Parallel interhemispheric processing in hemineglect: Relation to visual field defects

Eva M. Müller-Oehring, Tilman Schulte, Erich Kasten, Dorothe A. Poggel, Bernhard A. Sabel

Abstract

Parallel interhemispheric processing is required to explore our visual environment and to integrate visual information from both hemifields simultaneously. Damage to the right temporoparietal cortex can disrupt such parallel processing and result in neglect and visual extinction of stimuli in the left contralesional visual space. Neglected or extinguished stimuli can still be processed, yet without reaching the patient’s awareness. Such unconscious processing has been attributed to structurally intact primary visual areas in neglect. To study whether unconscious parallel processing depends on visual functional integrity, we compared the performance of neglect patients with visual field defects (VFDs) (n = 11) and hemianopic patients with partial or complete blindness of one visual hemifield (n = 11) on redundant targets effects (RTE). The RTE manifests as faster reaction times to redundant paired (two stimuli, one in each hemifield) than single stimulation (in one hemifield). We found RTEs, i.e., unconscious processing, in neglect patients but not in hemianopic patients. Furthermore, neglect patients showed large crossed–uncrossed differences (CUDs), i.e., faster response times to ipsi- than contralesional hemifield stimulation, reflecting a difference in processing speed for single stimuli in the two hemispheres that were correlated with VFDs and visual extinction. The finding that extinction, but not RTE, was correlated with the CUD suggests that under competitive bilateral stimulus conditions the delayed contralesional visual field input may not be detected by the intact left hemisphere, which presumably mediates the task given the impairment of the right hemisphere. By contrast, unconscious parallel processing of contralesional stimuli (RTE) occurred even when contralesional visual field input is lacking (VFD) or delayed (CUD) and is possibly mediated via subcortical visual pathways.

1. Introduction

Parallel interhemispheric processing is required to explore our visual environment and to integrate visual information from both hemifields simultaneously. Temporoparietal lobe damage, particularly to the right hemisphere, often results in visuospatial neglect of stimuli in the left visual space. Patients with visuospatial neglect fail to report, orient towards, or respond to stimuli contralateral to their lesions, a deficit that is not caused by primary motor or sensory dysfunction (Barrett et al., 2006; Heilman, Bowers, Coslett, Whelan, & Watson, 1985). Extinction is one aspect of neglect and is characterized by the perception of a contralesional stimulus when presented alone, but not when presented in conjunction with an ipsilesional stimulus, i.e., when it is extinguished from awareness in competitive situations (Brooks, Wong, & Robertson, 2005; Driver & Vuilleumier, 2001). It has been suggested that visual extinction reflects a deficit in the integration of visual information from both hemifields and can occur after unilateral brain damage (Marzi, Girelli, Natale, & Miniussi, 2001; Vuilleumier & Rafal, 2000) and section of the corpus callosum, a thick band of white matter fibers connecting the two cerebral hemispheres (Pollmann & Zaidel, 1998; Reuter-Lorenz, Nozawa, Gazzaniga, & Hughes, 1995).

Even though neglect patients do not report or react to contralateral stimuli, they may process perceptual stimulus properties unconsciously (Driver & Mattingley, 1998; Driver & Vuilleumier, 2001; Farah & Feinberg, 1997; Marzi, Girelli, Miniussi, Smania, &
Maravita, 2000; Mesulam, 1999; Rees et al., 2000; Volpe, Ledoux, & Gazzaniga, 1979). Volpe et al. (1979), for example, described four neglect patients with right parietal tumors who were not able to name objects presented in the left visual field, but succeeded in making correct same–different judgments on pairs of stimuli presented bilaterally. The same phenomenon was observed by Berti et al. (1992) in a patient with lobectomy of the right temporal lobe. These and other findings (e.g., Audet, Bub, & Lecours, 1991; Berti, Frassinetti, & Umlita, 1994; Marzi et al., 1996) suggest that contralesional stimuli can be processed, even when processing is not sufficient for conscious stimulus identification. Single case functional neuroimaging studies in neglect patients revealed that extinguished contralesional stimuli activated primary visual cortex and extrastriate visual areas in the damaged right hemisphere (Rees et al., 2000; Vuilleumier, Schwartz, Husain, Clarke, & Driver, 2001). Thus, it was hypothesized that unconscious stimulus processing in neglect patients relies on preserved visual functions but is restrained from conscious perception due to damage of higher-order processes responsible for coding of visuospatial attention (Rees et al., 2000; Vuilleumier et al., 2001; see Driver & Vuilleumier, 2001 for a review).

Another case of unconscious stimulus processing, albeit rare, is blindsight, which may be evident in patients with visual field defects due to lesions of visual pathways (Lachennay & Vivell, 1992; Zhang, Kedar, Lynn, Newman, & Bisouss, 2006). These patients have blind areas of the visual field, yet can still localize, detect and discriminate between unseen stimuli in the blind visual field (Blythe, Kennard, & Ruddock, 1987; Corbetta, Marzi, Tassinari, & Aglioti, 1990; Pererin & Jeannerod, 1978; Poppel, Held, & Frost, 1973; Pitto, Lepore, Pitto, & Lassonde, 1991; Stoerig, Hubner, & Poppel, 1985; Tassinari, Aglioti, Pallini, Berlucchi, & Rossi, 1994; Tomaiuolo, Pitto, Marzi, Paus, & Pitto, 1997; Weiskrantz, 1986). Visuospatial neglect and visual field loss can co-occur, providing an opportunity to investigate whether preserved visual functions are necessary for unconscious stimulus processing in patients with neglect (Kooistra & Heilman, 1989; Muller-Oehring et al., 2003; Walker, Findlay, Young, & Welch, 1991). Study of these patients may reveal further information about what brain systems may be involved in unconscious stimulus processing.

To investigate unconscious stimulus processing in neglect and visual field defects, we used the redundant targets paradigm. In this paradigm, shorter reaction times (RTs) are obtained when two stimuli are presented simultaneously in comparison to single stimulus presentations. This effect is called the redundant targets effect (RTE) and has been investigated in healthy subjects (e.g., Miller, 1982; Mordkoff, Miller, & Roch, 1996; Raab, 1962), patients with unilateral brain lesions (e.g., Marzi et al., 1996; Corbells, Corbells, Fabri, Paggi, & Manzoni, 2005) and split-brain patients (e.g., Corbells, Hamm, Barnett, & Corbells, 2000; Iacoboni, Pitto, Weekees, & Zaidel, 2000; Reuter-Lorenz et al., 1995). With this paradigm, unconscious processing in patients with unilateral brain lesions cannot be explained by the use of a lax decision criterion, because the patient is supposed to respond to stimuli in the normal hemifield only and is not asked to guess about the presence of a stimulus in the contralesional hemifield or to make a decision about the similarity of stimuli in each hemifield (Campion, Latto, & Pizzuti, 1983).

Neuromaging and lesion studies on parallel processing using the RTE paradigm suggest an underlying network involving extrastriate visual and extrastriate visual areas in the damaged right hemisphere (Rees et al., 2000; Vuilleumier et al., 2001; see Driver & Vuilleumier, 2001 for a review). The RTE paradigm suggest an underlying network involving extras-
Fig. 1. (a) High-resolution perimetry (HRP) data of patients with visuospatial neglect. (b) High-resolution perimetry (HRP) data of hemianopic patients. Visual field defects (VFD) range from partial to complete homonymous hemianopia. HRP measurements of each patient were superimposed, white and black areas representing intact and blind regions, respectively, and grey areas representing regions in which stimulus detection is unreliable. Each graph shows patient ID, age and sex. Size of visual field displayed in degrees of visual angle (°), i.e., 52° (±26°) horizontally and 40° (±22°) vertically.

Each subject performed a practice and three test trials. Participants were encouraged to complete each page as fast as possible. Sheets of paper were aligned to the body midline of the patient while testing. Left- and right-sided misses were analyzed. Completion times per page were recorded using a stopwatch. For confrontation testing of visual extinction, the patients had to indicate the experimenter’s movement of one versus both hands, positioned in the left and right visual field, respectively, while steadily fixating on the experimenter’s nose. This test was given to six neglect patients who reacted to single stimulus presentations in the contralesional visual field.

Eight patients showed symptoms of hemispatial neglect on the BIT (Table 3a). Three patients who presented severe neglect immediately after infarction showed neglect symptoms only under speed conditions in the cancellation task (ratio of left-to right-sided misses for each patient: 14/2; 7/1; 10/4) at the time of testing (3, 8, and 41 months post lesion). However, these patients had difficulties in every-day

<table>
<thead>
<tr>
<th>Table 1a</th>
<th>Demographic and clinical data of the study groups.</th>
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<tbody>
<tr>
<td></td>
<td>Age (years)</td>
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<tr>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>50 ± 13</td>
</tr>
<tr>
<td>Neglect</td>
<td>64 ± 11</td>
</tr>
</tbody>
</table>
| AL = age of lesion, VF % = percent of intact visual field, Fix % = fixation ability, i.e., percent correct responses, diagnosis of neglect: n, number of occurrences.
activities as reported by relatives or the patients themselves that led to the assumption of residual neglect; e.g., bumping into an opened door, not searching for objects located on the person's left, choosing the right one of two seats; the tendency to spontaneously turn rightward after leaving a room. The neglect patients’ mean BIT score was 126 ± 15 (SD) (n = 11; maximum score: 146). In contrast, all patients of the hemianopic group reached high scores in the BIT test (143 ± 2), which corresponds to the absence of visuospatial neglect. The score difference between these groups was highly significant (p < .0001; Mann–Whitney U). In the speed cancellation task, groups were significantly different in the contra- to ipsilesional ratio of misses with the neglect group showing significantly more contralesional misses (p < .001; Mann–Whitney U-test).

To confirm the diagnosis of hemianopia all patients underwent standard perimeter testing on a Tubinger Automated Perimeter (TAP-2000). For a spatially more detailed assessment of the central visual field, high-resolution perimetry (HRP) was also applied in repeated sessions (for a detailed description see Kasten, Strasburger, & Sabel, 1997). Since all visual field defects were approximately homonymous in the TAP-2000 measurements, HRP measurements were carried out binocularly. Subjects viewed stimuli on a 17” computer monitor at a viewing distance of 30 cm. Using a forehead–chin rest to minimize head movements during testing, the resulting visual angle was ±27° horizontally and ±20° vertically. HRP measurements of each patient were repeated three times and superimposed. Here, white and black areas represent intact and blind regions, and grey areas show regions in which stimulus detection was unreliable, i.e., in which a stimulus was not detected in all trials, either due to residual vision (Kasten, Wuest, & Sabel, 1998) or to limited attentional capacities. In a previous evaluation of HRP data, Kasten, Gothe, Bunzenthal, & Sabel (1999) showed that visual field data measured by TAP-2000 and by HRP are highly compatible (r = .78; p < .05).

2.2. Redundant targets paradigm

Stimuli were filled green circles (96 cd/m²), 1.5° in visual angle on grey background (44 cd/m²). The ratio of stimulus to background luminance minimized light radiation of stimulation across visual field locations. Stimuli were presented at four locations within the visual field, at ±13.3° and ±24.7° vertical eccentricity, and 6.7° above the horizontal meridian to avoid the blind spot. Each stimulus was presented for 20 ms. Stimuli were presented either alone or in pairs. We presented unilateral and bilateral paired stimulation: unilateral paired presentations to the left or to the right visual hemifield, and bilateral presentations to both hemifields with paired stimuli located at ±13.3° eccentricity (Fig. 3).

Fig. 2. (a) Schematic illustration of the lesion location of the neglect patient group (n = 11). (b) Schematic illustration of the lesion location of the hemianopic patient group (n = 11). Each patient's lesion data from radiologic scans were transposed into the Talairach-space using the program MRICro (Chris Rorden) and standardized into Talairach standard brain and then superimposed using MatLab 5.3. Figures show 15 transversal slices of the brain. Scale: percentage of overlap of lesion locations of the patients within one group, white = 100%, black 10% overlap. A = anterior; P = posterior; R = right cerebral hemisphere; L = left cerebral hemisphere.
Stimuli were presented in 9 blocks of 50 trials each. Stimulation conditions were randomly mixed. Twenty single trials (10 in the right and 10 in the left visual field) and 30-paired trials (10 in the right and 10 in the left visual field and 10 bilateral) were presented. Fixation performance was assessed by occasional brief color-changes of 150 ms duration of the fixation point which was positioned in the middle of the screen. All subjects used the right hand to press the space bar to indicate detection of a stimulus or a color-change of the fixation point. Subjects sat in a darkened room (1.5 lx/m²) 30 cm distance in front of a 17″ monitor, stabilized by a forehead–chin rest to prevent head movement. Body axis was aligned straight ahead and participants were instructed to sit with their arms and legs separated to avoid cross-cueing. Reaction times shorter than 150 ms were taken as anticipations and those longer than 900 ms as prolonged responses and were eliminated from statistical analysis of reaction time.

2.3. Testing the race model

The ‘race model’ (Raab, 1962) assumes that the processing of two simultaneous stimuli is stochastically independent. With parallel processing, the reaction to the stimulation is driven by the stimulus processed first, i.e., the one that won the race. With two stimuli (paired) the probability of shorter reaction times is twice as high as for the sum of two single stimuli, i.e., probability summation may explain the observed RT shortening. When RTs to redundant targets are even shorter than the race model would predict, i.e., an enhanced redundancy gain, some kind of co-activation can be assumed and a neural summation process has been inferred (Corballis et al., 2002; Miniussi, Girelli, & Marzi, 1998; Savazzi & Marzi, 2002; Turatto, Mazza, Savazzi, & Marzi, 2004).

Thus, according to the race model the stimulus winning the processing race will initiate the response, and with two stimuli a faster response is more likely than with one stimulus alone (probability summation). However, the probabilities for stimulus 1 ($P_{S1}$) and for stimulus 2 ($P_{S2}$) may be independent of one another (Meijers & Eijkman, 1974) or not (Duncan, 1980). Probability models assume (Miller, 1982):

$$P(\text{RT}_{S1S2}) \leq P(\text{RT}_{S1}) + P(\text{RT}_{S2}) \quad (1)$$

$P(\text{RT}_{S1})$ and $P(\text{RT}_{S2})$ is the probability of a response evoked by stimulus 1 and stimulus 2 at a given time, $P(\text{RT}_{S1S2})$ is the probability of a response to both stimuli in a given time. Eq. (1) provides an upper limit of the gain achieved by the detection of redundant targets (Miller, 1982). By transforming Eq. (1) into Eq. (2) it can be determined if the shortening of RTs under double stimulation conditions violates the predictions of the race model (Iacoboni et al., 2000). That is, the cumulative distribution function (CDF) for redundant targets ($P(\text{RT}_{S1S2})$) is compared with the sum of CDFs for single targets, $P(\text{RT}_{S1}) + P(\text{RT}_{S2})$, by using the race measure (Reuter-Lorenz et al., 1995):

$$R(t) = P(\text{RT}_{S1S2}) - [P(\text{RT}_{S1}) + P(\text{RT}_{S2})]$$

$$R(t) = P(\text{RT}_{S1S2}) - [P(\text{RT}_{S1}) + P(\text{RT}_{S2})]$$

(2)
When computing the race measure \( R(t) \) only values can be evaluated with \( P(\text{RT}_1) + P(\text{RT}_2) \leq 1 \). Positive values indicate that RTs to redundant targets are faster than the race model would predict.

This method was successfully applied in split-brain and stroke studies (Corballis, 1998; Iacoboni et al., 2000; Marzi et al., 1996; Reuter-Lorenz et al., 1995). Cerebral cortices of both hemispheres are intact in split-brain patients and healthy subjects, and an equal probability for RTs to S1 and S2 can be assumed. This is not the case in patients with unilateral brain lesions (Marzi et al., 1996). Ipsilateral stimuli have some benefits in processing speed. First, the left undamaged hemisphere can process ipsilesional (right) stimuli, and when the motor response is also performed with the right hand (as in our neglect patients because of a weakness in the contralesional upper limb), both processes can be performed within the intact hemisphere. Second, the probabilities were compared according to Eq. (2). Second, mean RT of all nine blocks was computed for each point in the ranking sequence of RTs (cumulative distribution function, CDF) for each condition in each subject. Third, the probabilities were compared according to Eq. (2).

2.4. Crossed–uncrossed difference (CUD)

We calculated the CUD with responses from the right hand in our patients. The CUD calculation was: \( [\text{right hand/LVF RTs} - \text{right hand/RVF RTs}] \). In the current study, we modified the paradigm to use only one hand for two reasons: (1) because of a weakness in the contralesional upper limb; (2) the reason for using two hands in the Poffenberger paradigm is to control for interfield differences. Yet, patients with neglect and those with visual field defects have interfield differences because of their unilateral brain damage. These differences cannot be controlled for. In principle crossed–uncrossed differences that are calculated with one hand only can reflect processing a stimulus as a function of visual field location (Van Essen, Newsome, & Maunsell, 1984).

Table 1b

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>AL (months)</th>
<th>VFD</th>
<th>Neglect</th>
<th>Extinction</th>
<th>Lesion side</th>
<th>Lesion site</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>51</td>
<td>M</td>
<td>6</td>
<td>+</td>
<td>Sev.</td>
<td>R</td>
<td>PO</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>75</td>
<td>M</td>
<td>3</td>
<td>+</td>
<td>Sev.</td>
<td>R</td>
<td>TP</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>62</td>
<td>M</td>
<td>8</td>
<td>+</td>
<td>Res.</td>
<td>+</td>
<td>R</td>
<td>TP</td>
<td>+</td>
</tr>
<tr>
<td>N4</td>
<td>68</td>
<td>M</td>
<td>17</td>
<td>+</td>
<td>Mild</td>
<td>+</td>
<td>R</td>
<td>T</td>
<td>+</td>
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<tr>
<td>N5</td>
<td>72</td>
<td>M</td>
<td>3</td>
<td>+</td>
<td>Res.</td>
<td>+</td>
<td>R</td>
<td>PO</td>
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<tr>
<td>N6</td>
<td>61</td>
<td>M</td>
<td>11</td>
<td>+</td>
<td>Sev.</td>
<td>+</td>
<td>R</td>
<td>P</td>
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<tr>
<td>N7</td>
<td>49</td>
<td>F</td>
<td>41</td>
<td>+</td>
<td>Res.</td>
<td>(+)</td>
<td>R</td>
<td>TP</td>
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<tr>
<td>N8</td>
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<td>M</td>
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<td>-</td>
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<td>+</td>
<td>R</td>
<td>P</td>
<td>+</td>
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<tr>
<td>N9</td>
<td>84</td>
<td>M</td>
<td>9</td>
<td>+</td>
<td>Mild</td>
<td>R</td>
<td>TPO</td>
<td>-</td>
<td></td>
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<tr>
<td>N10</td>
<td>73</td>
<td>M</td>
<td>20</td>
<td>+</td>
<td>Sev.</td>
<td>+</td>
<td>R</td>
<td>PO</td>
<td>+</td>
</tr>
<tr>
<td>N11</td>
<td>62</td>
<td>M</td>
<td>3</td>
<td>+</td>
<td>Mild</td>
<td>+</td>
<td>R</td>
<td>PO</td>
<td>+</td>
</tr>
<tr>
<td>H1</td>
<td>74</td>
<td>M</td>
<td>3</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td>59</td>
<td>M</td>
<td>24</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>O</td>
<td>+</td>
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<tr>
<td>H3</td>
<td>67</td>
<td>M</td>
<td>3</td>
<td>+</td>
<td>–</td>
<td>L</td>
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<tr>
<td>H4</td>
<td>61</td>
<td>M</td>
<td>3</td>
<td>+</td>
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<td>O</td>
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<tr>
<td>H5</td>
<td>42</td>
<td>M</td>
<td>216</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>TO</td>
<td>–</td>
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</tr>
<tr>
<td>H6</td>
<td>36</td>
<td>M</td>
<td>8</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>TP</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>H7</td>
<td>48</td>
<td>M</td>
<td>18</td>
<td>+</td>
<td>–</td>
<td>L</td>
<td>PO</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>H8</td>
<td>47</td>
<td>F</td>
<td>92</td>
<td>+</td>
<td>–</td>
<td>L</td>
<td>O</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>H9</td>
<td>38</td>
<td>F</td>
<td>116</td>
<td>+</td>
<td>–</td>
<td>R</td>
<td>O</td>
<td>–</td>
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<tr>
<td>H10</td>
<td>37</td>
<td>F</td>
<td>35</td>
<td>+</td>
<td>–</td>
<td>R</td>
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<td>H11</td>
<td>41</td>
<td>F</td>
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<td>+</td>
<td>–</td>
<td>L</td>
<td>O</td>
<td>–</td>
<td></td>
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</tbody>
</table>

H = hemispheric group; N = neglect group; AL = age of lesion; VFD = presence of a visual field defect in perimetry; M = male; F = female; Sev. = severe; Mild = mild; Res. = residual, R = right; L = left; F = frontal; P = parietal; T = temporal; O = occipital; SC = subcortical

H = hemispheric group; N = neglect group; AL = age of lesion; VFD = presence of a visual field defect in perimetry; M = male; F = female; Sev. = severe; Mild = mild; Res. = residual, R = right; L = left; F = frontal; P = parietal; T = temporal; O = occipital; SC = subcortical

### Stimulus conditions:

- **Single:** Stimuli are illustrated as white dots on a grey computer monitor background. During the task, fixation performance was assessed by occasional brief color-changes of 150 ms duration of the fixation point, which was positioned in the middle of the screen, here illustrated as a black dot.

**Fig. 3.** Redundant targets paradigm with five stimulus conditions: single stimuli in the left or in the right visual field; paired stimuli in the left or right visual field (paired unilateral); paired stimuli with one stimulus in each hemifield (paired bilateral). Stimuli are illustrated as white dots on a grey computer monitor background. During the task, fixation performance was assessed by occasional brief color-changes of 150 ms duration of the fixation point, which was positioned in the middle of the screen, here illustrated as a black dot.
3. Results

3.1. Reaction time and age

Mean reaction times (RTs) of each condition of the RTE paradigm were examined. The two clinical groups differed significantly in all conditions with neglect patients showing longer RTs (Table 2).

Age did not correlate with RT in either patient group or condition (for N: Rho = 0.00–0.07, n.s.; for H: Rho = 0.04 to 0.39, n.s.; for all conditions). Because neglect patients were older (Table 1) and showed longer reaction times than hemianopic patients, we tested for the contribution of age and group using multiple regression analysis. Mean-centered age values (individual age minus mean for the study groups “neglect” (N) and “hemianopia” (H). RTs to contralesional stimulations were entered as predictors for each analysis. Mean-centered age values (individual age minus mean for the contribution of age and group using multiple regression showed longer reaction times than hemianopic patients, we tested

Comparison of mean reaction times (RTs) in ms (±standard deviations) to single and paired stimulations to contralesional, ipsilesional and both (bilateral) visual hemifields in the study groups “neglect” (N) and “hemianopia” (H). RTs to contralesional stimulations were obtained in five patients with neglect.

Table 2

<table>
<thead>
<tr>
<th>Visual field</th>
<th>Stimulation</th>
<th>Study groups</th>
<th>Mann–Whitney U-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Neglect</td>
<td>Hemianopia</td>
</tr>
<tr>
<td>Contralesional (defect)</td>
<td>Single</td>
<td>562 ± 117</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Paired</td>
<td>569 ± 138</td>
<td>–</td>
</tr>
<tr>
<td>Ipsilesional (intact)</td>
<td>Single</td>
<td>489 ± 97</td>
<td>391 ± 51</td>
</tr>
<tr>
<td></td>
<td>Paired</td>
<td>478 ± 84</td>
<td>390 ± 56</td>
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<tr>
<td>Bilateral</td>
<td>Paired</td>
<td>481 ± 99</td>
<td>393 ± 53</td>
</tr>
</tbody>
</table>

3.2. RTE: parallel processing in patients with neglect and hemianopia

The primary goal of the present study was to determine parallel processing mechanisms for contra- and ipsilesional stimulation in patients with neglect and visual field defects. Redundant targets effects (RTEs) describe faster RTs to bilateral paired (S1S2) than unilateral single stimulation in the ipsilesional VF (S2) and redundancy gains indicate processing of both stimuli.

3.2.1. RTE — group statistic

Hemianopic patients as a group showed no redundancy gain (bilateral summation: RTE = 2.36 ms, Z = −.87, n.s.) with almost identical RTs in ‘single ipsilesional’ and ‘paired ipsilesional’ conditions, whereas neglect patients showed significant redundancy gains (RTE = 7.5 ms, Z = −2.3, p < 0.02; two-tailed, Wilcoxon test). To test the relationship between RTEs and visual field defects (VFDs) in neglect patients, RTEs were correlated with the percentage of stimulus detection in perimetry (HRP) at the respective visual field location of contralesional stimulation in the RTE paradigm. No significant relationships emerged between stimulus detection rate (in %) and amount of redundancy gains in neglect patients (Rho = −.15, n.s.). Since this finding was unexpected, we tested the validity of the results by correlating detection rates of single stimuli in both tests (perimetry and RTE paradigm) for comparative locations, and found a highly significant correlation (Rho = .80, p < .003) suggesting validity of measurements.

Furthermore, unilateral redundancy gains were computed as control condition by comparing mean RTs of unilateral single stimulation to unilateral paired stimulation in the ipsilesional intact hemifield. Both groups did not exhibit significant RTEs for unilateral conditions (hemianopia: RTE = 0.59 ms, Z = −.71, n.s., n = 11; neglect: RTE = 10.6 ms, Z = −1.2, n.s.; Wilcoxon test).

3.2.2. Single case statistic

For further testing of the RTE phenomenon and its relationships to visual field defects redundancy gains were analyzed for each patient individually.

Fig. 4. Single case analyses of the redundant targets effect (RTE). Mean reaction times of each patient for three stimulus conditions: single ipsilesional (intact visual field), paired ipsilesional (intact visual field), and paired bilateral stimulation (intact + defect visual field). Left: neglect patients; right: hemianopic patients. *1: bilateral summation, p < .05; *2: unilateral summation, p < .05; *p ≤ .05 and ≤ .1 (ANOVA, and comparison of single conditions, LSD-test).
Single case analysis of RTEs confirmed that none of the hemianopic patients showed redundancy gains, neither uni- nor bilaterally. Instead, two hemianopic patients (H6, H9) tended to show longer RTs with bilateral paired than single stimulation ($p \geq .05$ to $\leq .1$). In the neglect group, five patients exhibited significant RTEs for bilateral stimulation conditions, two of them also showed RTEs for unilateral conditions (ANOVA with one factor, and post hoc analysis between the conditions using the LSD-test) (Fig. 4).

Two of these five neglect patients with significant RTEs had complete hemianopias (N1 and N9), two had incomplete hemianopias (N10 and N11), and one had no visual field defect (N8). Surprisingly, neglect patients with RTEs and those without RTEs did not differ in stimulus detection rates in perimetry (HRP) at the visual field location that matched the test location of $S_1$ contralateral in the RTE paradigm (HRP detection rate in patients with RTE: $47 \pm 23\%$, $n = 5$; in patients without RTE: $40 \pm 15\%$, $n = 6$; $t = -.24$, n.s.) supporting the group finding (3.1) and indicating independence between RTEs and VFDs in neglect.

To examine the underlying mechanisms of RTEs in neglect patients we further tested the race model. Analyses indicated violations of the race model predictions (positive values on the y-axis) in all five neglect patients with significant RTEs (Fig. 5). Three additional neglect patients with small RTEs (N3, N5, and N7) also showed some violations of the race model, but only for RTs faster than 400 ms.

### 3.3. Crossed–uncrossed difference (CUD)

Five patients in the neglect group (N3, N4, N8, N10, and N11) responded to stimuli presented in the visual field contralateral to the lesion. Detection rate of contralesional stimulations was highly variable between patients (single$_{contralesional}$ ($S_1$): 52% in average; range 13–99%; paired$_{contralesional}$ ($S_1S_1$): 57% in average; range 18–100%). Reaction times to stimuli in the contralesional hemifield were significantly prolonged compared to stimuli appearing in the ipsilesional hemifield ($Z(S_i vs. S_c) = -2.02$, $p < .05$; $Z(P_i vs. P_c) = -2.02$, $p = .05$; $n = 5$). The mean CUD for single trials was 124.8 ms (see Table 3) and for paired trials 120 ms.

#### 3.3.1. CUD and extinction

Extinction rate was obtained in six neglect patients and the CUD in four of these six patients (Table 3). Although the sample was small, a high and significant correlation between extinction rate and CUD was observed ($Rho = .95$, $p = .05$, $n = 4$).

#### 3.3.2. CUD and visual field defects (VFD) in neglect patients

In order to test the relationship between CUDs and visual field effects, the percentage of stimuli detected in high-resolution perimetry (HRP) was extracted for those visual field locations that matched the stimulus locations in the RTE paradigm. CUDs did not significantly correlate with the percentage of detected contralesional stimuli in HRP ($Rho = .58$, n.s., $n = 5$). However, mean RTs to contralesional stimuli were related to VFD ($Rho = -.95$, $p = .02$, $n = 5$), i.e., longer RTs to left-sided stimuli were associated with lower detection rates in HRP.

### Table 3

Comparison of visual extinction rate (number bilateral trials with extinction and percent) with CUDs (difference RTs of contra- minus ipsilesional single stimulation) for six neglect patients with responses to single contralesional stimulation. Two neglect patients (N6 and N7) reacted to contralesional stimulation with finger confrontation testing but not with computerized testing, presumably because of short stimulus presentation times of 20 ms in the computer test.

<table>
<thead>
<tr>
<th>Patient code</th>
<th>Extinction rate Out of 40</th>
<th>CUD (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N3</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>N4</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>N6</td>
<td>38</td>
<td>95</td>
</tr>
<tr>
<td>N7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>N8</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>N11</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>
3.4. **VFDs and ipsilesional motor responses**

In principle, VFDs may reduce the strength of perceived stimuli and therefore modify reaction time. To tests whether visual field deficits modified reaction time given with the ipsilesional hand, we correlated RTs in the RTE paradigm with the size of VFD (including absolute and relative defects using the Tuebingen Automated Perimeter, TAP-2000; relative VFD means that stimuli were detected with a heightened luminance threshold). We found no relationship between visual field defects and RTs for the ipsilesional hand (hemianopic group: $Rho = \pm 15$, n.s., $n = 11$; neglect group: $Rho = \pm 11$, n.s., $n = 11$ for $RT_{rightVF}$, $Rho = \pm 30$, n.s., $n = 5$ for $RT_{leftVF}$).

4. Discussion

The majority of visual neglect patients lacked responses to contralesional stimuli in both perimetric measurements and the RTE paradigm. Only five neglect patients reacted to contralesional stimuli in the RTE paradigm. Contralesional responses were prolonged compared to RTs to stimuli in the ipsilesional visual field, i.e., neglect patients showed large CUDs. Large CUDs have been previously reported in patients with unilateral temporal–parietal brain damage (Kaizer, Kornet-Bitensky, Mayo, Becker, & Coopersmith, 1988; Marzi et al., 1996, 1997; Posner, Walker, Friedrich, & Rafal, 1984; Vuilleumier & Rafal, 2000), and are not unexpected because damage to visual association areas can be associated with disconnection between perceiving sensory and motor areas responsible for action planning and execution (Catani & ffytche, 2005). As a result, responses are delayed or behavioral output is not accomplished.

Despite such prolonged or even absent responses to contralesional stimuli, shortening of RTs from redundant bilateral stimulation (RTE) was observed in patients with neglect. In five neglect patients, we even observed enhanced redundancy gains that violated the predictions of the race model. Thus, in these patients redundancy gain can be best explained by neural summation and, i.e., that at some stage – perceptual, cognitive, or motor – neural co-activation occurs and facilitates sensorimotor processing (Mooshegan et al., 2008; Pollmann & Zaidel, 1999; Schulte et al., 2006).

Our finding of RTEs in neglect patients suggests unconscious processing of contralesional stimuli and is consistent with previous studies reporting processing of neglected and extinguished stimuli in these patients (Berti et al., 1992; Marzi et al., 1996; Mattingley, Davis, & Driver, 1997; Rees et al., 2000; Volpe et al., 1979; Vuilleumier et al., 2001). In these studies unconscious stimulus processing in neglect was explained with the integrity of visual pathways allowing visual input to be processed in visual cortical areas but being restrained from awareness by a compromised attentional network responsible for selective attention and response selection. Yet, most neglect patients in the current study showed partial or complete visual field defects thereby questioning the relevance of visual cortex integrity for unconscious stimulus processing.

4.1. **RTE and visual field defects in neglect**

If visual cortex functional integrity is necessary for unconscious stimulus processing, RTEs should correlate with VFDs thereby supporting the residual islands hypothesis for unconscious stimulus processing (e.g., Wust, Kasten, & Sabel, 2002). In our neglect patients, however, RTEs were not related to VFDs.

Responses to stimuli in residual vision areas are typically prolonged (i.e., not shortened as in the RTE) due an abnormally weak input to the visual cortex (Muller-Oehring et al., 2003; Poggel, Kasten, Muller-Oehring, Bunzenthal, & Sabel, 2006; Poggel, Kasten, Muller-Oehring, Sabel, & Brandt, 2001). Consequently, we found that RTs to single contralesional stimuli correlated with VFDs at that same stimulus location. Thus, in neglect patients, delayed processing of contralesional stimuli, but not redundancy gains (RTEs), were related to VFDs indicating different mechanisms and possibly different cortical and subcortical pathways subserving conscious (detection) and unconscious (redundancy gains) processing of stimuli in the contralesional hemifield in visuospatial neglect. Taken together, our data suggest that unconscious parallel processing in visuospatial neglect can occur independent of visual field defects.

4.2. **CUD and extinction**

In neglect patients, larger CUDs correlated with higher extinction rates. Extinction describes the phenomenon that contralesional stimuli are extinguished from awareness under paired stimulation but can be perceived with single stimulus presentations. The interpretation of this finding is twofold; because patients responded with their ipsilesional hand only, crossed–uncrossed differences (CUDs) might be related to interfield differences rather than to interhemispheric transfer time. For example, like in our study, patients in the Marzi et al. (1997) study could only use their ipsilesional hand and therefore, similar to our design, the CUD coincided with a difference in speed between the two visual hemifields. But Marzi et al. also recorded event related brain potentials (ERPs) in their patients and found a surprising result, namely that the ipsilesional (commissural) response was lacking or reduced in patients with a right hemisphere lesion but not in patients with a left hemisphere lesion. They speculated that this laterality difference may be related to a left–right asymmetry in callosal projections with callosally projecting neurons being more numerous in the right than the left hemisphere (Marzi, Bisiacchi, & Nicoletti, 1991). Consequently, they argued, it would be reasonable to assume that unilateral right hemispheric lesions will cause a greater loss of callosal fibers than similar left-hemispheric lesions. This speculation, however, still needs to be tested with diffusion tensor magnetic resonance imaging in right- and left-brain damaged patients.

In fact, our observation that CUDs were related to extinction in neglect patients supports the assumption that input from the left visual hemifield to the intact left hemisphere is lacking or reduced (see also Marzi et al., 1997). Under competitive bilateral stimulation conditions the reduced or delayed left visual field input may not be detected by the left hemisphere, which presumably mediates the task given the impairment of the right hemisphere, and extinction may occur.

A second possible reason for our finding that larger CUD correlated with higher extinction rates could be interhemispheric transfer time that exceeds an upper time limit for conscious stimulus perception and so results in extinction of the later processed stimulus in competing bilateral stimulation conditions. Neurophysiological data in healthy subjects provide evidence for such a time limit for interhemispheric transfer of bilateral information showing visual evoked potentials (VEPs) that appeared within 86 ms over parieto-occipital scalp regions (Murray, Foxe, Higgins, Javitt, & Schroeder, 2001). Following this line of thought, inputs from different visual hemifields may not have been combined within this time window because of the processing delay for contralesional stimuli in our neglect patients (Baylis, Simon, Baylis, & Rorden, 2002; Di Pellegrino, Basso, & Frassinetti, 1997).

Alternatively, correlation between CUD and extinction may simply reflect “brightness” of perception, i.e., interfield differences
favoring the hemifield ipsilateral to the lesion. Visual demands, e.g., brightness of stimuli, however, were largely different for CUD and extinction tests. The CUD was tested using filled green circles on grey background. By contrast, visual extinction was tested using a finger confrontation method in which the patients had to indicate the experimenter’s movement of one versus both hands. Thus, ‘brightness of perception as a common correlate for CUD and extinction’ under these different testing conditions could then be understood in terms of similar ‘bright’ activation of visual processing areas.

4.3. RTE in hemianopia

Unconscious stimulus processing in hemianopia, i.e., blindsight, is a rather rare phenomenon and most research has been carried out on the same patients (Marzi et al., 1986; Morland et al., 1999; Scharli, Harman, & Hogben, 1999; Stoerig & Cowey, 1997; Tomaiuolo et al., 1997). Thus, it is not unexpected that hemianopic patients in the current study did not show redundancy gains.

One theory concerning the neural substrate of blindsight is that visual information reaches extrastriate cortices through secondary subcortical pathways, e.g., via the superior colliculus or pulvinar, bypassing the lesion site in the primary visual cortex (Mohler & Wurtz, 1977; Pereren & Jeannerod, 1978; Stoerig et al., 1985; Weiskrantz, 1986). Unconscious processing of stimuli in the blind visual hemisphere was found, for example, in two out of four hemispherectomized patients in whom the collicular visual system had survived hemidectomy (Tomaiuolo et al., 1997). A recent diffusion tensor imaging (DTI) tractography study investigated cerebral connectivity by reconstructing white matter tracts in vivo and tracking pathways between grey matter structures (Leh et al., 2006). In that study, hemispherectomized patients with blindsight showed ipsi- and contralateral connections from the superior colliculus to striate, extrastriate, parietal and prefrontal areas in contrast to healthy subjects and hemispherectomized patients without blindsight who mainly demonstrated ipsilateral connections. Thus, one might speculate that in our hemianopic patients lacking blindsight collicular connectivity was mainly ipsilateral as in healthy subjects (Leh et al., 2006). Alternatively, blindsight may rely on residual islands of vision in the anopic field (Campion et al., 1983; Fendrich, Wessinger, & Gazzaniga, 1992, Fendrich, Wessinger, & Gazzaniga, 2001; Wessinger, Fendrich, & Gazzaniga, 1999; Wessinger, Fendrich, Pittlo, Villlemure, & Gazzaniga, 1996; Wust et al., 2002).

Under this condition an admittedly speculative account is that the hemianopic patients in our study did not show blindsight because of insensitive testing using the same stimulus locations for each patient instead of multiple test locations adapted to form and size of the individual’s anopic area.

In summary, our data indicate the following dissociation between extinction and unconscious stimulus processing in neglect patients: unconscious parallel stimulus processing of contralateral stimuli (RTE) in neglect patients is independent of visual field defects and possibly mediated by subcortical pathways, whereas conscious processing or the extinction rate of contralesional stimuli (RTE) in neglect patients is independent of visual field defects and possibly mediated by subcortical pathways, whereas conscious processing or the extinction rate of contralesional stimuli depends on the CUD. If CUDs in our study reflect strong interfield differences for unilateral stimuli, redundant targets effects (RTEs) should be abolished due to reduced or delayed visual input from the contralateral visual hemifield (Marzi et al., 1997). However, our right hemisphere damaged neglect patients exhibited RTEs. Thus, even though our behavioral CUD data cannot distinctly differentiate between interfield differences and interhemispheric transfer time, the finding that extinction, but not RTE, was correlated with the CUD may provide behavioral evidence for a role of cortical pathways in visual awareness and of subcortical pathways in unconscious processing (Marzi et al., 1997; Silvanto, Walsh, & Cowey, 2009).

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References


