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Uni- and cross-modal temporal modulation of tactile extinction in right brain damaged patients

Domenica Bueti [a], Marcello Costantini [b], Bettina Forster [c], Salvatore M. Aglioti [a,*]

[a] *Dipartimento di Psicologia, Università di Roma "La Sapienza" and Centro Ricerche di Neuropsicologia, IRCCS, Fondazione Santa Lucia, Via dei Marsi 78, 00185, Roma, Italy*

[b] *Dipartimento di Scienze Cliniche e delle Bioimmagini, Università "G. D' Annunzio", Chieti, Italy*

[c] *Department of Psychology, Birkbeck College, University of London, London, UK*

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Abstract

The influence of ipsilesional tactile and visual stimuli on the ability to detect contralesional tactile stimuli was investigated in eight right brain damaged patients (RBD) with tactile extinction and in eight healthy subjects by delivering a series of single and double stimuli. Double stimuli were unimodal (tactile or visual) or cross-modal (tactile and visual) and could be delivered simultaneously or sequentially at three possible intervals (65, 125, 305 ms). In sequential double trials, left-sided stimuli preceded or followed right-sided stimuli. Subjects were asked to verbally report number (1 or 2), side (left or right) and modality (tactile, visual, visuo-tactile). Control subjects were highly accurate in detecting single and double stimuli. RBD patients detected all right-sided stimuli and left single visual or tactile stimuli with high accuracy; however, they omitted left-sided tactile stimuli in a high proportion of double trials due to the presence of tactile extinction.

Omissions of left-sided tactile stimuli were minimal at the longest SOA. Moreover, at 0 and 65 ms SOA omissions were significantly higher in unimodal than in cross-modal combinations. This figure indicates that detection of contralesional tactile stimuli is modulated over time both uni- and cross-modally.

Keywords: Tactile extinction; Cross-modal integration; Visuo-tactile interactions; Brain damaged patients; Temporal attention

1. Introduction

The term 'extinction' is used to indicate a phenomenon frequently observed following unilateral cerebral lesions centred upon cortical or subcortical structures of the brain (Vallar, Rusconi, Bignamini, Geminiani & Perani, 1994). Patients with extinction are typically able to detect any single sensory stimulus, but fail to detect the same stimulus delivered in the contralesional personal or extrapersonal space when it appears concurrently with an ipsilesional stimulus (Critchley, 1949). Since extinction patients can detect single stimuli delivered contralesionally, it is unlikely that primary sensory disorders play a crucial role in determining this disorder. Several lines of evidence hint at the role of spatial attention in modulating extinction (Critchley, 1949; Karnath, Niemeier & Dichgans, 1998). Competitive models of selective spatial attention (Bundesen, 1990; Husain & Rorden, 2003; Koch & Ullman, 1985) postulate that two simultaneous stimuli delivered in opposite hemispaces compete with one another. Cerebral lesions, particularly when they involve the right hemisphere, may induce attentional imbalances that bias the competition in favour of the ipsilesional stimulus (Smania, Martini, Prior & Marzi, 1996).

Studies of extinction to double simultaneous stimulation typically employ pairs of unimodal visual, tactile, auditory (Barbieri & De Renzi, 1989) and, in a few reports, olfactory (Bellas, Novelly, Eskenazi & Wasserstein, 1988) or gustatory stimuli (Andre, Beis, Morin & Paysant, 2000; Berlucchi, Moro, Guerrini & Aglioti, 2004). However, in daily life conditions, sensory stimuli competing for attentional resources may arise in the same or in different modalities (Driver & Spence, 1998; Spence, Shore & Klein, 2001). Therefore, it is surprising that studies of extinction using competing stimuli from different modalities have been carried out only recently. Moreover, one of the first clinical studies on this issue failed to find cross-modal visuo-tactile extinction in patients with unimodal tactile and visual extinction (Inhoff, Rafal & Posner 1992). A resurgence of interest in cross-modal extinction is related to recent neurophysiological studies in monkey cortical (premotor and parietal) and subcortical (putamen)

* Corresponding author. Tel.: +39-06-49917601; fax: +39-06-49917635.
E-mail address: salvatoremaria.aglioti@uniroma1.it (S.M. Aglioti).

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areas. These studies recorded neurons sensitive to touches on one hand and to visual stimuli delivered in a 3D area extending about 20–30 cm around the space ipsilateral to the hand itself. Remarkably, when the hand was moved towards the contralateral space, the visually responsive area of these neurons followed the hand and thus maintained a precise spatial register between touch and vision (Graziano, Yap & Gross, 1994; Graziano, 2001). It may be that this type of neuron is the neural basis of integrated representation of tactile and visual inputs in the peripersonal reaching space (Rizzolatti, Fadiga, Fogassi & Gallese, 1997). More recent clinical studies have found cross-modal visuo-tactile extinction in brain damaged patients (Di Pellegrino, Làdavas & Farné, 1997b; Ladavas, Di Pellegrino, Farne & Zeloni, 1998; Mattingley, Driver, Beschin & Robertson, 1997). In most of these studies, however, visual and tactile stimuli were delivered manually. This procedure is potentially confounding since it is impossible to accurately control for the physical parameters of the stimuli. Similar to a series of studies on a single patient (Maravita, Husain, Clarke & Driver, 2001; Maravita, Spence, Clarke, Husain & Driver, 2000), this source of spurious variance is taken into account here by controlling the experimental stimuli with a computer.

Studies on healthy subjects show that once a visual stimulus is identified, the ability to discriminate a second stimulus in the same modality presented in a rapid serial visual presentation (RSVP) task is impaired for time lags of about 400 ms (Duncan, Ward & Shapiro, 1994; Shapiro, Raymond & Arnell, 1994; Raymond, Shapiro & Arnell, 1992). This phenomenon, called attentional blink or dwell time, indicates that attentional processing of the first target interferes with processing of the second stimulus, and that the temporal interval during which this interference occurs provides an index of the ability to deploy attention in time (Chun & Potter, 1995). Interestingly, a recent fMRI study on normal subjects provided evidence for activation of right intraparietal and frontal structures associated with the attentional blink (Marois, Chun & Gore, 2000). Husain et al. (Husain, Shapiro, Martin & Kennard, 1997) found that visual attentional blink effects in neglect patients were three times longer than in normal individuals. Since visual stimuli were presented at the same central spatial location, the observed difficulty in identifying the second stimulus indicates a pure temporal dimension of neglect. Di Pellegrino and co-workers (Di Pellegrino, Basso & Frassinetti, 1998) tested a single extinction patient in a version of an attentional blink task that required the identification of two letters presented bilaterally and separated temporally by SOAs ranging from 0 to 1000 ms. Detection of the left contralesional stimulus increased with the temporal interval of asynchrony, regardless of which letter appeared first. In another experiment with the same patient, Di Pellegrino and colleagues (Di Pellegrino et al., 1998) examined the same attentional dwell time task. However, this time both stimuli were presented in the contralesional or the ipsilesional field. As expected, the ability to identify the second stimulus was related to its temporal separation from the first. Interestingly, temporal intervals that minimised interference effects were twice as long in the contralesional as in the ipsilesional conditions (600 ms vs. 300 ms), an effect found also by Cate and Behrmann (Cate & Behrmann, 2002). Synchronous bilateral stimulation has been frequently used to study tactile extinction (Aglioti, Smania & Peru, 1999; Shore, Spence, & Klein, 2001; Titchener, 1908). By contrast, asynchronous bilateral stimulation has been largely restricted to investigations on visual extinction. Only three previous studies have been carried out with non-visual asynchronous bilateral stimuli, namely, a pioneering experiment with tactile stimuli by Birch and colleagues (Birch, Belmont & Karl, 1967) and two more recent studies with tactile (Guerrini, Berlucchi, Bricolo & Aglioti, 2003) and auditory stimuli (Karnath, Zimmer & Lewald, 2002).

The present study expands on previous research by testing whether temporal modulation of extinction has comparable characteristics when pairs of stimuli competing for attentional resources belong in the same or in a different modality. With this aim, we assessed the ability of RBD patients with tactile extinction and of healthy subjects to detect unimodal (visual or tactile) or cross-modal (visuo-tactile) pairs of stimuli delivered simultaneously or sequentially in the two hemispaces.

2. Methods

2.1. Subjects

Eight right-handed patients (three women) with unilateral lesions to the right side of the brain, selected for the presence of tactile extinction (ascertained by means of the tests described below), participated in the study. Site and extent of the lesions are shown in Fig. 1.

Mean age of RBD patients was 61.9 years (S.D. = 13.3, range = 32–76) and mean schooling was 8 years (S.D. = 5.1, range = 3–18). Eight age (mean 65.7 years, S.D. = 12.7, range = 51–79) and education (8 years of school, SD = 4.8, range = 3–15) matched healthy subjects served as controls. All patients completed series of neuropsychological tests aimed at assessing visual and sensorimotor deficits and visual and tactile extinction. The presence of hemispatial deficits was assessed by using a series of standard tests (Aglioti et al., 1999; Peru, Moro, Avesani & Aglioti, 1996). Tactile extinction was tested by delivering single or double light touches to the dorsum of the hands with flexible plastic sticks (9.5 cm long with a diameter of 2 mm). Each stick was bent to obtain the same curvature. Thus, it was possible to deliver touches of about 0.34 N on both sides. Visual and tactile extinction were both tested in blocks of 20 unilateral (10 on the left and 10 on the right) and 10 bilateral trials. Subjects were considered to have visual or tactile extinction when the value of the extinction rate (difference in accuracy between single and

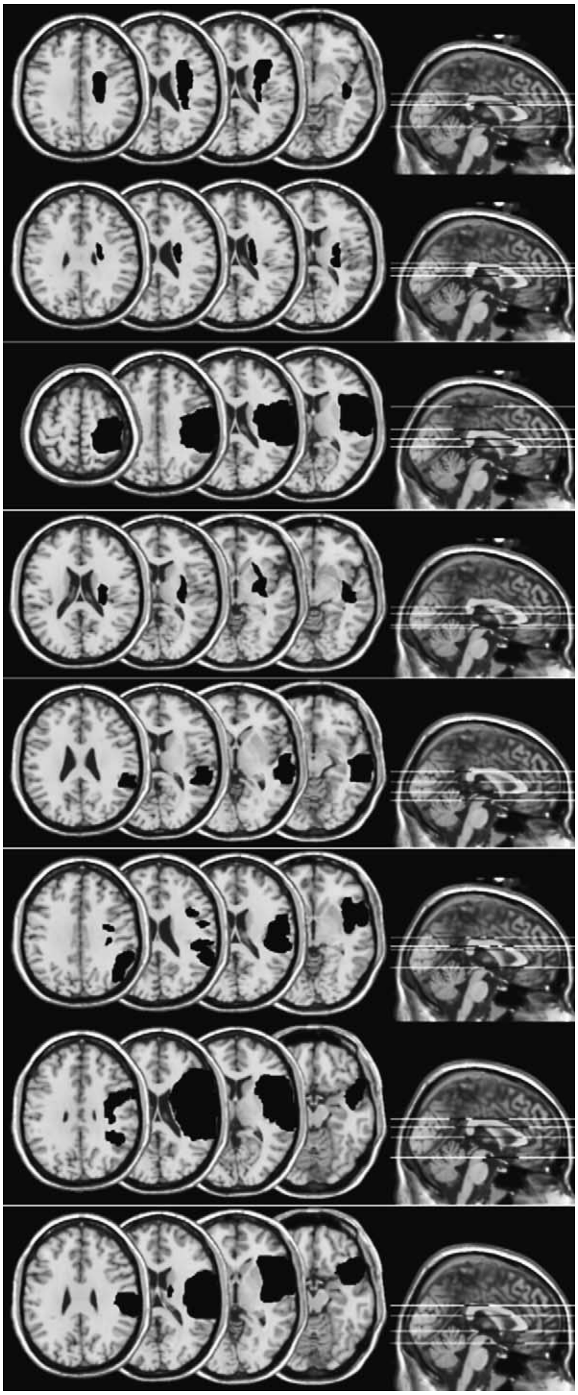

Fig. 1. Lesion reconstruction for RBD patients using MRIcro software (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). The figure shows site and size of lesion (coloured in black) for each RBD patient.

double) was at least 30%. Visual extinction was assessed by a confrontation technique in which the examiner moved one or both index fingertips for about 1 s in the left, the right, or in both visual hemifields. This confrontation procedure was also used to ascertain that the contralateral visual field was intact in all patients. No patient showed signs or symptoms of widespread mental deterioration or of psychiatric disease. Further clinical details on the patients are provided in Table 1.

Table 1
Characteristics of the experimental group

RBD	L–T (days)	Md	An.	ExN	PeN
1	75	+	−	−	−
2	36	−	−	−	−
3	63	+	−	+	−
4	72	+	−	−	−
5	60	+	+	+	+
6	210	−	−	+	+
7	150	+	−	−	+
8	92	+	−	−	−

L–T: interval between lesion and test; Md: motor deficit; An.: anosognosia; N: neglect; Ex: extrapersonal; Pe: personal; The sign (+) indicates the presence of deficit.

All subjects gave their informed consent after the non-therapeutic nature of the experimental tests was explained to them. The experimental protocol was approved by the local ethical committee.

2.2. Materials and procedure

The experimental stimuli consisted of series of single (tactile or visual, left- (L-) or right- (R-)) or double stimuli which were unimodal (two tactile or two visual, L and R) or cross-modal (one tactile L/1 visual R and one visual L/1 tactile R). Double stimuli could be delivered simultaneously (stimulus onset asynchrony 0) or sequentially (at three SOAs, namely, 65, 125 or 305 ms). In half of the asynchronous trials, left-sided stimuli preceded right-sided stimuli. The opposite was true in the other half. A monophasic electric current stimulator (STM 140, High Technology Laboratory, Udine, Italy) was used for the tactile stimulation. Tactile stimuli were non-noxious electric shocks delivered by electrodes (1 mm diameter) positioned on the palmar surface of the distal phalanx of the left and the right index finger. The intensity of the tactile stimulation was determined for each subject and in each experimental session. This procedure allowed us to deliver stimuli which were clearly detected and which were perceived with comparable subjective intensity on both fingers. Thus, it is not surprising that the intensity of the stimuli delivered to the contralesional finger was typically higher than that used for stimuli delivered to the ipsilesional finger (right side: mean±S.D. $= 4.4 \pm 4.3$ mA; Left side $= 12.2 \pm 15.4$ mA). Mean intensity values used in control subjects were 8.6 ± 14.7 mA for the right and 7.9 ± 9.6 mA for the left side. Visual stimuli were two red rectangles (1.5 cm high and 2 cm wide) made up of 12 square LEDs (each with 0.5 cm sides) fixed on a table and positioned about 7° L and R of a central fixation point. The LED luminance was 70 cd/m^2. The duration of visual and tactile stimuli was 5 ms. The LEDs and the electric stimulators were controlled by an IBM-compatible computer. The MEL2 (Micro Experimental Laboratory) software

(Schneider, 1988) was used to control presentation of the stimuli.

Each experimental block consisted of 64 trials, eight single (four visual and four tactile), eight double simultaneous (four unimodal, four cross-modal), 16 double sequential stimuli (eight L-first, eight R-first) for each of three SOAs. Each subject was tested in at least eight experimental blocks, thus providing a minimum of 512 values for analysis. Subjects were seated in a semi-dark room (approximately 10 cd/m^2 of background luminance) in front of the examiner. Their body midline was aligned with a fixation point located 57 cm from the plane of their eyes, and their hands were palm down on the table. Each hand was in its homonymous hemispace with each index finger in close contiguity with each LED (see Fig. 2). The experimental apparatus is schematically represented in Fig. 2.

Before starting the experiment, the subjects were trained with at least 10 practice trials. In each trial, an experimenter provided a verbal "ready" signal and pressed the computer spacebar to start the sequence of sensory events. The subjects, previously informed that the stimuli could be single or double, were requested to report verbally on number (one or two), side (left or right), and modality (tactile, visual or visuo-tactile). Moreover, in trials where two stimuli were detected subjects also reported which stimulus occurred first. Given the presence of extinction, however, the number of temporal order responses was unevenly distributed at the different inter-stimulus intervals. Thus, temporal order data will not be presented in the present paper. There were no constraints on the order of the responses. The subjects were instructed to wait for a verbal signal from the examiner before responding. It is important to note that after a few trials both patients and controls spontaneously reported all the attributes of the response (i.e., number, side, sensory modality and stimulus which occurred first). The verbal responses of the experimental subjects were keyed into the computer by one of the examiners. The order of presentation of each combination of stimuli was randomised. Since the experimenter was in front of the subjects, maintenance of fixation was checked on each perception–verbal response cycle by direct observation.

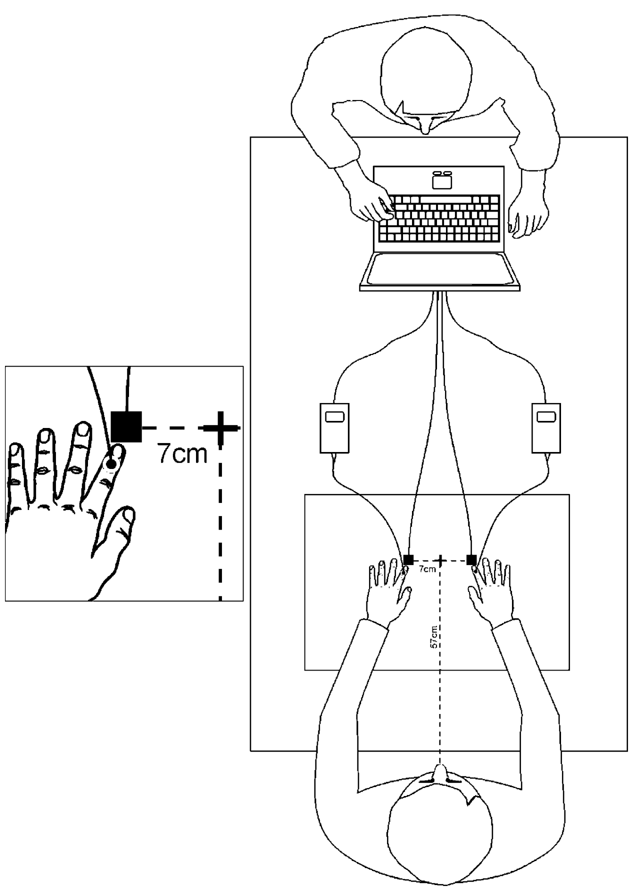

Fig. 2. Bird's eye view of the experimental apparatus. Subjects' verbal responses were stored in the computer and analysed off-line.

3. Results

Trials in which subjects failed to maintain fixation (<1%) or did not detect any stimulus in double stimulation conditions (<0.5%) were discarded. The ability to detect side and number of stimuli was close to 100% in control subjects. RBD patients detected visual and tactile ipsilesional (right-sided) stimuli with high accuracy in single (96.7%) and double simultaneous (97.7%) and sequential combinations (97.8%).

3.1. Omissions of contralesional stimuli

In single stimulation combinations, RBD patients detected 89.9% of left tactile stimuli and 95.9% of left visual stimuli. By contrast, they omitted the contralesional (left) tactile stimulus in a high percentage of the trials where double stimuli were delivered. It is relevant to note here that when single stimuli are detected with high accuracy, as in our conditions, omissions of left-sided stimuli in double stimulation conditions are a measure of extinction. Exploring how detection of contralesional tactile stimuli was temporally modulated by ipsilesional stimuli in the same or in a different sensory modality is relevant to the purposes of the present study. RBD omissions of left-sided touches and of left-sided visual stimuli are respectively plotted in Fig. 3 and Table 2. Since patients were selected on the basis of tactile extinction, it is no surprise that most of the 'extinguished' left-sided stimuli were tactile instead of visual. Percent omissions of left-sided

Table 2
Patients' percent omissions of left-sided visual stimuli in double uni- and cross-modal combinations

SOA	0	65	125	305
LR visual	**3.6** (2.5)	**5.5** (3.1)	**6.2** (2.4)	**7.3** (2.2)
L visual–R tactile	**6.6** (2.9)	**5.5** (2.6)	**4.7** (2.7)	**7.4** (2.3)

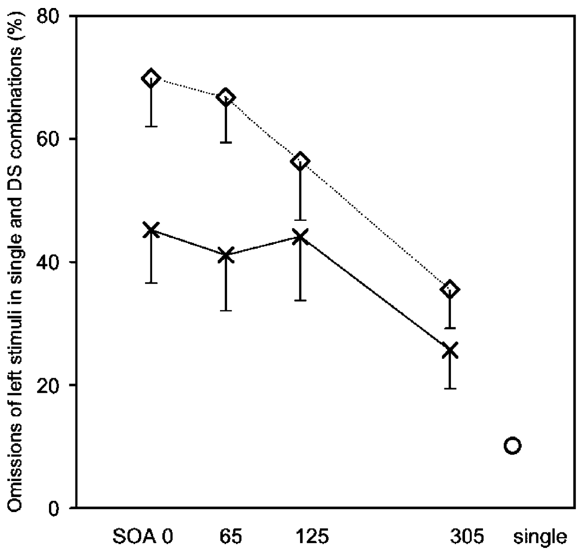

Fig. 3. Percent omissions of left-sided tactile stimuli under single and double uni-and cross-modal combinations. Means (and standard error) for asynchronous conditions are plotted independently from the sequence of presentation, i.e., after collapsing left-first and right-first combinations for each SOA. (Legend: (○) single; (◇) unimodal; (×) cross-modal.)

stimuli were entered in two separate ANOVAs, one for tactile and one for visual stimuli. Each analysis had two main factors: cross-modality (unimodal vs. cross-modal) and condition of stimulation (single, double SOA 0, SOA 65, 125, 305 ms). Post-hoc comparisons were carried out using the Newman–Keuls test.

3.1.1. Omissions of left-sided tactile stimuli

The factor cross-modality [$F(1, 7) = 6.14$, $P = 0.04$] was significant because more omissions of left-sided stimuli were made in unimodal tactile (47.7%) than cross-modal touch-left/visual-right (33.2%) combinations (see Fig. 3).

The significance of the factor condition of stimulation [$F(4, 28) = 16.14$, $P < 0.0001$] is explained by the fact that fewer omissions occurred in single-stimulus (10.1%) than in all double stimuli conditions (SOA 0 = 57.5%; SOA 65 = 53.9%; SOA 125 = 50.2%; SOA 305 = 30.6%). Moreover, omissions were significantly lower at SOA 305 than in all other double stimuli conditions ($P < 0.002$).

The interaction cross-modality × condition of stimulation was significant [$F(4, 28) = 3.68$, $P = 0.015$]. Post-hoc analysis revealed the following: in the unimodal combination, accuracy in the single stimulus condition was significantly higher than in all other conditions ($P < 0.001$), and accuracy at SOA 305 was significantly higher than at the other SOAs ($P < 0.001$). Moreover, accuracy at SOA 125 was marginally higher than at SOAs 0 and 65 ($0.05 < P < 0.07$) which in turn did not differ from one another. In the cross-modal combinations, accuracy in the single stimuli condition was significantly higher than in all other conditions ($P < 0.009$), and accuracy at SOA 305 was significantly higher than at the other three SOAs ($P < 0.01$), which in turn were not different from each other. It is important to note that at SOAs 0 and 65 ms performance was significantly better in cross-modal than in unimodal combinations ($P < 0.002$); by contrast, differences between uni- and cross-modal combinations failed to reach significance at S0As 125 and 305 ($P > 0.091$).

3.1.2. Omissions of left-sided visual stimuli

Table 2 shows percentage omissions of left-sided visual stimuli. No main effects or interactions were significant.

3.2. Influence of space and modality on contralesional omissions in double asynchronous conditions

It is important to emphasise here that in half of the asynchronous trials left-sided stimuli preceded right-sided stimuli and in the other half the opposite was true. Thus, hereafter SOAs will be arbitrarily indicated as negative or positive depending on whether left-sided stimuli preceded or followed right-sided stimuli. Omissions of left-sided stimuli in double asynchronous conditions, split according to which side was stimulated first, provided data for two repeated measures ANOVAs (one for left-sided tactile and one for left-sided visual stimuli). Each ANOVA had cross-modality (unimodal vs. cross-modal), stimulus onset asynchrony (double SOA 65, 125, 305 ms), and hemispace stimulated first (L-first, R-first) as main factors.

3.2.1. Influence of the hemispace stimulated first on left-sided omissions of tactile stimuli

Percent omissions of left-sided tactile stimuli in double asynchronous stimulation are reported in Fig. 4.

The ANOVA showed the following: the factor cross-modality [$F(1, 7) = 6.38$, $P = 0.030$] was significant because omissions of the contralesional stimulus were higher in unimodal (53.6%) than in cross-modal (37.0%) combinations. The factor SOA [$F(2, 14) = 14.79$, $P = 0.0003$] was significant because left-sided omissions at SOAs 65 and 125 (53.9 and 50.3%) were higher than at SOA 305 ms (31.7%, $P < 0.001$ in both cases). The interaction SOA × hemispace stimulated first [$F(2, 14) = 6.79$, $P = 0.008$] was

Table 3
Patients' percent omissions of left-sided visual stimuli in uni- and cross-modal combinations separated according to the precedence of stimulation

SOA	−305	−125	−65	65	125	305
LR visual	**3.6** (2.5)	**5.3** (2.0)	**6.1** (3.1)	**4.8** (3.2)	**7.0** (3.6)	**11.0** (2.9)
L visual–R tactile	**6.4** (2.7)	**5.4** (2.8)	**5.3** (3.8)	**5.6** (3.2)	**4.1** (2.8)	**8.5** (2.9)

Negative values indicate that the left hemispace was stimulated first.

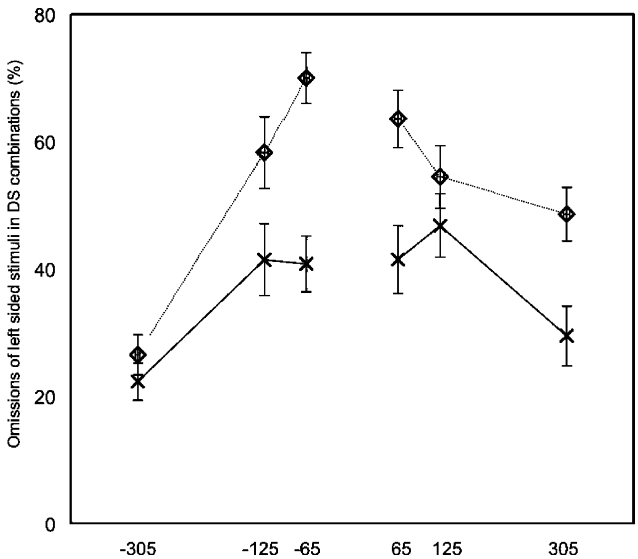

Fig. 4. Percent omissions of left-sided tactile stimuli in the different double asynchronous stimulation conditions for RBD patients. Negative SOAs indicate trials in which the first stimulus in a pair was delivered to the left hand and positive SOAs indicate trials in which the first stimulus in a pair was delivered to the right hand (in the unimodal combination) or to the right hemispace (in the cross-modal combination). Legend as for Fig. 3.

significant because omissions were higher when the right hemispace was stimulated first only at SOA 305 (R-first, 39.1%; L-first, 24.4%; $P = 0.001$). No other effects or interactions were significant.

3.2.2. Influence of the hemispace stimulated first on left-sided omissions of visual stimuli

As shown in Table 3 and confirmed by ANOVA, omissions of left-sided visual stimuli were not influenced by the hemispace which was stimulated first.

4. Discussion

Classical studies of extinction have been typically conducted by using pairs of simultaneous stimuli delivered in the same modality. In the past few years, however, research has been carried out on cross-modal visuo-tactile (Di Pellegrino, Basso & Frassinetti, 1997a; Di Pellegrino, Làdavas & Farné, 1997b; Ladavas et al., 1998; Maravita et al., 2000; Mattingley et al., 1997), audio–visual (Frassinetti, Pavani & Ladavas, 2002), and audio-tactile (Farné & Làdavas, 2002) extinction in brain damaged patients. Moreover, research in patients with unilateral brain damage and unimodal visual (Di Pellegrino, Basso & Frassinetti, 1997a; Di Pellegrino et al., 1998), auditory (Karnath et al., 2002), or tactile extinction (Guerrini et al., 2003) has provided important indications about the temporal course of awareness of bilateral stimuli in line with neuroimaging and neurophysiological studies suggesting that sensory stimuli compete for attentional resources in time as well as in space (Coull, Frith, Buchel & Nobre, 2000; Griffin, Miniussi & Nobre, 2002).

Results of the tactile extinction patients in the present study show, for the first time, that detection of a contralesional tactile stimulus is temporally modulated both uni- and cross-modally.

Omissions of contralesional stimuli under double stimulation conditions were much more pronounced for tactile than for visual stimulation. This cannot be attributed to sensory factors since accuracy was high and comparable for the two modalities in single stimulation combinations. Thus, it may be due to the impairment of some higher-order processing of somatic stimuli. One potentially important result of the current study is that significantly more left-sided tactile stimuli went undetected in unimodal (with another touch on the right) than in cross-modal (with a visual stimulus on the right) conditions. This figure would indicate that detection of contralesional tactile stimuli is modulated over time both uni- and cross-modally and that attention does not completely operate on a supramodal representation of the space. Duncan et al. (Duncan, Martens & Ward, 1997) provided clear evidence that there are separate attentional resources, at least for vision and hearing. Their study was elegantly simple. Two streams of stimuli were presented to the subject, and each could be visual or auditory. One target item appeared in each stream, and the subject just reported the targets. The authors found that attentional blink occurred when both streams were visual or when both streams were auditory. However, if one stream was visual and the other was auditory, there was no blink. In other words, when a visual target consumes visual attentional resources, it leaves resources available for an auditory task. However, these resources must be specifically auditory, because they are not available for a second visual task. In agreement with Duncan et al. (1997), we suggest that attentional resources must at least partly reside in modality-specific sensory systems.

In keeping with attentional blink studies on the temporal (Di Pellegrino, Basso & Frassinetti, 1997a; Di Pellegrino, Làdavas & Farné, 1997b; Husain et al., 1997) and spatio-temporal (Cate & Behrmann, 2002; Di Pellegrino et al., 1998) factors underlying visual extinction, the current study shows a clear time-related decrease of tactile extinction in both uni- and cross-modal combinations. Previous attentional blink studies in brain damaged patients found that dwell time effects (i.e., the interference of a first stimulus with processing of the second in a pair) are still detectable with SOAs within 1200 ms (Husain et al., 1997). Given the high number of possible combinations of sensory events, we had to use a limited number of SOAs. That a significant proportion of left-sided touches in double stimulation combinations is omitted even at the longest SOA (305 ms) may simply be due to the fact that this interval still falls within the attentional dwell time window. The earlier occurrence of temporal modulation in unimodal tactile but not in cross-modal visuo-tactile conditions may be related to the fact that visual stimuli are processed slower than tactile stimuli. Another effect deserving discussion is the higher number of left-sided omissions in right-first than in left-first conditions at an SOA of 305 ms. This result is accounted for by a model of extinction based on a presumed pathological difficulty in disengaging attention once it has been allocated to ipsilesional targets (Posner, Walker, Friederich, & Rafal, 1984). A novel implication of this result is that difficulties in attentional disengagement depend on selected temporal windows for both uni- and cross-modal stimuli.

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