, and is not required to be a unitary spotlight surrounding the attended stimuli (McMains and Somers, 2004). This finding suggests that paired trials with two attentional spotlights in paired target blocks can be compared with the sum of two spotlights from single target blocks. If attention had accounted for differences in the "paired vs. (sum of two) single" contrast in the present study, the "attention network", i.e., primarily frontal and parietal brain areas, should have been activated, which was not the case. Furthermore, Feintuch and Cohen (2002) showed in one of their experiments that attention-induced coactivation does not occur for targets at the same dimensional module, suggesting that a major role of attention is postperceptual. In addition, our behavioral results indicate that trial repetition, measured by beta values using regression models for each condition block, did not differentially influence single and paired events. Furthermore, the effect of spatial attention on the response of extrastriate cortex is not explicit; for example, Seidemann and Newsome, (1999) found that, in contrast to Treue and Maunsell, spatial attention alone is not enough to induce strong attentional modulations in extrastriate areas. Together, these findings support the position that extrastriate activations in the present study are related to redundancy gain and not to other factors like attention or trial repetition effects, supporting the hypothesis that the locus of the RTE is perceptual.

A further possibility for extrastriate activation with redundant targets is that symmetric visual displays lead to enhanced activations in higher-order regions of human visual cortex (Sasaki et al., 2005). However, Roser and Corballis (2002) found in split-brain and acallosal patients that redundancy gains to both symmetrical and asymmetrical displays evidently violated the race model predictions and concluded that enhanced redundancy gains did not depend on topographic mapping in the split brain. Extended investigations may reveal whether the RTE depends on stimulus symmetry subtending the two hemispheres and visual fields in healthy subjects and whether this is related to extrastriate activation patterns in symmetric displays.

Premotor mechanisms of individual differences in processing redundant stimuli

In contrast to the position that the neural substrate of the RTE is extrastriate, others contend that the locus of summation processing is premotor (Iacoboni and Zaidel, 2003) and occurs at a response selection stage in healthy subjects (Miller and Reynolds, 2003). Using event-related fMRI, Iacoboni and Zaidel (2003) found activations in precentral gyri bilaterally and in the left postcentral gyrus that were associated with RTE. Although split-brain studies often revealed enhanced RTEs, suggesting neural summation (Corballis et al., 2004), an enhanced RTE in healthy subjects was not always forthcoming (Corballis, 2002; Iacoboni and Zaidel, 2003).

A possible explanation for the contradictory findings in healthy subjects may be high interindividual variability in the amount of response facilitation elicited by redundant targets. To test this possibility, we compared healthy subjects with statistically significant enhanced RTEs suggesting neural coactivation (violation of probability models) and those with RTEs suggesting probability summation (no violation). The no violation vs. violation contrast yielded activations primarily in bilateral premotor and motor areas and right frontal areas. The activation in the precentral gyrus in the no violation vs. violation contrast was supported by a within-subject experiment including the remaining subjects with ambiguous results from the right and the left hand. Activation of these frontal brain areas is associated with less redundancy gain and implicates inhibitory influences on facilitation processing. When the RTE does not violate probability models, the RTE may be reduced because of the additional recruitment of frontal brain areas. Support for frontal activations in response to simple visual stimulation comes from an ERP study (Saron et al., 2001), which reported that passive viewing of stimuli as well as the performance of simple RT task resulted in early frontocentral activations over the right hemisphere peaking 124 to 148 ms after onset of visual stimulation. These frontal activations were independent of visual field input or motor response requirement and clearly separate in the time course from posterior responses elicited by visual input. Moreover, a diffusion tensor imaging (DTI) study showed that the extent of RTE attenuation correlated with a measure of tissue degradation present in the genu of the corpus callosum in alcoholics (Schulte et al., 2005b). Similarly, patients with anterior resection of the corpus callosum exhibit rather small RTEs that do not violate probability models (Corballis et al., 2004). That association supports the hypothesis that frontal involvement reduces response facilitation availed by redundant targets. Although frontal RTE attenuation was repeatedly found in an intersubject and in an intrasubject experiment, generalization of these results are limited by the small sample size of the comparisons and should merit additional investigation on RTE in healthy subjects that account for interindividual differences in redundancy gains.

Despite the simplicity of the detection task used here, it posed relatively high demands on processes of sustained attention and likely affected individual processing of redundant stimuli. Subjects with a small RTE (no violation of the race model) may have found it more difficult to stay focused in the scanner than subjects with a large RTE. The no violation vs. violation contrast additionally showed activation of the right inferior parietal cortex, which is typically involved in attentional processing of the fronto-parietal attentional control system (Coull et al., 1998, Jordan et al., 2001, Schulte et al., 2005a). There is also evidence that the RTE magnitude can be modulated by spatial attentional demands as

evidenced by an attenuation of the RTE when attention is allocated to only one side of bilateral presentations (Miniussi et al., 1998).

Conclusion

The extrastriate activation occurring regardless of RTE enhancement may be indicative of an attention-independent, automatic process suitable for efficient and fast transmission of redundant information at an early sensory processing stage. However, subjects with an attenuated RTE used processing strategies indicated by recruitment of premotor and frontal brain areas associated with reduced response facilitation. Thus, differences in neural systems recruited to achieve a common task define differences in processing strategies that are implemented. These results provide evidence for dissociation between fundamental perceptual processes used in parallel processing and individual differences in recruitment of frontal systems for handling redundancy.

Altogether split-brain data on patients with anterior or posterior section of the corpus callosum (Corballis et al., 2004), data on alcoholics with frontal degradation of the corpus callosum (Schulte et al., 2004) and the current fMRI data from healthy subjects suggest two neural processes involved in redundancy gain, a posterior one associated with response facilitation from redundant targets that depends on posterior callosal connectivity (Corballis et al., 2004) and is related to extrastriate activation (Omura et al., 2004, Miniussi et al., 1998, Murray et al., 2001) with possible involvement of the superior colliculus (Iacoboni et al., 2000) and an anterior one that is associated with the modulation and mainly attenuation of response facilitation from redundant targets (see also Corballis et al., 2002). We conclude that the primary processing level of response facilitation, observed as the RTE, is perceptual, but the modulation of the RTE magnitude is premotor and associated with basic aspects of response selection and preparation.

Acknowledgments

The authors thank Gary Glover, Ph.D. for the spiral sequences and Susan Gabrieli, M.A. and Eve DeRosa, Ph.D. for help with SPM2 and Ian Colrain, Ph.D. for his assistance in setting up the fMRI equipment. This study was supported by grants from the National Institute on Aging (AG17919) and from the National Institute on Alcohol Abuse and Alcoholism (AA12388, AA05965, and AA10723).

References

- Barr, M.S., Corballis, M.C., 2003. Redundancy gain in the acallosal brain. *Neuropsychology* 17, 213–220.
- Cohen, J.D., MacWhinney, B., Flatt, M., Provost, J., 1993. PsyScope: a new graphic interactive environment for designing psychology experiments. *Behav. Res. Methods Instrum. Comput.* 25, 257–271.
- Corballis, M.C., 1998. Interhemispheric neural summation in the absence of the corpus callosum. *Brain* 121, 1795–1807.
- Corballis, M.C., 2002. Hemispheric interactions in simple reaction time. *Neuropsychologia* 40, 423–434.
- Corballis, M.C., Hamm, J.P., Barnett, K.J., Corballis, P.M., 2002. Paradoxical interhemispheric summation in the split brain. *J. Cogn. Neurosci.* 14, 1151–1157.

- Corballis, M.C., Corballis, P.M., Fabri, M., 2004. Redundancy gain in simple reaction time following partial and complete callosotomy. *Neuropsychologia* 42, 71–81.
- Coull, J.T., Frackowiak, R.S., Frith, C.D., 1998. Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia* 36, 1325–1334.
- Diederich, A., Colonius, H., 1987. Intersensory facilitation in the motor component? A reaction time analysis. *Psychol. Res.* 49, 23–29.
- Feintuch, U., Cohen, A., 2002. Visual attention and coactivation of response decisions for features from different dimensions. *Psychol. Sci.* 13, 361–369.
- Friston, K.J., Frith, C.D., Frackowiak, R.S., Turner, R., 1995. Characterizing dynamic brain responses with fMRI: a multivariate approach. *NeuroImage* 2, 166–172.
- Giray, M., Ulrich, R., 1993. Motor coactivation revealed by response force in divided and focused attention. *J. Exp. Psychol. Hum. Percept. Perform.* 19, 1278–1291.
- Glover, G.H., Lai, S., 1998. Self-navigated spiral fMRI: interleaved versus single-shot. *Magn. Reson. Med.* 39, 361–368.
- Gondan, M., Lange, K., Rosler, F., Roder, B., 2004. The redundant target effect is affected by modality switch costs. *Psychon. Bull. Rev.* 11, 307–313.
- Iacoboni, M., Zaidel, E., 2003. Interhemispheric visuo-motor integration in humans: the effect of redundant targets. *Eur. J. Neurosci.* 17, 1981–1986.
- Iacoboni, M., Pito, A., Weekes, N.Y., Zaidel, E., 2000. Parallel visuomotor processing in the split brain: cortico-subcortical interactions. *Brain* 123, 759–769.
- Jordan, K., Heinze, H.J., Lutz, K., Kanowski, M., Jancke, L., 2001. Cortical activations during the mental rotation of different visual objects. *NeuroImage* 13, 143–152.
- Kastner, S., De Weerd, P., Desimone, R., Ungerleider, L.G., 1998. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science* 282, 108–111.
- Leichnetz, G.R., 1990. Preoccipital cortex receives a differential input from the frontal eye field and projects to the pretectal olivary nucleus and other visuomotor-related structures in the rhesus monkey. *Vis. Neurosci.* 5, 123–133.
- Livingstone, M.S., Hubel, D.H., 1987. Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J. Neurosci.* 7, 3416–3468.
- Lunenburg, L., Kleiser, R., Stuphorn, V., Miller, L.E., Hoffmann, K.P., 2001. A possible role of the superior colliculus in eye–hand coordination. *Prog. Brain Res.* 134, 109–125.
- Marcar, V.L., Loenneker, T., 2000. The BOLD response: a new look at an old riddle. *NeuroReport* 15, 1997–2000. (Review).
- Marcar, V.L., Loenneker, T., Straessle, A., Jaggy, S., Kucian, K., Martin, E., 2004. An fMRI study of the cerebral macro network involved in ‘cue invariant’ form perception and how it is influenced by stimulus complexity. *NeuroImage* 23, 947–955.
- Marzi, C.A., Tassinari, G., Aglioti, S., Lutzemberger, L., 1986. Spatial summation across the vertical meridian in hemianopsia: a test of blindsight. *Neuropsychologia* 24, 749–758.
- Marzi, C.A., Perani, D., Tassinari, G., Colletuori, A., Maravita, A., Miniussi, C., Paulesu, E., Scifo, P., Fazio, F., 1999. Pathways of interhemispheric transfer in normals and in a split-brain subject. A positron emission tomography study. *Exp. Brain Res.* 126, 451–458.
- McMains, S.A., Somers, D.C., 2004. Multiple spotlights of attentional selection in human visual cortex. *Neuron* 42, 677–686.
- Miller, J., 1982. Divided attention: evidence for coactivation with redundant signals. *Cogn. Psychol.* 14, 247–279.
- Miller, J., 1986. Timecourse of coactivation in bimodal divided attention. *Percept. Psychophys.* 40, 331–343.
- Miller, J., 1991. Channel interaction and the redundant-targets effect in bimodal divided attention. *J. Exp. Psychol. Hum. Percept. Perform.* 17, 160–169.
- Miller, J., Reynolds, A., 2003. The locus of redundant-targets and nontargets effects: evidence from the psychological refractory period paradigm. *J. Exp. Psychol. Hum. Percept. Perform.* 29, 1126–1142.
- Miniussi, C., Girelli, M., Marzi, C.A., 1998. Neural site of the redundant target effect electrophysiological evidence. *J. Cogn. Neurosci.* 10, 216–230.
- Moran, J., Desimone, R., 1985. Selective attention gates visual processing in the extrastriate cortex. *Science* 229, 782–784.
- Mordkoff, J.T., Yantis, S., 1991. An interactive race model of divided attention. *J. Exp. Psychol. Hum. Percept. Perform.* 17, 520–538.
- Mordkoff, J.T., Yantis, S., 1993. Dividing attention between color and shape: evidence of coactivation. *Percept. Psychophys.* 53, 357–366.
- Murray, M.M., Foxe, J.J., Higgins, B.A., Javitt, D.C., Schroeder, C.E., 2001. Visuo-spatial neural response interactions in early cortical processing during a simple reaction time task: a high-density electrical mapping study. *Neuropsychologia* 39, 828–844.
- Omura, K., Tsukamoto, T., Kotani, Y., Ohgami, Y., Minami, M., Inoue, Y., 2004. Different mechanisms involved in interhemispheric transfer of visuomotor information. *NeuroReport* 15, 2707–2711.
- Raab, D.H., 1962. Statistical facilitation of simple reaction times. *Trans. N. Y. Acad. Sci.* 24, 574–590.
- Reuter-Lorenz, P.A., Stanczak, L., 2000. Differential effects of aging on the functions of the corpus callosum. *Dev. Neuropsychol.* 18, 113–137.
- Reuter-Lorenz, P.A., Nozawa, G., Gazzaniga, M.S., Hughes, H.C., 1995. Fate of neglected targets: a chronometric analysis of redundant target effects in the bisected brain. *J. Exp. Psychol. Hum. Percept. Perform.* 21, 211–230.
- Roser, M., Corballis, M.C., 2002. Interhemispheric neural summation in the split brain with symmetrical and asymmetrical displays. *Neuropsychologia* 40, 1300–1312.
- Roser, M., Corballis, M.C., 2003. Interhemispheric neural summation in the split brain: effects of stimulus colour and task. *Neuropsychologia* 41, 830–846.
- Saron, C.D., Schroeder, C.E., Foxe, J.J., Vaughan Jr., H.G., 2001. Visual activation of frontal cortex: segregation from occipital activity. *Brain Res. Cogn. Brain Res.* 12, 75–88.
- Sasaki, Y., Vanduffel, W., Knutsen, T., Tyler, C., Tootell, R., 2005. Symmetry activates extrastriate visual cortex in human and nonhuman primates. *Proc. Natl. Acad. Sci. U. S. A.* 102, 3159–3163.
- Savazzi, S., Marzi, C.A., 2002. Speeding up reaction time with invisible stimuli. *Curr. Biol.* 12, 403–407.
- Savazzi, S., Marzi, C.A., 2004. The superior colliculus subserves interhemispheric neural summation in both normals and patients with a total section or agenesis of the corpus callosum. *Neuropsychologia* 42, 1608–1618.
- Schulte, T., Pfefferbaum, A., Sullivan, E.V., 2004. Parallel interhemispheric processing in aging and alcoholism: relation to corpus callosum size. *Neuropsychologia* 42, 257–271.
- Schulte, T., Muller-Oehring, E.M., Rosenbloom, M.J., Pfefferbaum, A., Sullivan, E.V., 2005a. Differential effect of HIV infection and alcoholism on conflict processing, attentional allocation, and perceptual load: evidence from a Stroop match-to-sample task. *Biol. Psychiatry* 57, 67–75.
- Schulte, T., Sullivan, E.V., Muller-Oehring, E.M., Adalsteinsson, E., Pfefferbaum, A., 2005b. Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb. Cortex* 15, 1384–1392.
- Seidemann, E., Newsome, W.T., 1999. Effect of spatial attention on the responses of area MT neurons. *J. Neurophysiol.* 81, 1783–1794.
- Servos, P., Osu, R., Santi, A., Kawato, M., 2002. The neural substrates of biological motion perception: an fMRI study. *Cereb. Cortex* 12, 772–782.
- Talairach, J., Tournoux, P.A., 1988. *A co-Planar Stereotaxic Atlas of The Human Brain*. Thieme, Stuttgart.

- Tettamanti, M., Paulesu, E., Scifo, P., Maravita, A., Fazio, F., Perani, D., Marzi, C.A., 2002. Interhemispheric transmission of visuomotor information in humans: fMRI evidence. *J. Neurophysiol.* 88, 1051–1058.
- Theeuwes, J., 1994. The effects of location cuing on redundant-target processing. *Psychol. Res.* 57, 15–19.
- Treue, S., Maunsell, J.H., 1996. Attentional modulation of visual motion processing in cortical areas MT and MST. *Nature* 382, 539–541.
- Turatto, M., Mazza, V., Savazzi, S., Marzi, C.A., 2004. The role of the magnocellular and parvocellular systems in the redundant target effect. *Exp. Brain Res.* 158, 141–150.
- Van Essen, D.C., Newsome, W.T., Bixby, J.L., 1982. The pattern of interhemispheric connections and its relationship to extrastriate visual areas in the macaque monkey. *J. Neurosci.* 2, 265–283.
- Wust, S., Kasten, E., Sabel, B.A., 2002. Blindsight after optic nerve injury indicates functionality of spared fibers. *J. Cogn. Neurosci.* 14, 243–253.