Temporal Modulation of Spatial Tactile Extinction in Right-Brain-Damaged Patients

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Abstract

■ Unilateral and bilateral electrotactile stimuli were delivered to both hands of 11 right-brain-damaged (RBD) patients with left tactile extinction and 20 healthy subjects. Bimanual stimuli could be presented simultaneously or with varying stimulus onset asynchronies (SOAs). Subjects indicated their detection of unilateral or bilateral stimuli, their judgements of whether stimuli were simultaneous or successive, and, in the latter case, which side came first. In RBD patients, extinction was maximal with simultaneous presentations and decreased as SOA increased. With short SOAs, omissions of left-sided stimuli occurred with both right-side and left-side stimulus precedence, suggesting a forward and backward interference of the right stimulus on the processing of the left stimulus within a time window of at least 100 msec. In contrast, there was no interference of the left stimulus on the detection of the right stimulus. Unlike controls, extinction patients rarely expressed simultaneity judgements, but those that were produced tended to be veridical or nearly so, like in normal controls. Whereas controls expressed generally accurate judgements of right or left precedence, patients showed a bias toward a right precedence and a maximal uncertainty between left-first and right-first choices when the left stimulus had a lead between 100 and 200 msec. The results are consistent with the hypothesis that, as in other sensory modalities, tactile extinction is associated with an abnormal persistent bias of attention toward the ipsilesional side that delays the processing of contralesional stimuli. However, the finding that both extinction and explicit judgements of simultaneity tended to occur with simultaneous bilateral stimuli suggest the presence of some residual neural capacity to detect precise temporal coincidence. ■

INTRODUCTION

Extinction is a neurological disorder caused by brain lesions (Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994; Barbieri & De Renzi, 1989). Extinction patients are fully able to detect single lateralized sensory stimuli, but they find it hard to detect contralesional stimuli presented simultaneously with identical or similar ipsilesional stimuli (Vallar, 1998). Extinction is particularly frequent following cortical or subcortical right-sided lesions, and, therefore, it is left-sided stimuli that are most often extinguished (Vallar, 1998). It is widely agreed that extinction reflects a higher-order deficit of spatial selective attention rather than a simple sensory deficit. Visual extinction has been attributed to an unbalanced competition among multiple stimuli (Driver & Vuilleumier, 2001), to an attentional bias towards the ipsilesional hemispace (Smania, Martini, Prior, & Marzi, 1996), to impairments of allocation of spatial selective attention (Di Pellegrino & De Renzi, 1995), or to a disruption of the ability to disengage attention from invalidly cued locations in the ipsilesional space (Posner, Walker, Friederich, & Rafal, 1984). Recent studies suggest that the attentional mechanisms supposedly altered in extinction operate in object-centered coordinates (see review by Shapiro, Hillstrom, & Husain, 2000) and that other nonspatial variables, such as target–distractor grouping (Ward, Goodrich, & Driver, 1994), competition between spatially overlapping stimuli (Humphreys, Romani, Olson, Riddoch, & Duncan, 1994), or salience of the competing stimuli (Aglioti, Smania, Moro, & Peru, 1998), can also influence extinction. Most of these nonstrictly spatial effects are predicted and explained by competition models of selective attention in which each stimulus competes for gaining access to limited pools of attentional resources (Duncan, 1996; Cohen, Romero, Servan-Schreiber, & Farah, 1994; Ward et al., 1994; Bundesen, 1990; Koch & Ullman, 1985).

Competition among stimuli may also depend on the timing of their respective occurrences. Studies in normal subjects show that once a visual stimulus is identified, the ability to discriminate a second stimulus presented shortly thereafter (rapid serial visual presentation, RSVP) is impaired for time lags of about 400 msec (Duncan, Ward, & Shapiro, 1994; Shapiro, Raymond, & Arnell, 1994; Raymond, Shapiro, & Arnell, 1992). This phenomenon, termed attentional blink or dwell time, implies

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that attending to the first stimulus interferes with the processing of the second stimulus, and that the duration of this interference can provide an index of the deployment of attention in time (Chun & Potter, 1995). For example, with foveal stimuli, the duration of the attentional blink is three times longer in patients with left visual neglect than in control subjects (Husain, Shapiro, Martin, & Kennard, 1997), suggesting that these patients suffer from temporal alterations of processing of visual stimuli in addition to their visuospatial deficit.

One can ask whether temporal abnormalities of visual processing are present in left-sided visual extinction as well, because abnormally long attentional blinks have been demonstrated in brain damaged patients with various visual disorders other than neglect (Rizzo, Hiromi, & Dawson, 2001). A study by Di Pellegrino, Basso, and Frassinetti (1997) provided the first affirmative answer to this question. They tested one extinction patient with a lesion centered on the right parietal lobe in a task that required the identification of two letters presented bilaterally with stimulus onset asynchronies (SOAs) ranging from 0 to 1000 msec. Failures to detect the left contralesional stimulus decreased as the SOA increased, regardless of which letter appeared first, showing that the interference of the ipsilesional stimulus on the processing of the contralesional stimulus could extend both forward and backward in time for hundreds of milliseconds. In another experiment with the same patient, Di Pellegrino, Basso, and Frassinetti (1998) found that detection of the second stimulus in a stimulus pair delivered either in the contralesional or the ipsilesional field improved as a function of the SOA duration. However, the SOA with minimal interference was twice as long in the contralesional condition than in the ipsilesional condition (600 vs. 300 msec), an effect also found with a similar paradigm by Cate and Behrmann (2002). Other studies on patients with acute (Robertson, Mattingley, Rorden, & Driver, 1998; Rorden, Mattingley, Karnath, & Driver, 1997) or chronic parietal brain damage (Ro, Rorden, Driver, & Rafal, 2001) showed a significant abnormal bias towards reporting the ipsilesional stimulus first in tasks requiring a forced-choice behavioral indication of the precedence of a visual stimulus in a bilateral pair. The patients of Rorden et al. (1997) consistently reported that the ipsilesional stimulus preceded the contralesional stimulus unless the latter stimulus led the former by over 200 msec, suggesting that the time course of the awareness of contralesional visual stimuli lagged behind that of ipsilesional stimuli. Similarly, in three extinction patients tested in an attentional blink task and a temporal order judgement (TOJ) task, Baylis, Simon, Baylis, and Rorden (2002) found that visual extinction was maximal when bilateral visual stimuli were simultaneous, and that the ipsilesional item was consistently reported first unless the contralesional stimulus had a large lead. In brief, contralesional visual stimuli are mostly excluded from awareness when they occur at the same time as ipsilesional visual stimuli, whereas they can reach awareness, though in an apparently delayed manner, if they are presented before ipsilesional stimuli. As a result, extinction patients are assumed to experience subjective simultaneity of the two visual stimuli in a bilateral pair only when the contralesional stimulus physically precedes the ipsilesional stimulus by about 200 msec. Longer time leads favoring contralesional stimuli are thought to be required for the occurrence of a subjective precedence of such stimuli over ipsilesional stimuli in extinction patients (Baylis et al., 2002).

While synchronous bilateral stimulation has been frequently used to study unilateral extinction in nonvisual sensory modalities, especially in the tactile modality (Vaishnavi, Calhoun, Southwood, & Chatterjee, 2000; Vaishnavi, Calhoun, & Chatterjee, 2001; Aglioti, Smania, & Peru, 1999; Neppi-Modona, 1999; Nico, 1999), asynchronous bilateral stimulation has been largely restricted to investigations on visual extinction. Only two previous studies have been carried out with nonvisual asynchronous bilateral stimuli, namely a pioneering study with tactile stimuli by Birch, Belmont, and Karl (1967) and a recent research with auditory stimuli by Karnath, Zimmer, and Lewald (2002). Like visual extinction, auditory and tactile extinction are likely to entail an alteration of the subjective ordering of ipsilesional and contralesional stimuli in time, so that the latter stimuli appear to be delayed in reaching awareness compared to the former stimuli.

The present study was aimed at extending the analysis of temporal modulation of tactile extinction in 11 right-brain-damaged (RBD) patients clinically selected for the presence of spatial tactile extinction, as compared with one RBD patient without tactile extinction and 20 neurologically intact controls. Two main experimental tasks, hereafter called computerized spatial extinction and computerized spatio-temporal extinction, were used. In the computerized spatial extinction task, RBD patients and controls were asked to report the number (1 or 2) and side (left, right, or both sides) of nonpainful electrotactile stimuli delivered to the index finger of one or the other hand or simultaneously to the index fingers of both hands. This task was comparable to the standard clinical test used for assessing spatial extinction, with the important difference that timing and intensity of the experimental stimuli were computer controlled. Temporal aspects of tactile extinction were assessed by means of a spatio-temporal task in which the same single or double stimuli as in the previous spatial task were delivered to the index fingers, but double stimuli could be simultaneous or separated by 14 different time intervals. The ratio of synchronous to asynchronous stimuli was 1:3.5. Subjects were requested to judge whether the stimuli were single or double and, in the latter case, to provide TOJs. One RBD extinction patient (PB) was also tested in a

modified version of the spatio-temporal test in which the number of simultaneous trials was equal to the sum of all the asynchronous trials; that is, the synchronous/asynchronous ratio was 1:1.

All previously mentioned studies of TOJs in visual and nonvisual extinction patients required forced choices between a right or left precedence, thus excluding simultaneity judgements. It is known that in two-alternative forced-choice procedures, the occurrence of response biases may contaminate the analysis of the subjective estimates of the temporal occurrence of events (Spence, Shore, & Klein, 2001; Pashler, 1998). In the TOJs of the present study, subjects were left free to report if stimuli felt as double were either simultaneous or conveying a left or right prior entry impression. The rationale behind the adoption of this procedure was twofold. First, the added possibility to express a simultaneity judgement is likely to diminish the chance of response biases inherent in forced two-choice successivenes judgements (Spence et al., 2001). Second, we thought that it would be of interest to assess the contralesional–ipsilesional interstimulus interval at which patients would most frequently report simultaneity and to compare it with the interstimulus interval at which they would express an equal number of contralesional and ipsilesional precedence judgements. In all previous TOJ studies of extinction patients, the latter interstimulus interval has been regarded as the marker of maximal uncertainty between right or left precedence, and by inference of the stimulation condition causing subjective stimulus simultaneity.

RESULTS

Clinical and Computerized Spatial Extinction Tasks

False alarms occurred in only 1% of the catch trials in extinction patients and 0% in healthy controls. Table 1 reports the accuracy of the extinction patients' performance in the clinical and computerized spatial extinction tests. Virtually all errors were omission errors because mislocalizations of single stimuli to the other side were never observed. The RBD patient without extinction exhibited no false alarms and made no errors in both clinical and computerized spatial extinction tests. Accuracy of healthy subjects in the computer-controlled spatial extinction test amounted to 98.7% of the trials.

The percent correct detections of the extinction patients in each combination of stimuli in the two spatial extinction tests were entered in a repeated-measures analysis of variance (ANOVA) with the following within-subjects factors: Type of Test (clinical vs. computerized spatial extinction test), Side (left vs. right), and Number (single vs. double). Among the main factors, significant effects were obtained for Side [$F(1,10) = 117.3$, $p < .0001$], detection accuracy being higher for right stimuli (97.2%) than for left stimuli (59.9%), and Number [$F(1,10) = 53.4$, $p < .0001$],

Table 1. Percentage of Accuracy in the Clinical and Computer-Controlled Tests for Assessing Spatial Extinction in RBD Patients

	Computerized Spatial Extinction Test				*Clinical Extinction Test*			
	L		*R*		*L*		*R*	
Patients	*S*	*D*	*S*	*D*	*S*	*D*	*S*	*D*
CL	40	20	100	100	100	60	100	100
RS	100	20	95	80	100	20	100	100
WH	100	65	100	100	100	50	100	100
AZ	57	23	82	83	100	60	100	100
BS	90	10	100	100	70	70	100	100
TG	90	20	90	90	100	20	100	100
PG	95	0	100	100	70	10	100	100
SD	95	60	80	90	70	70	100	100
BL	90	0	100	100	100	10	100	100
TO	95	57.5	97.5	95	100	10	100	100
PB	98.3	8.3	100	96.7	90	25	100	100
Mean	86.4	25.8	94.6	94.4	90.9	36.8	100	100
Standard Deviation	(5.8)	(7.2)	(2.2)	(2.2)	(4.1)	(7.6)	(0)	(0)

Controls performed nearly perfectly in the computer-controlled test (the clinical test was not performed). S = single; D = double; L = left-hand; R = right-hand.

accuracy being higher upon single stimulation (92.9%) than upon double stimulation (64.2%). In the latter case, errors were failures to detect one stimulus in a pair, almost always the left stimulus. Failed detections of left stimuli occurred almost exclusively with double stimulations, accounting for a significant Side × Number interaction [$F(1,10) = 66.7, p < .0001$]. In contrast, detection of right side stimuli was the same regardless of whether or not the right stimulus was associated with a left stimulus. The difference between the percentages of correct detections of single and double stimuli, a typical measure of extinction, was as high as 57.3% for left side stimuli, as contrasted with a 0.1% difference for right side stimuli. The insignificance of the Type of Test factor [$F(1,10) < 1$], as well as of the Type of Test × Side × Number interaction [$F(1,10) < 1$], reflects the fact that in the two tests, both the levels of performance and the degree of left-sided extinction (54.1% in the clinical test and 60.6% in the computerized spatial extinction test) were comparable. The percentage of correct detections of right-sided stimuli by patients was 97.2% in the computer-controlled test as well as in the clinical test, a performance quite similar to that of controls (98.2%).

Percent correct detections of left-sided stimuli in the spatial computer-controlled test were compared in patients and controls by means of an ANOVA with one between-subjects factor (Group, patients vs. controls) and one within-subjects factor (Number, single vs. double). Group was significant [$F(1,29) = 138.6, p < .0001$], patients being altogether less accurate than controls (percent correct detections 56.1% vs. 99.4%). Number was also significant [$F(1,29) = 92.9, p < .0001$], because overall accuracy was higher with single stimuli than with double stimuli (92.8% vs. 62.6%). However, the latter difference was limited to the patients group, given that the difference in percent correct detections between the single and double conditions was as high as 60.6% in patients, and virtually nil in controls (−0.3%). Accordingly, the Group × Number interaction was highly significant [$F(1,29) = 94.5, p < .0001$].

Computerized Spatio-Temporal Extinction Task

Analysis of performance in this task will consider detection accuracy and TOJs separately.

Detection Accuracy

False alarms occurred in only about 2% of the catch trials in extinction patients and 0.1% of the catch trials in healthy controls. Correct detections consisted in appropriate identifications of double and single stimuli and, in the latter case, of their right or left localization in accordance with the side of stimulation. The percentages of correct detections in the different stimulation conditions were entered into two separate repeated-measures ANOVAs, one for healthy controls and the other for tactile extinction patients.

In both ANOVAs, Side (Left vs. Right) and Stimulation Condition (Single, SOA 0, 50, 100, 200, 300, 500, 700, 900 msec) were the within-subjects factors. Control subjects detected left- and right-sided stimuli with an accuracy close to 100% under both single and double stimulation conditions, hence, in the related ANOVA, no factors or interactions were significant.

The performance of extinction patients in detecting stimuli in the different conditions is illustrated in Figure 1.

In the ANOVA for the patients, Side was significant [$F(1,10) = 14.2, p = .004$], accuracy being higher with right-sided stimuli than with left-sided stimuli (percent

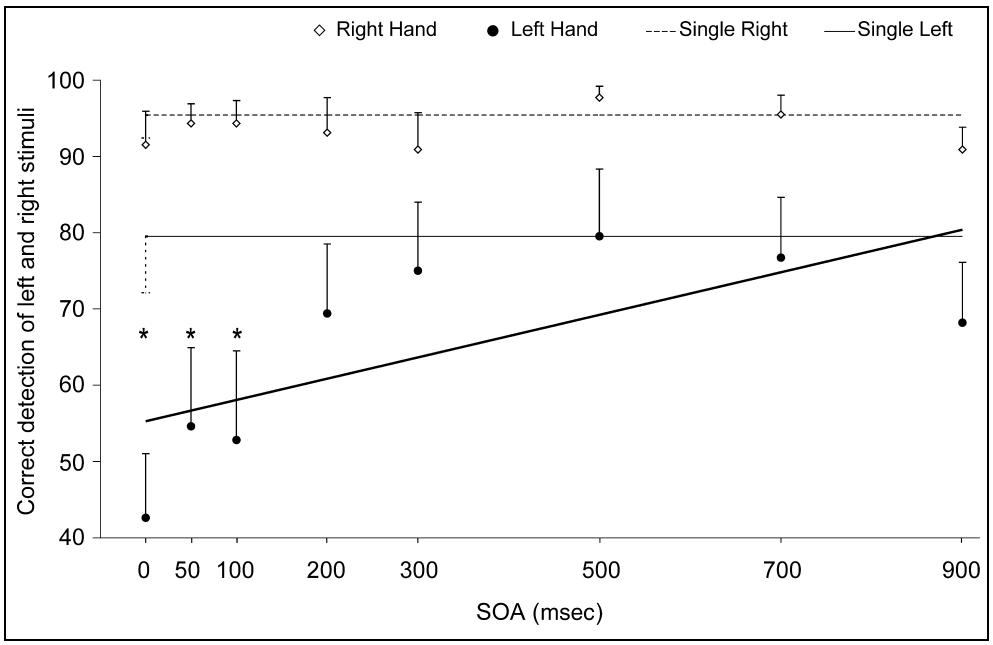

Figure 1. Accuracy of RBD extinction patients in reporting left-sided and right-sided stimuli under double stimulation conditions. Mean accuracy (plus standard error) for asynchronous conditions is plotted independently from the sequence of presentation, that is, after collapsing left-first and right-first combinations. The horizontal lines represent accuracy under single left (continuous) and right (stippled) stimulation conditions. The thick, continuous line represents the curve which fits best the distribution of correct detections of left-sided stimuli under double stimulation (DS) conditions. Asterisks indicate significant comparisons with respect to single stimuli.

correct detections: Right 93.7%; Left 66.5%). The significance of Stimulation Condition [$F(8,80) = 5.5, p = .0001$] reflects an increase in accuracy as a function of increasing SOAs. The significance of the Side × Stimulation Condition interaction [$F(8,80) = 4.9, p = .0001$] reflects the fact that the increase in accuracy with increasing SOA appeared to occur only with left-sided stimuli. Post hoc comparisons showed that detection of left-sided stimuli was significantly more successful with single stimuli (79.5%) than with double stimuli at the 0 msec SOA (42.6%), the 50 msec SOA (54.6%), and the 100 msec SOA(52.8%). In contrast, the rate of detection of right stimuli on double stimulation at each SOA was indistinguishable from the rate of detection of single right stimuli (see Figure 1). Trend Analyses were used to test the dependence of detection accuracy on SOA separately for right and left stimuli (Keppel, 1982). The detection of left-sided stimuli as a function of SOA duration was best fitted by a linear relation [$F(1,10) = 14.4, p = .004, R = .7$], whereas no significant trend was found for detection of right-sided stimuli (see Figure 1).

Figure 2 shows percent correct detections of left-sided stimuli in the bilateral stimulation condition according to whether the left stimulus preceded (negative SOAs) or followed the right stimulus (positive SOAs). In an ANOVA with two within-subjects factors, Precedence (left first vs. right first) and SOA (0, 50, 100, 200, 300, 500, 700, 900 msec), the only significant main factor was SOA [$F(7,70) = 7.8, p < .0001$], accuracy being lower at the 0, 50, and 100 msec SOAs than at longest SOAs.

The insignificance of the Precedence factor and the Precedence × SOA interaction suggests that detection was not influenced by right or left stimulus precedence. This suggestion was confirmed by a Trend Analysis showing that the curve which fitted best the observed distribution was a symmetrical curve of fourth order [$F(1,10) = 7.2, p = .02, R = .76$]. Moreover, the symmetry of the distribution was confirmed by paired t tests showing an absence of statistically significant differences in accuracy between corresponding negative and positive SOAs.

One of the 11 extinction patient (PB) was tested in four additional blocks of a modified version of the spatio-temporal test in which the number of simultaneous trials was equal to the sum of all the asynchronous trials. A comparison of PB's omissions of left-sided stimuli under double stimulation conditions in the standard and modified version of the spatio-temporal test is given in Table 2. The increase of accuracy in detecting left sided stimulus paralleled the increase of SOA in both spatio-temporal tests. Differences between single and double conditions turned out to be significant [$\chi^2(1) > 5.1$, $p < .05$ in all cases] at SOAs 0, 50, and 100 msec in the 1:1 ratio condition and at SOAs 0 and 50 msec in the 1:3.5 ratio [$\chi^2(1) > 3.84, p < .05$ in all cases].

One additional RBD patient (CG) with no clinical signs of extinction and a virtually perfect performance in the spatial computerized test (100% correct with single stimuli and 99.25% correct with double stimuli) was tested in the spatio-temporal task. His accuracy in detecting stimuli was almost perfect (100% correct with single stimuli and 99.1% correct with double stimuli).

Temporal Order Judgement (TOJ)

When subjects correctly detected double stimuli, they were asked to make TOJs; that is, they were asked to report whether the two stimuli were simultaneous, or

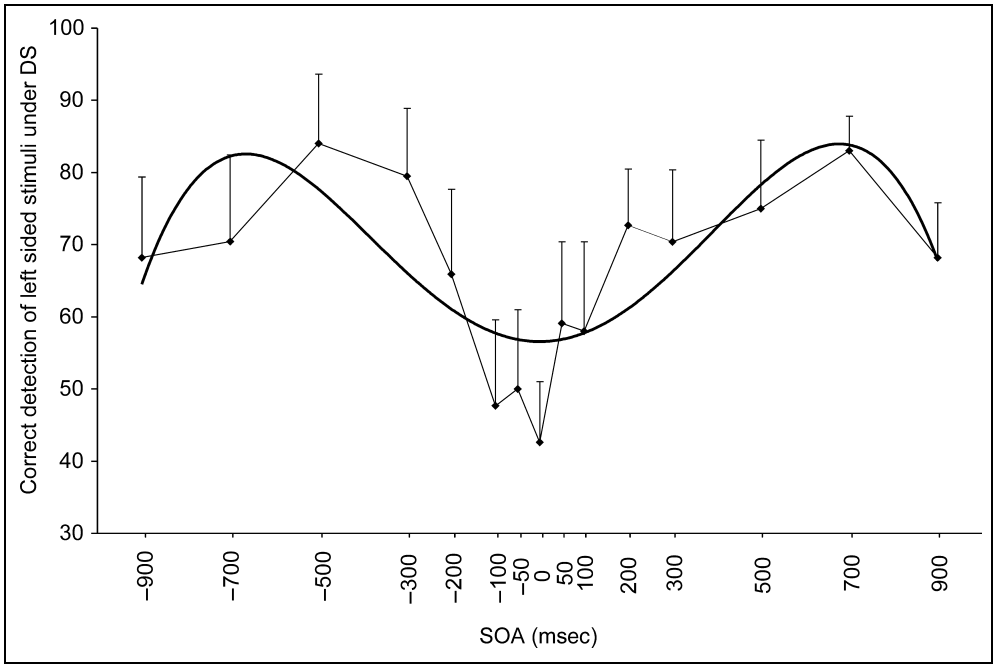

Figure 2. Percent correct detections of left-sided stimuli in RBD patients on double stimulation. Negative SOAs indicate trials in which the first stimulus in a pair was delivered to the left hand and positive SOAs indicate trials in which the first stimulus in a pair was delivered to the right hand. An SOA of zero refers to the case wherein both stimuli were delivered simultaneously. The thick, continuous line represents the curve which fits best the distribution of correct detections of left-sided stimuli under double stimulation conditions.

Table 2. Accuracy of Patient PB in Detecting Left-Sided Stimuli Under Double Stimulation Conditions in the Two Versions of the Spatio-Temporal Computerized Tests

SOA	*−900*	*−700*	*−500*	*−300*	*−200*	*−100*	*−50*	*0*	*50*	*100*	*200*	*300*	*500*	*700*	*900*
1:1 Condition	14/16	15/16	14/16	16/16	15/16	10/16	3/16	53/224	10/16	10/16	15/16	14/16	15/16	13/16	13/16
1:3.5 Condition	8/8	8/8	8/8	8/8	8/8	6/8	3/8	8/32	6/8	7/8	8/8	8/8	8/8	7/8	8/8

The denominator indicates the number of double trials for each conditions. The numerator indicates the number of double trials in which the left stimulus was detected.

the right stimulus preceded the left, or vice versa. Theoretically, an ability to make perfect TOJs would be attested by the consistent production of ''simultaneous'' responses at the 0 msec SOA, ''left-first'' responses at negative SOAs, and ''right-first'' responses at positive SOAs. Figure 3 shows the percentages of correct TOJs at each SOA for patients (upper part) and healthy controls (lower part). It must be kept in mind that detection of bilateral stimuli was virtually perfect in controls (98.5%), because these percentages were calculated with respect to the total number of bilateral stimulations in which two stimuli were actually reported, whereas in extinction

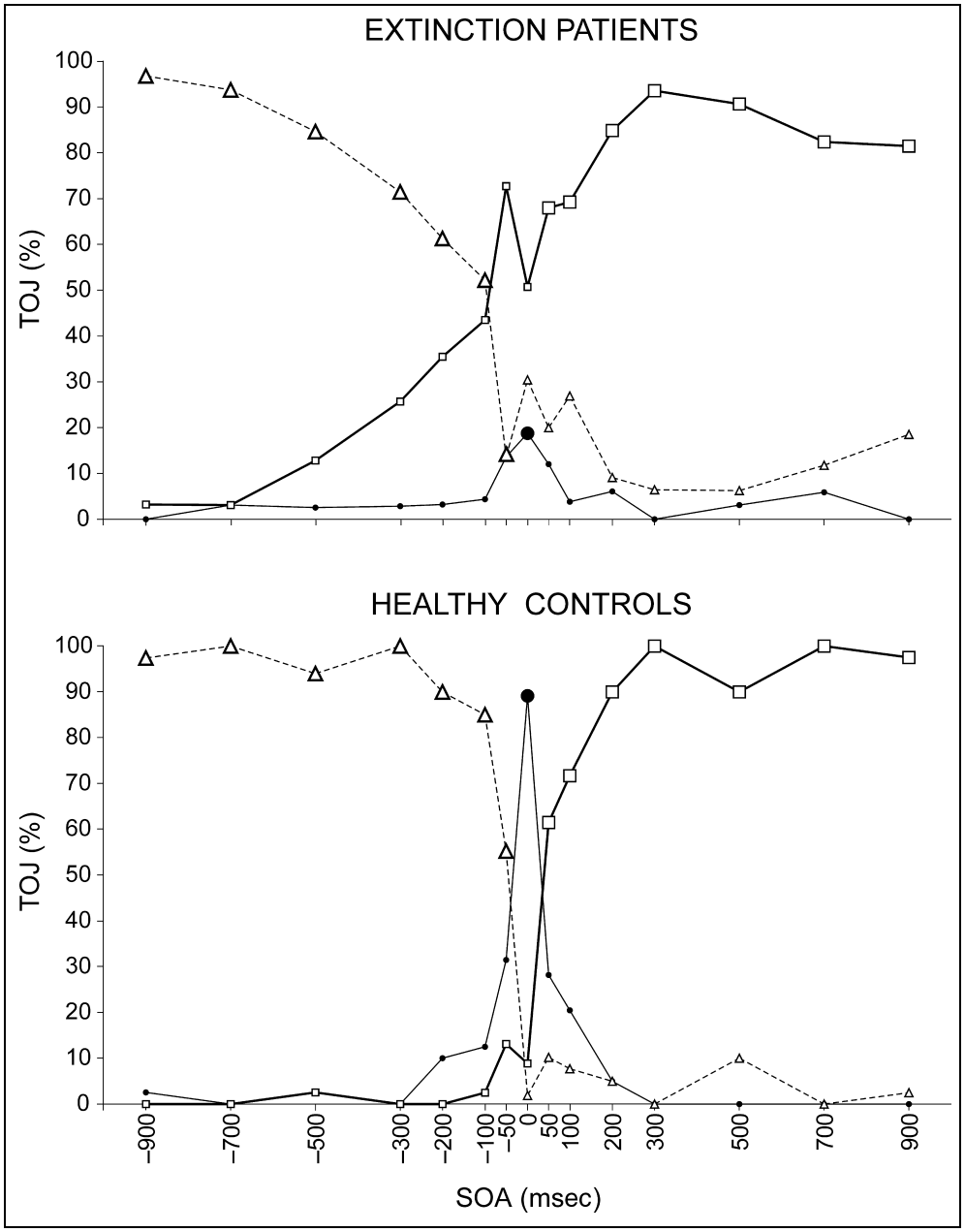

Figure 3. Representation of the three possible ''temporal'' responses (in percentage of trials in which two stimuli were correctly detected) for extinction patients (top) and controls (bottom). Negative SOAs indicate trials in which the first stimulus in a pair was delivered to the left hand and positive SOAs indicate trials in which the first stimulus in a pair was delivered to the right hand. An SOA of zero refers to the case wherein both stimuli were delivered simultaneously. Black circles, white squares, and white triangles indicate ''Simultaneous'', ''Right-first,'' and ''Left-first'' responses, respectively. In each curve, large symbols indicate responses corresponding to the actual physical order of the stimuli, that is, ''temporally'' correct responses.

patients, the corresponding percentage was only 63.8% because of their pathognomonic tendency to miss the left stimulus on double stimulations.

A striking difference between controls and extinction patients was that in the latter group, simultaneity judgements were very rare, as if the patients suffered from some restraint in perceiving or reporting that the two stimuli were synchronous. Nevertheless, the kind of the relation between frequency of simultaneity judgements and SOA type was very similar, if not identical, in the two groups. In both groups, the overwhelming majority of simultaneous judgements was expressed at the SOAs comprised between −100 and 100 msec with a clear peak in coincidence with the 0 msec SOA, indicating that reported simultaneity tended to match physical simultaneity in controls and patients alike. However, at the 0 msec SOA peak, the percentage of simultaneous judgements was only 19% in the patients, as contrasted with a corresponding 89% in healthy controls [$\chi^2(1) = 104.1$, $p < .0001$]. At negative and positive SOAs of 50 and 100 msec, the percentages of incorrect simultaneity judgements were again considerably higher in controls than in patients (Figure 3), but the differences between the two groups failed to reach statistical significance in comparisons by χ^2 tests. At SOAs longer than 100 msec, both controls and patients were essentially correct in judging double stimuli as asynchronous, regardless of which side came first.

The accuracy of precedence judgements was examined by comparing the percentages of ''right-first'' and ''left-first'' responses on stimulations incorrectly reported as asynchronous at the 0 msec SOA, and correctly reported as asynchronous at the other SOAs. Among incorrect ''asynchronous'' responses to simultaneous double stimuli (0 msec SOA), ''right-first'' judgements were significantly more numerous than ''left-first'' judgements in both controls [$\chi^2(1) = 11.4$, $p < .01$] and extinction patients [$\chi^2(1) = 5.98$, $p < .05$]. Among correct asynchronous judgements, right precedence judgements at positive SOAs and left precedence judgements at negative SOAs were nearly perfect in control subjects when SOA duration equalled or exceeded 100 msec. With a positive 50 msec SOA, control subjects produced significantly more correct ''right-first'' than incorrect ''left-first'' judgements [62% vs. 10%, $\chi^2(1) = 25.3$, $p < .001$], whereas with a negative 50 msec SOA, they produced significantly more correct ''left-first'' than incorrect ''right-first'' judgements [55% vs. 13%, $\chi^2(1) = 16.9$, $p < .001$], indicating that even the shortest interstimulus interval was compatible with fairly accurate evaluations of right or left precedence.

Patients with extinction produced significantly more ''right-first'' than ''left-first'' judgements at all positive SOAs (all p values $< .017$ by χ^2 tests), and significantly more ''left-first'' judgements at negative SOAs equalling or exceeding 300 msec (all p values $< .001$ by χ^2 tests). A trend towards more ''left-first'' than ''right-first'' judgements was found at the negative 200 msec SOA [$\chi^2(1) = 3.21$, $p = .07$], whereas at the negative 100 msec SOA, the difference between the two types of judgement fell far from statistical significance [$\chi^2(1) = .19$, *ns*]. At the latter SOA, the number of ''right-first'' and ''left-first'' judgements was indeed about equal, suggesting that extinction patients experienced a maximal subjective uncertainty about the precedence of right or left tactile stimuli when the left stimulus preceded the right stimulus by at least 100 msec. In contrast, a significant prevalence of ''right-first'' over ''left-first'' judgements was found at the negative 50 msec SOA [''right-first'': 72.7% vs. ''left first'': 13.6%; $\chi^2(1) = 13.4$, $p < .001$], consistent with a presumable subjective right precedence at variance with the physical left precedence. As mentioned above, the patients' subjective left precedence tended to become increasingly veridical as the physical precedence of the left stimulus over the right stimulus increased beyond 100 msec.

In order to check if the paucity of simultaneity judgements by patients could be due to the asynchronous

Table 3. TO Responses of Patient PB in the Two Versions of the Spatio-Temporal Computerized Tests

SOA	*−900*	*−700*	*−500*	*−300*	*−200*	*−100*	*−50*	*0*	*50*	*100*	*200*	*300*	*500*	*700*	*900*
1:1															
Simultaneous	0	0	0	0	0	0	0	**12.5**	16.6	0	0	0	0	0	0
Right First	0	0	0	12.5	37.5	50	66.6	75	**83.3**	**100**	**100**	**100**	**100**	**100**	**100**
Left First	**100**	**100**	**100**	**87.5**	**62.5**	**50**	**33.3**	12.5	0	0	0	0	0	0	0
1:3.5															
Simultaneous	0	0	0	0	0	0	0	**0**	0	10	0	0	0	0	0
Right First	0	0	7.2	12.5	33.3	40	66.6	81.1	**80**	**90**	**100**	**100**	**100**	**100**	**100**
Left First	**100**	**100**	**92.8**	**87.5**	**66.6**	**60**	**33.3**	18.9	20	0	0	0	0	0	0

Values are in percentage of trials in which both the left and right stimuli were detected. **Bold** values indicate responses matching the actual physical order of the stimuli.

stimulations being 3.5 times more frequent than synchronous stimulations, extinction patient PB was tested both in the standard version (simultaneous/sequential ratio 1:3.5) and a modified version (simultaneous/sequential ratio 1:1) of the spatio-temporal test. The results obtained in the two conditions, shown in Table 3, were fully comparable, supporting the conclusion that the pattern of the TOJ in the extinction patients did not depend on the ratio between the number of synchronous and asynchronous stimulus presentations.

Finally, the RBD patient without any sign of extinction (CG) was tested with the aim of ascertaining whether the pattern of results exhibited by the extinction group of patients was strictly associated with extinction or due to a cerebral lesion per se. As reported above, this patient was quite accurate in detecting the number and side of the stimuli. Moreover, he was also able to judge the precedence order of the stimuli almost as correctly as the healthy controls (82.9%). The pattern of TOJ responses of this patient was indeed definitely more similar to that of controls than to that of the extinction group, insofar as his performance was rather good even at the shortest SOA. Indeed, at the −50 msec SOA, he produced 33% of left-first responses versus 0% of right-first responses, and at the 50 msec SOA, he produced 40% right-first responses versus 0% left-first responses. It is also worth noting that, like controls, this patient produced a consistent number of ''simultaneous'' responses at the positive and negative 50 msec SOA (60% and 67%, respectively). On these grounds, it seems safe to propose that in order to yield the pattern of results observed in the present group of RBD patients, the brain damage must be such as to cause left tactile extinction as well, perhaps because both extinction and altered TOJ of tactile stimuli depend on a specific alteration of attentional and stimulus processing mechanisms.

DISCUSSION

The results support, extend, and qualify previous evidence on the temporal course of awareness of bilateral stimuli in patients with unilateral brain damage and extinction of contralesional sensory inputs. Only non-noxious electrical stimulations of the skin, demonstrably equivalent to tactile stimulations, were used in the present study on RBD patients with left-sided tactile extinction, but the findings can be compared and contrasted with those of previous studies on patients with unilateral visual or auditory extinction (Karnath et al., 2002; Di Pellegrino et al., 1997, 1998).

When analyzing detection and localization of unilateral and bilateral stimulations of right and left fingers by extinction patients and healthy controls, three different conceptual levels of stimulus processing were considered in the present study. The first level involved the simple detection of unilateral contralesional and ipsilesional stimuli, as well as of bilateral stimuli, either synchronous or separated in time by variable SOAs. The second level involved a judgement of whether bilateral stimuli were synchronous or asynchronous. The third level involved a judgement of whether in bilateral stimuli perceived as double and asynchronous, the right stimulus preceded the left or vice versa. The relative involvement of the three levels in each response could be inferred from single responses, whether correct or incorrect. For example, a ''one left'' response was taken to mean that a decision was made to report a single stimulus on the left, thus making simultaneity or successiveness judgements unnecessary. A ''simultaneous'' judgement was taken to mean that a decision was made to report two synchronous stimuli, eliminating the possibility of successiveness. A single ''left-first'' judgement was taken to imply that a decision was made to report two successive stimuli with the left leading the right.

An analysis of the patients' performance at the detection level showed that while left-sided tactile extinction was clearly maximal when the stimuli on the two sides were simultaneous, it also occurred when the two stimuli were separated by variable intervals within a definite time window. More specifically, patients found it difficult to detect the left, contralesional stimulus when it either preceded or followed an ipsilesional stimulus by 50 or 100 msec, the degree of extinction being approximately the same at each of these SOAs, independent of right or left stimulus precedence. Within this time window, the patients' detection of contralesional stimuli was significantly inferior to their own detection of single contralesional stimuli, whereas with longer temporal separations between ipsilesional and contralesional stimuli, the detection rate of the latter stimuli approached the detection rate of contralesional stimuli presented alone. In contrast, the patients' detection of right stimuli was not interfered with by the concurrent presentation of left stimuli, because at no SOA did the right stimulus detection on bilateral stimulation differ from the detection of single right stimuli. Normal controls detected all right and left stimuli in a pair regardless of stimulus simultaneity or successiveness, and regardless of right or left precedence at any SOA.

Models of extinction based on a presumed pathological difficulty to disengage attention once it has been allocated to ipsilesional targets predict that detection of contralesional stimuli should be more interfered with by preceding than by following or simultaneous ipsilesional stimuli (Posner et al., 1984; Posner & Petersen, 1990). To the extent that the present findings demonstrated a maximal extinction of contralesional stimuli at the 0 msec SOA, in agreement with previous studies of visual extinction (Baylis et al., 2002; Di Pellegrino et al., 1997; Rorden et al., 1997), they are inconsistent with such pathological disengagement accounts of tactile extinction. Other accounts of extinction postulate that

different sensory inputs occurring in close temporal proximity compete for limited pools of attentional resources, so that, for example, attending to a region of space interferes with the processing of targets occurring at other locations (Duncan, 1996; Cohen et al., 1994; Ward et al., 1994; Bundesen, 1990; Koch & Ullman, 1985). Unilateral brain lesions, especially lesions of the right hemisphere, would bias attention away from the contralesional space and towards the ipsilesional space, with the result that contralesional inputs would lose in the competition with ipsilesional inputs and would thus be subject to extinction. Our findings on the detection of contralesional stimuli on synchronous and asynchronous bilateral stimulation by tactile extinction patients are generally compatible with such models of extinction.

Estimates of the time windows within which contralesional stimuli can be extinguished by preceding or following ipsilesional stimuli in studies on visual extinction have varied from about 200 msec (Baylis et al., 2002) to about 600 msec (Di Pellegrino et al., 1997). These estimates are greater than the 100 msec time window described here for tactile extinction, most probably because a simple detection–localization paradigm was used in the present study, whereas the studies on visual extinction additionally required shape or color discriminations and were thus more demanding in terms of attentional requirements. In the old study on somatosensory extinction by Birch et al. (1967), extinction was found to be maximal when ipsilesional and contralesional stimuli were simultaneous. It was also found to decrease as a 300- or 600-msec lag was introduced between the ipsilesional and the contralesional stimulus. The differences in the results between these different studies on visual and tactile extinction are most probably due to procedural differences, pointing to the need for a comparative analysis of the temporal course of extinction from synchronous and asynchronous bilateral stimulations using exactly the same paradigm in different sensory modalities.

Temporal Order Judgements

Attentional modulation of stimulus processing can influence not only detection of sensory events, but also awareness of their temporal order. Classical studies of attentional biases in normal subjects show that a sensory stimulus is perceived earlier when it is expected than when it is not. Accordingly, the ''prior entry'' theory (Titchener, 1908) maintains that attended stimuli tend to be perceived before unattended concurrent stimuli, so that judgements of simultaneity or successiveness of two or more stimuli can be strongly affected by attentional biases. Normal observers allocating attention to a visual field region experience an illusion of a precedence of a stimulus in that region over simultaneous stimuli presented elsewhere (Stelmach & Herdman, 1991; Stelmach, Herdman, & McNeil, 1994). One may ask whether the attentional imbalance assumed to underlie extinction can by itself affect judgements of simultaneity and temporal order. Rorden et al. (1997) and Baylis et al. (2002) found that when two bars were flashed to the right and left visual fields of patients with unilateral visual extinction, the patients reported a precedence of the contralesional bar only when its appearance preceded that of the ipsilesional bar by about 200 msec. Similarly, the present study has shown that with tactile stimuli correctly reported as bilateral, extinction patients tended to judge that the right (ipsilesional) stimulus had occurred before the left (contralesional) stimulus, unless the left stimulus preceded the right by more than 100 msec. By contrast, normal controls and a patient with right brain damage but no extinction were able to judge the successiveness of bilateral tactile stimuli with a significant accuracy even at SOAs of 50 msec, regardless of physical right or left precedence. Taken together, the findings of Baylis et al. (2002) and Rorden et al. (1997) and those of the present study are consistent with the hypothesis that in unilateral extinction, whether visual or tactile, the processing of stimuli from the affected side is delayed relative to the processing of stimuli from the normal side because the latter stimuli are favored by an attentional bias.

As a logical counterpart of their altered ability to judge stimulus successiveness, extinction patients should also misjudge stimulus simultaneity by incorrectly perceiving as synchronous stimulus pairs in which the unfavored stimulus precedes the favored stimulus by an appropriate interval. Such distorted perception of stimulus simultaneity was inferred from the finding that in a forced choice between left-first-then-right and right-first-then-left judgements, patients with visual (Baylis et al., 2002; Rorden et al., 1997) or auditory extinction (Karnath et al., 2002) produced an equal number of the two types of judgements (i.e., they expressed maximum uncertainty between the two choices) in coincidence with a definite temporal lead of the contralesional stimulus. In comparison, normal controls exhibit maximal uncertainty between right-then-left and left-then-right choices with exactly simultaneous bilateral stimuli.

The two-alternative forced-choice procedures used in previous studies suffers from the fact that all stimuli are double and the subjects are misled to believe that all pairs of stimuli are asynchronous. Thus, the subjects' responses did not directly indicate whether two stimuli were actually perceived in all cases, nor did they explicitly indicate whether subjects actually experienced awareness of simultaneity on any particular trial.

The present study involved a different experimental procedure. Subjects knew that stimuli in a pair could be single or double, synchronous or asynchronous, and were specifically instructed to report perceived simultaneity and to indicate which side came first only in the

case of perceived successiveness. The expected potential advantages of this paradigm were, first, that the chance of response biases seems to be reduced when there are more than two alternatives for response (Spence et al., 2001; Shore, Spence, & Klein, 2001) and, second, that any relation between interstimulus interval and subjective simultaneity could be assessed on the basis of explicit simultaneity judgements, in addition to successiveness judgements indexing maximal uncertainty between right and left.

In comparison to normal controls, extinction patients expressed simultaneity judgements very sparingly, a finding that could not be attributed to the lower frequency of synchronous compared to asynchronous presentations (ratio 1:3.5), because similar results were obtained in an extinction patient for whom a 1:1 ratio was adopted. Contrary to the expectation that simultaneity judgements should occur with stimulus pairs in which the contralesional stimulus preceded the ipsilesional stimulus, extinction patients, like normal controls, expressed all their explicit simultaneity judgements at the SOAs comprised between −100 and 100 msec, with a modest peak at 0 msec. The incidence of simultaneity judgements at the negative 100 msec SOA, at which the patients' successiveness judgements tended to be equally divided between right-first and left-first judgements, was very low and certainly not higher than at the positive 100 msec SOA, at which most successiveness judgements were correctly in favor of a right lead.

These findings raise the question of whether extinction patients do actually experience an awareness of simultaneity of bilateral stimuli. Such awareness may be made difficult by uneliminable differences in sensorial qualities between ipsilesional and contralesional stimuli. To the extent that extinction patients can become aware of the simultaneity of bilateral tactile stimuli, the present results suggest that such awareness tends to reflect the physical reality of the stimuli rather accurately, in contrast with the ipsilesional bias displayed in successiveness judgements. Baylis et al. (2002) have called attention to the contrast between two phenomena exhibited by extinction patients, namely, the occurrence of a maximal degree of contralesional extinction with simultaneous bilateral stimuli and the temporal bias in favor of ipsilesional stimuli revealed by successiveness reports. These two phenomena suggest that in extinction patients, at least one level of the nervous system is able to detect coincidence in time of bilaterally stimuli, accounting for the maximal suppression of contralesional stimuli on simultaneous bilateral stimulation. On the other hand, the erroneous TOJs biased toward the ipsilesional sides seem to indicate that at another level of the nervous system, perhaps related to the emergence of awareness, the correct detection of temporal coincidence or noncoincidence is lost (Baylis et al., 2002). The present results complicate the picture further by raising the possibility that maximal uncertainty between right and left choices is not a faithful index of subjective stimulus simultaneity. It indeed appears that such simultaneity can be experienced veridically by extinction patients on the rare occasions in which contralesional stimuli escape extinction on simultaneous bilateral stimulation.

In conclusion, the present results provide novel evidence on temporal aspects of tactile extinction, as well as on possible differences between objective and subjective estimates of temporal order in extinction patients, based on detection and discrimination responses to unilateral and bilateral tactile stimuli and on TOJs about ipsilesional and contralesional stimuli. An abnormal persistent attentional bias toward the ipsilesional side, similar to that reported in visual studies, seems to afford the most plausible explanation of the differences between the present extinction patients and normal controls. It must be mentioned, however, that there was some evidence for a rightward bias also in normal controls, who exhibited a significance tendency to express ''right-first'' responses when they wrongly judged simultaneous stimuli as successive. While it cannot be excluded that this effect reflected a slight physiological attentional bias toward the right hemispace (Geffen, Mason, Butterworth, McLean, & Clark, 1996), or a left hemisphere dominance for the task (Nicholls & Lindell, 2000), one cannot exclude the possibility of a simple response bias, that is, a tendency to say ''right'' more frequently than ''left'' when uncertain. If the hypothesis of a physiological rightward attentional bias is proven true by appropriate controls of response biases, then left-sided extinction may be viewed as an abnormal accentuation of this bias. This possibility is not easy to reconcile with the finding that ipsilesional leftward attentional biases are found in extinction patients with left brain damage (Baylis et al., 2002).

METHODS

Subjects

All patients and normal subjects gave their informed consent to participate in the study, and the protocol was approved by the institutional review board. Eleven brain-damaged, right-handed patients (3 women and 8 men) with clinical and CT or MRI evidence for an ischemic or hemorrhagic lesion of the right hemisphere, participated in the study. A reconstruction of the lesions site and extent is shown in Figure 4.

Their mean age was 63.8 years (*SD* 9.8, range 43–74), and their mean education was 9.8 years of schooling (*SD* 5.3, range 5–18 years). The main criterion for inclusion in the study was the presence of left tactile extinction in the standard clinical test described below. Severity of motor impairment, anosognosia, visual, tactile and auditory extinction, and personal and extrapersonal

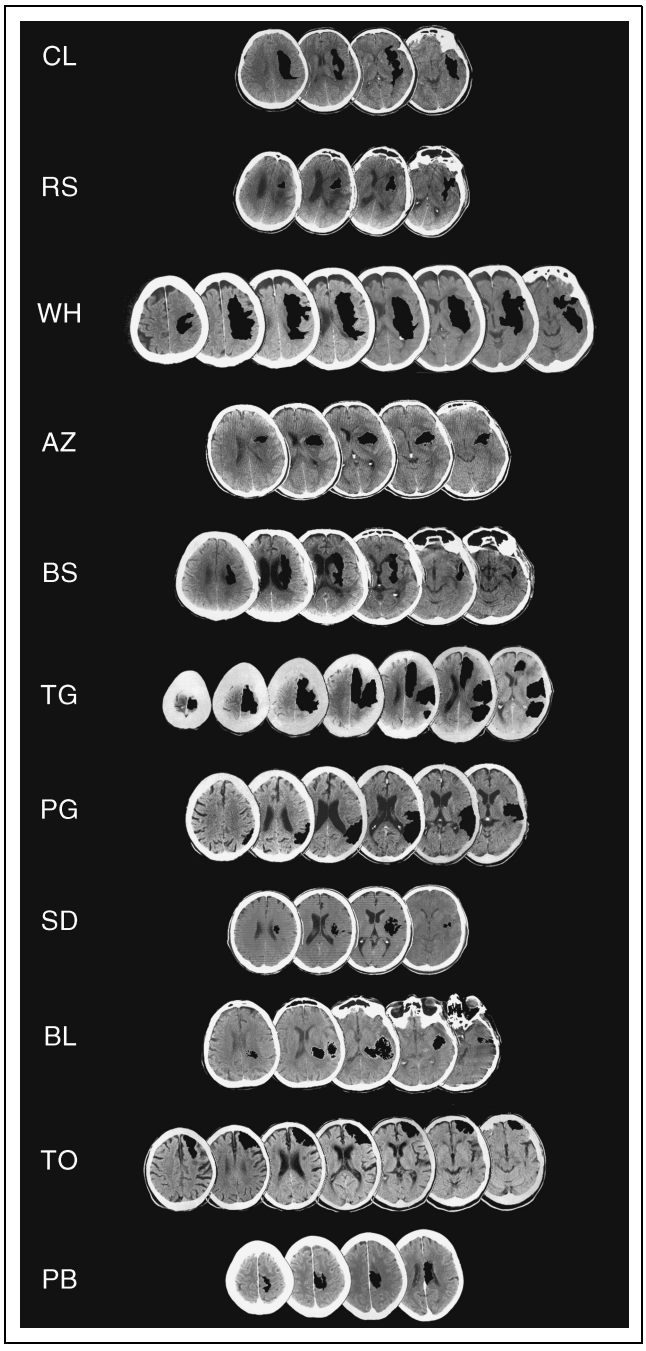

Figure 4. Lesion reconstruction for RBD patients using MRIcro software (www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). The figure shows the site and the size of the lesion (colored in black) for each extinction patient.

neglect were assessed and scored according to a standard neurologic examination (Aglioti et al., 1998, 1999). Motor impairment was examined by asking subjects to maintain arms flexed at 45°, forearms extended with the palms up, and fingers abducted for 30 sec. Anosognosia was tested by recording the patients' spontaneous reports about their deficits. Personal neglect was assessed by asking subjects to touch with the ipsilesional hand different body parts pointed to by an examiner. Extrapersonal neglect was assessed by drawing from copy, drawing from memory, sentence reading, and cancellation tests. Extinction was clinically assessed by delivering to each patient a fixed random sequence of 10 single left, 10 single right, and 20 bilateral simultaneous light touches for tactile extinction, 10 single left, 10 single right, and 20 bilateral simultaneous finger twitches for visual extinction and 10 single left, 10 single right, and 20 bilateral simultaneous finger snaps for auditory extinction. Patients were considered to have extinction when they omitted at least 30% stimuli upon double stimulation and detected at least 70% of single stimuli. Further clinical information is reported in Table 4.

One ambidextrous and 19 right-handed normal subjects (8 men and 12 women) served as controls. Their mean age was 55.4 years (*SD* 15.8, range 24–77), and their mean education was 12.7 years (*SD* 5.4 years, range 4–19 years). Two separate two-tailed t tests showed the absence of statistically significant difference between the two groups in age or education [Age: $t(29) = 1.6$, $p = .12$; Education: $t(29) = -1.42$, $p = .16$]. An additional 59-year-old, right-handed man (CG) with 8 years of education was tested in the spatial and spatio-temporal tasks. CG suffered from an ischemic lesion centered upon the right internal capsule, but he did not show any signs of extinction or neglect. Patients and controls were submitted to two types of computer-controlled tactile tasks, one spatial and the other spatio-temporal, with the order of the two tasks counterbalanced across participants. Moreover, the performances of extinction patients were compared in the clinical and computer-controlled tasks for assessing spatial extinction.

Apparatus, Stimuli, and Procedure

Subjects were seated with the hands resting on a table. In order to avoid influences of shifts of visual attention on tactile attention (Vaishnavi et al., 2001), subjects were requested to maintain fixation on a central point aligned with their corporeal midline. Tactile stimuli consisted of nonnoxious 1 msec electric stimuli delivered by means of punctiform electrodes, 1 mm in diameter, positioned on the left and right index fingers. The electrodes were activated by Single Phase Current Stimulators (STM 140, High Technology Laboratory, Udine, Italy) under the control of a PC computer programmed with the software package Micro Experimental Laboratory (MEL), Version 2 (Schneider, 1988).

For each subject, the intensity of single stimuli delivered to the contralesional hand was set at a value that allowed the detection of 5 stimuli out of 10 (threshold level). Then, the intensity was increased so as to obtain that at least 8 out of 10 single stimuli were detected. Stimuli with this intensity delivered to the ipsilesional hand were typically perceived as too

Table 4. Additional Clinical Information on RBD Extinction Patients

Patient	Extinction			Motor Deficit	Anosoagnosia	Neglect		Interval (months) Lesion Test
	Tactile	Visual	Auditory			Personal	Extrapersonal	
CL	+	+	NT	+	−	−	−	1
RS	+	+	+	+	−	−	−	91
WH	+	−	−	+	−	−	−	3
AZ	+	+	+	+	−	−	−	1
BS	+	+	−	+	−	−	−	4
TG	+	−	−	+	−	−	−	28
PG	+	+	+	+	−	−	−	3
SD	+	−	−	+	−	−	−	5
BL	+	−	+	+	−	−	−	4
TO	+	−	−	+	+	−	−	1
PB	+	−	+	+	−	−	−	6

The + sign indicates the presence of deficit.

much intense. Thus, intensity adjustments were made for avoiding painful sensations on the ipsilesional side and for ensuring an approximate intermanual perceptual equivalence. In the patients group, the resulting mean intensity values were 21.2 (*SD* 16.4) mA for the left hand and 10.8 (*SD* 7.6) mA for the right hand. Although intensity values were higher on the contralesional than on the ipsilesional side, the difference was not statistically significant according to a paired t test [$t(10) = 1.9$, $p = .09$]. Mean intensity values used in healthy controls were 9.9 (*SD* 14.1) mA for the left hand and 8.0 (*SD* 10.4) mA for the right hand, a difference that was not statistically significant according to a paired t test [$t(19) = .8$, $p = .4$].

On each trial, responses were entered into a computer by an experimenter and stored for automatic analysis. Comprehension of the instructions for each task was checked by giving to each subject at least 20 practice trials. Pauses were commensurate to the subject's fatigue. No feedback about response correctness was given during testing.

Spatial Extinction Computer-Controlled Task

An experimenter pressed a key on the computer keyboard to initiate a trial. After an interval, which varied randomly from 1100 to 2300 msec, stimuli were delivered singly to either hand or simultaneously to both hands. On each trial, subjects were asked to report verbally the number of stimuli (one or two) and their side (left, right, or both). Subjects were previously informed that stimuli could be single or double, and they were asked to respond only after hearing a beep signal. All subjects performed at least two blocks of trials. Each block consisted of 20 left and 20 right single stimuli, 20 double simultaneous stimuli and four catch trials.

Spatio-Temporal Extinction Computer-Controlled Task

Single and double stimuli were delivered as in the spatial task, except that bilateral stimuli could be not only simultaneous (SOA 0), but also separated by 1 out of 14 possible SOAs. The stimulus to the left hand could precede the stimulus to the right hand by 50, 100, 200, 300, 500, 700, 900 msec (these SOAs will be arbitrarily designated as negative), and the stimulus to the right hand could precede the stimulus to the left hand by the same SOAs (these SOAs will be arbitrarily designated as positive). Each subject performed in at least four blocks of trials. Each block was constituted by two single left stimuli, two single right stimuli, eight simultaneous bilateral stimuli, and two bilateral stimuli for each possible positive or negative SOA, plus four catch trials without stimuli. The ratio between synchronous and asynchronous stimuli was therefore 1:3.5. The sequence of single and bilateral stimuli and catch trials was randomized. SOAs and sequence of presentation (left-first or right-first) were also randomized. Subjects were informed prior to testing that stimuli could be single or bilateral, and that bilateral stimuli could be synchronous or asynchronous. On each trial, they were asked to report, verbally or through gestures, the number of the stimuli (1 or 2), their side (left, right, or both hands). In trials where double stimuli were correctly detected, subjects reported whether stimuli were simultaneous or whether one stimulus in the pair preceded or followed the other. The order of the number and location reports was not constrained. In a similar vein, either right- or

left-first, or right- or left-second responses were allowed. It is important to note that subjects typically summarized in a single answer (e.g., right-first) all the possible questions (one or two stimuli, simultaneous or sequential, the right preceded or followed the other) of each trial. Subjects were instructed not to respond until after hearing a beep signal which was delivered within a random interval of 300–800 msec after the second stimulus.

Modified Version of the Spatio-Temporal Computer-Controlled Task

One of the 11 extinction patients (PB) was also tested in a modified version of the spatio-temporal task in which the ratio between synchronous and asynchronous trials was 1:1 (instead of 1:3.5). Each block consisted of 4 single trials (two left and two right), 56 double simultaneous and 56 double sequential trials (4 for each out of 14 SOAs), and 4 catch trials. Patient PB was tested in four blocks thus providing a total of 224 double simultaneous and 224 double sequential trials.

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