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What exactly is extinguished in unilateral visual extinction? Neurophysiological evidence

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Abstract

We propose a model of unilateral visual extinction following right hemisphere lesions based on competition between contralesional and ipsilesional input to access a decision centre located in the left hemisphere. During bilateral presentations, the contralesional signal is on average less likely to activate the decision centre than the ipsilesional signal. This is because an intra-hemispheric lack of top-down attentional influences and an inter-hemispheric impairment of callosal transmission delay and/or weaken the contralesional input. Here we provide behavioural as well as event-related potential evidence for both these impairments. Finally, we argue that an essential prerequisite for contralesional extinction is the presence of a restricted general attentional capacity which often follows large right hemisphere damage.

Keywords: Event-related potentials; Reaction time; Right hemisphere lesions; Callosal transmission

1. Introduction

A lack of attention can exclude sensory information from consciousness. This happens only under certain perceptual conditions in normal subjects [43] but is a relatively frequent and disturbing perceptual phenomenon in patients with a large right hemisphere lesion usually including the parietal cortex. Spatial hemineglect and unilateral extinction are pathological consequences of right hemisphere damage in which awareness of the contralesional space may be absent despite lack of sensory loss [18,19,50]. In contrast to hemineglect, in extinction the perceptual impairment occurs only with bilateral simultaneous stimulus presentations. Thus, a stimulus in the contralesional space can be perceived or not depending upon the presence of another stimulus in the ipsilesional space. Despite the fact that often the two impairments are concomitant and that they share an exaggerated attentional bias toward the ipsilesional side and a lack of attention to events on the contralesional side, they should be considered as separate entities because they can occur independently [9] and may have different anatomical bases [66]. Both of these impairments can tell us a great deal about the mechanisms of normal perception and attention [18]. However, extinction, because of its presence only during stimulus competition, is more amenable to experimental investigation under controlled conditions in which neural responses to the same stimuli can be compared during lack of awareness and during normal perception [21,48,70]. Both neglect and extinction occur much more frequently following right than left hemispheric lesions but extinction can be not infrequently found following left hemisphere lesions [61]. The responsible lesion is often centred in the parietal lobe but usually includes neighbouring areas in temporal or frontal lobes or involves subcortical ascending pathways [66]. The presence of extinction only during bilateral stimulation is strongly suggestive of a competition mechanism [14,22] whereby the presence of a more salient stimulus presented on the same side of space as that of the brain lesion (ipsilesional side) captures attention and hampers the perception of a less salient stimulus on the opposite (contralesional) side. In normal perception a stimulus may be made more or less salient by manipulating its intrinsic properties such as size, brightness, colour, form, movement and so on, or

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by manipulating the observer's attentional bias. In extinction, saliency is manipulated by brain damage which renders ipsilesional stimuli more salient than contralesional stimuli. These therefore lose the competition for general attentional resources which are likely to be restricted given the prominent general role of the right hemisphere in attention [50].

Here we put forward a model of extinction that is essentially, but not exclusively, based on data gathered in brain-lesioned patients with the technique of event-related potentials (ERPs), a functional brain imaging technique which has contributed a great deal to an understanding of normal attentional mechanisms [23,30,42,44,51] and which is being used increasingly often to study selective attentional impairments [12]. Although we believe that the basic mechanisms of extinction can be generalised to all sensory modalities, we will explicitly refer in the model to vision since it is by far the modality for which most neurophysiological and behavioural evidence has been obtained. Our model is concerned with the simplest way of assessing extinction, namely stimulus detection with briefly presented unilateral versus bilateral patches of light. This is an experimentally controlled version of the clinical confrontation technique in which the stimuli are represented by the examiner's moving fingers. The tasks commonly used to test for extinction are either a simple numerosity judgement ('how many stimuli do you see?') or a more demanding task in which the patient is asked either to discriminate or to identify the stimuli in a pair. Extinction is considered to occur when detection, discrimination or identification of the contralesional stimulus (but not of the ipsilesional stimulus) is reliably worse during bilateral than unilateral presentations. Typically, the pairs of stimuli are presented to both hemifields across the vertical meridian but occasionally they have been presented within a single hemifield [7,15,58]. The implications of these various ways of testing extinction are noteworthy in terms of the cognitive operations as well as the neural pathways involved. In the simplest way of assessing extinction only detection is required, while in other occasions various more complex operations such as discrimination, identification or even classification [5] are required. By the same token, the neural pathways involved will obviously be different depending upon whether extinction is tested with pairs of stimuli presented initially to one or both hemispheres, as is the case for intra- versus inter-field testing in vision. The latter of course implies an interhemispheric interaction while in the former condition both stimuli in a pair are projected to a single hemisphere. Given the diversity of the methods a model of extinction must specify the cognitive operations involved in the task used and therefore our model refers to stimulus detection only. However, we believe that although the locus of extinction may differ in the different tasks [68,69], the basic mechanism is likely to be generalisable across tasks (detection vs discrimination) and across mode of stimulus presentation (inter- vs intrafield).

The model is based on the following three assumptions: (i) the pair of stimuli used to test for extinction race to access a centre in the left hemisphere where the decision about stimulus numerosity is made; (ii) the signal resulting from stimulation of the contralesional hemifield is weaker and on average reaches the decision centre after the ipsilesional stimulus; (iii) extinction occurs during double stimulation because of a competition between a stronger contralesional and a weaker ipsilesional signal in the presence of a generally restricted processing capacity. On single trials, in the absence of competitive stimuli, there is no race and even a weak contralesional stimulus can activate the decision centre.

In the following, we will try and bring evidence justifying the above three assumptions and will expand on the mechanisms whereby competition leads to unilateral extinction in brain damaged patients but not in normals, apart from special circumstances.

2. Evidence for a left hemisphere centre for numerosity judgement

Our model puts emphasis on the information processing aspects of the task commonly used to assess extinction and assumes that the decision about the numerosity of the stimuli presented across the whole visual field is made in the left hemisphere. The reasons why we assume a left hemisphere locus for this centre go beyond the very fact that usually extinction is assessed verbally and therefore numerosity information must eventually reach the hemisphere dominant for language. There are indications in the neuropsychological literature that decisions of the sort required in the simple version of the extinction task may be subserved by the left hemisphere independently from the verbal nature of the response [28,57,58,62,65]. At any rate, the type of response is undoubtedly an important factor influencing extinction rate as has been shown by Smania et al. [58]. A patient (CZ) with a vast frontal-parietal-temporal ischaemic lesion in the right hemisphere was tested for extinction under a variety of experimental conditions. Overall, it was found that the manipulation of response rather than input variables affected extinction rate to a larger extent. In particular, there was a considerable decrease of extinction when the patient used a non-verbal response such as moving the eyes to indicate the position of the stimuli (right deviation for right field stimuli, left deviation for left field stimuli and upward deviation along the vertical meridian of the visual field for bilateral stimuli). With such a

procedure, extinction rate of contralesional stimuli dropped significantly from 90% when using a verbal response to 22% with the oculomotor response. A similar drop in extinction was found when the number of stimuli had to be reported by the patient in a go-no-go paradigm by refraining from responding when he saw two stimuli rather than one. In both the above conditions, no verbal report was required and the task could have presumably be mastered by decision centres located in the right hemisphere with no need for an interhemispheric transfer to the left hemisphere of the visual information presented to the contralesional hemifield. Results seemingly at odds with Smania et al.'s [58] have been described by Bisiach et al. [6] on a large group of right brain damaged patients. These authors found a relatively modest, albeit reliable, improvement of detection rate of bilateral stimuli when using a verbal response (25% correct) in comparison to a motor response (13%). Their patients, however, showed a similar improvement with single contralesional stimuli (54% vs 34%) and therefore the mechanism of such improvement may not be specifically related to a decrease of extinction.

3. Evidence for an abnormal contralesional signal

3.1. Behavioural evidence

The conventional view that contralesional input is substantially normal in extinction, as supposedly shown by preserved detection of isolated contralesional stimuli on unilateral trials, is no longer tenable following behavioural demonstrations that the input from the contralesional side is abnormal. Using a simple reaction time (RT) paradigm involving detection of brief light flashes, Marzi et al. [47] and Smania et al. [59] have shown in extinction, as well as in neglect patients, that the unilateral contralesional input is detected with a greater difficulty and with a longer latency than the ipsilesional input. Interestingly, Marzi et al. [47] found a positive correlation between contra-ipsilesional RT differences and severity of extinction. That is, patients with a higher disadvantage of the contralesional hemifield showed a higher extinction rate than patients in whom this difference was smaller. This is supportive of a race model whereby a degraded contralesional signal is on average slower to activate a putative decision centre than its ipsilesional counterpart. To try and clarify the role of any primary sensory loss in the contra-ipsilesional difference in extinction patients, in our laboratory, we recently compared right brain damaged extinction patients without field loss (in the area of stimulus presentation) with right brain damaged patients without extinction and normal controls, see (Table 1) in speed of response to brief single visual stimuli presented in the contralesional and ipsilesional hemifields; for methods and statistical results, see caption of Fig. 1.

The results are shown in Figs. 1 and 2: For both the contra- and the ipsilesional side, patients with extinction showed longer RTs than right brain damaged without extinction and normal controls. Furthermore, for both extinction and right brain damaged controls, RT was slower in the contralesional than in the ipsilesional hemifield but this difference was more evident in the extinction group, as shown in Fig. 2.

Table 1

Patients	Age/Sex	Time since lesion (days)	Lesion side (CT or MRI)
RBD with extinction			
S.P.	66/M	926	Right temporo-parietal
B.M.	82/M	153	Right thalamic, capsular
S.A.	74/M	155	Right fronto-temporo-parietal; right insula, basal ganglia, internal capsule
P.R.	58/M	996	Right fronto-temporo-parietal; right basal ganglia, optic radiations, internal capsule
M.T.	68/M	388	Right temporo-parieto-occipital; right optic radiations
A.C.	67/F	85	Right fronto-temporo-parietal
C.Z.	48/M	691	Right fronto-temporo-parietal; right insula, basal ganglia, optic radiations, internal capsule
C.M.	71/M	183	Right fronto-temporo-parietal; right insula, basal ganglia, optic radiations, internal capsule
RBD controls			
B.C.	62/M	10	Right basal ganglia
R.M.	77/F	15	Right centrum semiovale
M.D.	69/F	31	Right pontine
E.N.	18/M	66	Right paracapsular
O.C.	79/M	11	Right frontal
E.B.	71/M	26	Right capsular
L.C.	68/M	37	Right capsular
A.V.	46/M	56	Right surgical ablation of a ventricular tumour

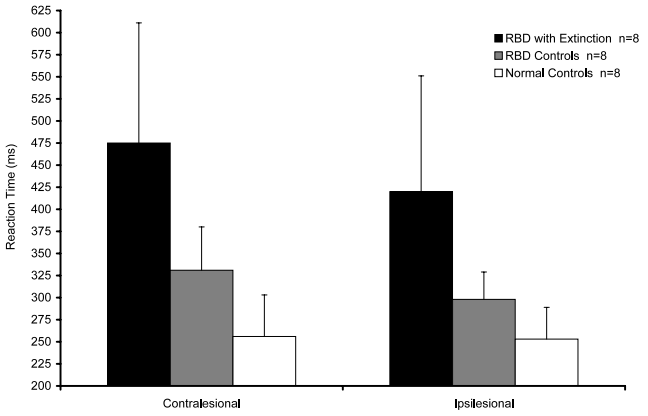

Fig. 1. Mean reaction time for stimuli presented at 10° in the contralesional or ipsilesional hemifield of right brain damaged (RBD) patients with extinction, RBD patients without extinction and matched normal controls. In normal controls contra- and ipsilesional refer to left and right hemifield, respectively. The subjects were seated in front of a horizontal arc perimeter with the head restrained by a chin- and a front-rest. Attached to the bar at 10° of visual angle from a central fixation point were two 0.5° diameter LEDs emitting a light of ~ 100 cd/m^2 luminance against a background of ~ 1 cd/m^2 luminance. Activation of the LEDs was controlled by means of a portable PC which allowed us to program the stimulus duration (10 ms) and to randomly alternate the side of stimulus presentation (left or right visual hemifield). Subjects were asked to keep fixation on the central point of the perimetric bar and to respond to the presentation of a lateralised flash by pressing as quickly as possible with the index finger of the ipsilesional hand the space bar of the PC keyboard placed in front of them. Subjects' fixation was carefully controlled by the examiner and in the rare occurrence of an eccentric fixation the trial was cancelled. We also discarded trials in which RTs were shorter than 140 ms (anticipations) or longer than 800 ms (retards). Two separate sessions were carried out and in each of them 20 trials were run for each side of stimulus presentation. Therefore, the overall number of stimuli presented to each subject was 80. A Kruskal–Wallis H test revealed significant differences between subjects groups ($\chi^2 = 14.601$; $P < 0.001$). Post hoc U tests showed significant differences for all comparisons between the three groups, RBD patients with and without extinction ($P = 0.028$), patients with extinction and normal controls ($P < 0.0001$), RBD and normal controls ($P = 0.015$).

By extrapolating these results obtained with single stimuli to what presumably occurs during bilateral stimulation, one can conclude that there is a perceptual advantage of the ipsilesional stimulus that may amount to several tens of milliseconds. In a patient with a restricted processing capacity and with an ipsilesional attentional bias, as is the case with patients with large right hemisphere lesions, this may lead to extinction because by the time the contralesional input arrives, the decision centre is already committed to processing the ipsilesional signal. A crucial question of course, concerns the nature of the contralesional input's abnormality. One possibility is that it is related to an attention imbalance favouring the ipsi- at the expenses of the contralesional hemifield [20,59]. We have recently obtained evidence in neglect patients as well as in extinction patients, that the contralesional impairment is related to a deficient exogenous orienting of spatial attention (Natale et al., in preparation). In contrast to endogenous attention, exogenous attention is stimulus driven and uncontrolled [4,34,64]. It is the typical kind of attention subserving quick responses to rapidly appearing unexpected stimuli. By using a simple RT paradigm for the detection of brief light flashes presented at various eccentricities along the horizontal meridian we confirmed previous results that neglect as well as extinction patients showed an abnormally prolonged RT and a lower detection rate in the contralesional hemifield in comparison to the ipsilesional hemifield [59]. In addition, in the latter hemifield there was a paradoxical tendency to respond more quickly and accurately at progressively increasing eccentricities up to about 20°. This is a paradoxical effect because in normal subjects RT tends to become progressively slower as one goes from central to more peripheral portions of the visual field [8,45]. How can one interpret the contralesional slowing down and the ipsilesional speeding up of RT? Is it related to an asymmetric distribution of exogenous or endogenous attention? To disentangle the relative contributions of the two kinds of attention, we manipulated the probability of stimulus occurrence in given positions of the visual field. We compared RT and detection rate in a condition of randomised stimulus presentation (i.e. each stimulus equiprobable at a given position) with a condition in which the stimuli were presented to one particular position throughout a block of trials. In the former condition, the patients' performance should depend upon exogenous attention while in the latter it should depend on active focusing of endogenous attention on the point of stimulus presentation. This simple technique avoids the complexities of central and peripheral cueing inherent in the well known paradigm used by Posner and collaborators to study covert visual attention [53] while enabling a separation of controlled and

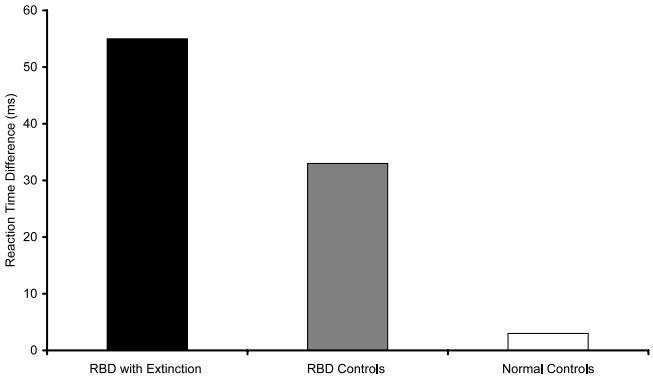

Fig. 2. Difference between mean reaction time for stimuli presented contra- or ipsilesionally at 10° in right brain damaged (RBD) patients with extinction, in RBD patients without extinction and in normal controls.

automatic components of spatial attention. Not unexpectedly, the blocked conditions yielded faster RTs than the randomised condition. Interestingly, however, this was true for the contralesional as well as the ipsilesional hemifield. This suggests that neglect patients can still benefit from focusing their attention on the contralesional side, hence that they have a relatively preserved endogenous attention, see also [4,35,53]. In spite of that, overall speed and accuracy of response in the contralesional field were still very much impaired in comparison to the ipsilesional field and this suggests that the bulk of the deficit is related to exogenous attention. In other words, the automatic triggering of attention related to the sudden onset of a peripheral visual stimulus is delayed for contralesional stimuli in neglect and extinction patients and this cannot be overcome by an endogenous attentional focusing. In principle, the contralesional slowing down of RT as well as the lower detection rate might be ascribed to a mild undetected sensory loss rather than to defective exogenous attention. This possibility is made unlikely by our results reported above and shown in Figs. 1 and 2 in which we made sure to present the stimuli in areas without a field loss. In addition, the possibility of a sensory explanation is made unlikely by the observation that the impairment shows a left–right gradient with a maximum in the contralesional periphery and a minimum in mid-periphery areas of the ipsilesional visual field. It is not easy to think of a sensory loss which increases progressively as one goes from central to peripheral retinal locations, while this is predicted by attentional theories of neglect such as Kinsbourne's ([38], see also [18,19]). The idea that automatic attentional processes are selectively impaired in neglect patients has been put forward repeatedly [13,26,39,40]. Recently, Bartolomeo et al. [4] in a series of cued RT experiments on neglect patients have shown a clear dissociation between stimulus-driven attentional focusing, which was impaired, and endogenous attentional focusing, which was preserved but slowed.

That the impairment in the detection of single contralesional stimuli may lie in a deficit of automatic attentional mechanisms is indirectly confirmed by recent results obtained in our laboratory on a motoric correlate of extinction, which suggests a forceful attentional capture by ipsilesional stimuli. Fanini and Marzi [24] used a simple manual RT paradigm, with eccentric left- or right-hemifield visual stimuli, and found that extinction patients showed a relatively high proportion of unwanted reflex-like saccades despite their being instructed to keep fixation steady on a central fixation point. The average latency of these reflex-like saccades was much longer than the duration of the visual stimulus and therefore they could not be possibly responsible for the contralesional extinction observed. The interesting result was that with unilateral stimuli the proportion of unwanted saccades was roughly similar for the two hemifields. In contrast, with bilateral stimulation, the vast majority of unwanted saccades was directed toward the ipsilesional field. Furthermore, there was a tendency for a higher proportion of ipsilesional saccades with extinguished (24%) than non-extinguished (14%) left hemifield stimuli during bilateral trials, although this difference did not reach statistical significance. This result represents a 'motoric' analogue of extinction and shows that stimulus competition concerns reflex-like saccades and not only perceptual processing. This is in broad keeping with previous observations in neglect patients [13,26] showing forceful ipsilesional overt orienting of attention toward the ipsilesional space. These results may be related to unilateral damage to a human analogue of the LIP area in the monkey's parietal lobe whose reversible inactivation impairs contralesional saccades [41]. It is interesting, however, to point out that in Fanini and Marzi's [24] study the contralesional impairment appeared only with bilateral stimuli and therefore cannot be related to an abnormal programming of saccades but to a visual extinction-like effect.

3.2. Electrophysiological evidence from ERPs

The behavioural experiments mentioned above provide evidence that in extinction patients contralesional stimuli are responded to more slowly because of impaired stimulus-driven attentional processes. However, the neural bases of this impairment are difficult to assess with behavioural experiments alone, while it is possible to get further understanding of the possible neural mechanisms by using ERPs [12]. Spinelli and her collaborators have found that in neglect patients the contralesional signal is delayed and shows varies other abnormalities. They argue for a sensory type of loss even in patients without a clinically manifest hemianopia [1,2,17,60]. An impairment in processing left hemifield stimuli in patients with attentional impairment as a result of right parietal damage has also been described by Verleger et al. [67] as well as by Marzi et al. [46] and Rees et al. [54]. Finally, in the auditory modality, Deouell et al. [11] have demonstrated that an early process related to exogenous orienting such as the mismatch negativity in auditory tasks is impaired in neglect patients. Further evidence showing an impairment of the contralesional input has been provided recently in our laboratory. We recorded visual ERPs from four extinction patients (see Table 2) by using small luminous rectangles briefly presented at 7° either to the contra- or to the ipsilesional hemifield in a randomised sequence. Data analysis was performed using measures of the mean voltage value (mean-amplitude) over successive time bins in steps of 20-ms intervals (10 data points) between 0 and 400 ms. Differences

Table 2

Patients	Age/sex	Time since lesion (days)	Visual deficit	Lesion side in the right hemisphere (Brodmann areas)							
				Frontal	Parietal	Temporal	Occipital	BG	OR	IC	Th
B.M.	82/M	153	Absent	–	–	–	–			**	**
C.Z.	48/M	663	Left partial haemianopia	4-6-44-45	1-2-3-5-7-39-40	21-22-38	–	*	*	*	
R.P.	58/M	996	Left sensory reduction	4-6-44-45	1-2-3-40	22-37-41-42	–	*	*	*	
L.G.	59/M	61	Left partial haemianopia	6	1-2-3-40	19-37-38-22-41-42	19		**	*	*

BG = basal ganglia; OR = optic radiations; IC = internal capsule; * = small lesion; ** = large lesion.

in mean-amplitudes were assessed by repeated-measures analysis of variance (ANOVA), using the Greenhouse–Geisser epsilon correction for non-sphericity where appropriate, with hemifield (right and left), hemisphere (right and left) and electrodes (T5/6, P3/4, O1/2, TCP1/2 and PO1/2) as factors. The experimental sessions consisted of 400 trials: 200 left visual field stimuli and 200 right visual field stimuli, see caption of Fig. 3 for further details.

While the P1 component was rather variable across the four patients and could not be statistically analysed, the ERP responses to unilateral stimuli were characterised by an early visual response in the N1 latency range (140–200 ms), with a distribution over parieto-occipital sites. The ANOVA showed no significant main effects but yielded a significant interaction of hemifield by hemisphere [$F(1,3) = 13.98$; $P = 0.03$], with post-hoc t-tests indicating a significant difference ($P = 0.03$) between direct and indirect (callosal) responses. These differences, showing a much higher amplitude of direct versus indirect responses, can be clearly appreciated by comparing the left and the right graphs in Fig. 3. Further post-hoc tests showed a significant difference ($P = 0.03$) between the two direct responses (see Fig. 3 on the left-hand side), with a clearly larger amplitude of N1 recorded in the left hemisphere for right hemifield stimulation in comparison to the response of the right hemisphere for left hemifield stimulation. In contrast, no differences were present between the two right and left indirect responses ($P = 0.19$); see right-hand side part of Fig. 3. Thus, these results show that the contralesional signal in extinction patients is abnormal at the level of the N1 generator and that there is a severe impairment of callosal transmission. As is well known, N1 is a negative early component thought to reflect visual discrimination processes that can be modulated by covert spatial attention [30,42]. While the shorter latency positive P1 component is thought to be generated in the extrastriate cortex in an area of the fusiform gyrus roughly corresponding to V4 in the monkey [27,29], N1 probably has generators in parietal and frontal lobes. One could argue, therefore, that the decrease in amplitude of N1 observed in the right hemisphere of our extinction patients in response to single contralesional stimuli reflects an abnormal processing of visual stimuli beyond V1 at a level that in terms of information processing corresponds to focusing of spatial attention. We believe that this is the result of an abnormal top-down modulation from frontal-parietal areas onto extrastriate cortex. In broad keeping with this possibility, Barcelo et al. [3] recently found a reduced P1 in the ERP response to contralesional stimuli in patients with unilateral prefrontal lesions. They interpreted this effect as a consequence of a reduced intrahemispheric tonic modulation of early attention to the contralesional field. Such a deficit may be reflected

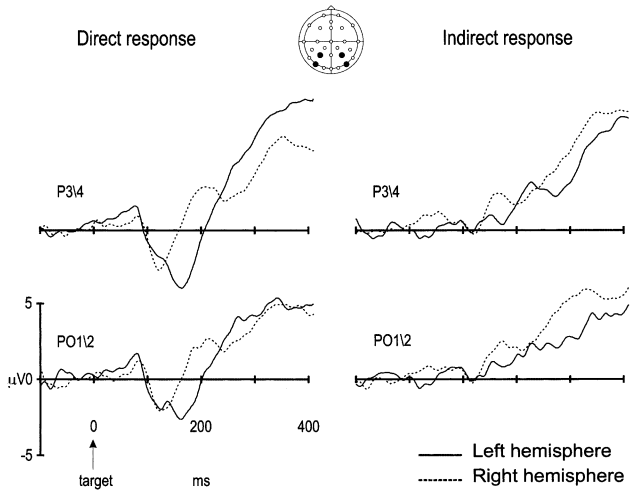

Fig. 3. Grand Average waveforms of four neglect patients (BM, CZ, RP, LG) recorded from parietal sites (P3/P4) [upper row], and parietal-occipital sites (PO1/PO2) [lower row]. ERP waveforms elicited by stimuli contralateral to the recording sites are depicted in the left column labelled 'direct response'; ERP waveforms elicited by stimuli ipsilateral to the recording sites are depicted on the right column labelled 'indirect response'. Thick lines represent ERP waveforms recorded in the left hemisphere; thin lines represent ERP waveforms recorded in the right (lesioned) hemisphere. When artefact rejection for saccadic eye movements, blinks and behavioural errors was applied to the data, the averages for each condition consisted of the following number of trials for each patient and for left and right visual field stimuli, respectively: BM 129–122; CZ 114–112; RP 94–96; LG 153–120. The percentage of saccadic eye movement artefacts with respect to the total number of trials for each patient was as follows: BM right field: 26.5%, left field 24.0%; CZ right field: 3.5%, left field: 1.0%; RP right field: 4.0%, left field: 3.5%; LG right field: 26.0%, left field: 21.0%.

by a lowered extrastriate P1 response to all stimuli presented to the damaged hemisphere. In addition to the effects on ERP there was a behavioural impairment for both detection rate and speed of response when stimuli were presented to the contralesional hemifield. This effect is similar to that we have repeatedly described behaviourally in neglect and extinction patients [47,59] and electrophysiologically, albeit limited to N1, in the results described above. It has been shown [31,36,37] that top-down influences increase baseline activity of visual cortical neurones and that such influences are thought to lead to an increased response to visual stimuli following focusing of attention. The lack of this top-down modulation results in a diminished response of the visual extrastriate cortex even with single contralesional stimulus but its consequences become dramatic with bilateral stimuli as is the case in extinction patients. This is in keeping with Marzi et al.'s [48] recent result of a disappearance of the P1 and N1 components, as well as of awareness of contralesional stimuli during bilateral presentations in a patient with a lesion involving frontal as well as parietal and temporal areas. Comparable ERP and behavioural data have been provided by Driver et al. [21] in parietal extinction patients. Our results show that, in addition to a degradation along the visual processing route from V1 to higher centres, a second reason for the contralesional signal to access decision centres long after the ipsilesional signal may be a severe impairment of interhemispheric transmission. This has been documented in patients with extinction, see [46] and present results, as well as in patients with large unilateral cortical lesions [49], probably as a result of the lesion affecting neurones giving rise to or receiving callosal connections.

All in all, these data show that in extinction patients signals from the contralesional hemifield cannot be normally relayed to the ipsilateral left hemisphere and therefore these patients have an 'amputated' representation of contralesional space in the hemisphere subserving the verbal numerosity decision typically used to tap extinction. In the absence of a competitor in the other hemifield, a signal might be extracted from the noisy commissural response but this is unlikely to occur during bilateral presentations.

An interhemispheric inhibitory mechanism has been advocated by Fink et al. [25] to explain extinction. These authors used positron emission tomography (PET) in a task in which normal subjects were to report several visual characters presented either unilaterally or bilaterally. An extinction-like pattern was found behaviourally, with characters in one hemifield reported less accurately when competing characters appeared (and had to be reported first) in the other hemifield. Correspondingly, a greater activation of striate and extrastriate areas was found for stimuli presented without competing stimuli in the opposite hemifield. Thus, simultaneous bilateral stimulation led to a significant reduction in activity, in visual cortex. These data bring weight to the idea that extinction can involve interhemispheric rivalry and a suppression mechanism inhibiting the weaker input. However, Fink et al.'s [25] results might also be explained by a division of attentional resources to both hemifields during bilateral presentation. This would decrease allocation of attention to each hemifield and might account for the observed reduction of activation for bilateral versus unilateral presentations. Given the abnormality of the callosal pathway interconnecting parietal areas documented above, a normal commissural interhemispheric suppression mechanism does not seem likely as the sole explanation for pathological extinction, although it might apply to subjects with a normal commissural system.

4. What exactly is extinguished?

One fundamental question is whether extinction consists of a wiping out of all information present in the affected visual hemifield or instead of a selective cancel-

lation of one item. One would expect that extinction occurring at early stages, i.e. at the level of striate or extrastriate cortex, might consist of a cancellation of visual responses from a whole hemifield or from retinotopically defined areas, while extinction occurring at later cognitive stages might represent a feature- or object-specific suppression effect. Recent studies of the neural correlates of extinction still leave this question partly unanswered. Our own recent ERP study [48] used brief, relatively faint, flashes presented in the peripheral visual field. During extinction on bilateral trials the patient reported having seen nothing at all in the contralesional field despite instruction to report even the faintest visual sensation. Therefore, one might argue that extinction represents a total erasure of the input from a whole hemifield. In keeping with the patient's subjective report, the extinguished contralesional stimulus yielded no early ERP components such as P1 and N1. In contrast, these components were present in those trials in which there was no extinction despite bilateral presentations (see Fig. 4). The lack of a signal even at relatively early stages of cortical visual processing suggests that extinction affects not only upstream but also downstream visual processing probably

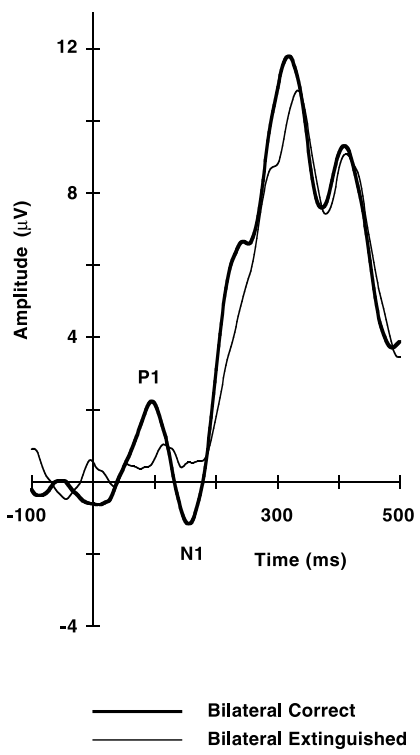

Fig. 4. ERP waveforms recorded at the right parietal site (P4), over the right (lesioned) hemisphere, in extinction patient RM in response to bilateral stimuli yielding extinction of the contralesional stimulus, (thin lines), or correct report (thick lines). It is clear from the figure that extinguished stimuli do not yield any observable P1 or N1 component. The figure has been modified from Marzi et al. [48] to which the reader is referred for technical details.

because of the lack of top-down facilitatory influences A similar total wiping out of contralesional information has been found by Rees et al. [54] and Vuillemier et al. [70] who used structured stimuli such as faces and houses to study extinction. In Rees et al. [54] a single detection task was used and the patient reported seeing nothing on extinction trials. Vuilleumier et al. [70] used a detection of schematic faces versus meaningless symmetrical shapes. Their patients reported a complete failure of detecting faces during extinction but it is not specified in their reports if the patients actually perceived some form of visual stimulation on the extinguished side or not. Overall, the above studies tend to support the idea of a profound perceptual loss during extinction. However, only specifically dedicated studies testing the spatial or featural selectivity of the perceptual erasure during extinction can answer the question of total versus selective black-out.

5. What is the neural locus of extinction?

A series of recent studies using ERP and/or fMRI has provided important clues as to the neural sites of extinction. Our own study [48] showed a profound effect of extinction on the P1 and N1 components of the ERP during trials with contralesional extinction but not during trials in which the same bilateral stimuli did not provoke extinction (see Fig. 4). Both components are generated at relatively early stages of cortical visual processing and therefore the implications of this result is that during extinction visual processing is abnormal already at extrastriate levels. In our study we did not record components such as C1 which are believed to be generated by the striate cortex [44] and therefore we could not ascertain whether there was a response during extinction. Rees et al. [54] in a face detection task found some residual activation in the striate cortex during extinction in another patient in whom Driver et al. confirmed our ERP findings [21]. It is possible therefore, that the discrepancy between Rees et al. [54] and Marzi et al. [48] results reflects differences inherent in the two methods of brain imaging. For ERP temporal factors are very important and the crucial technique of averaging is based on synchronised signals. Therefore, if the signals reaching extrastriate cortex are temporally dispersed no summation occurs and ERP components do not show up. On the contrary, fMRI has a sluggish temporal resolution and activation builds up over a considerable time range. Therefore, even a weak and temporally irregular signal reaching the extrastriate cortex during extinction may lead to some activation. Interestingly, Vuillemier et al. [70] found that while some striate cortex activation was present for extinguished stimuli, it was significantly stronger for bilateral trials without extinction (and then showed

coupling with left parietal and frontal areas). Therefore, also in their study one can find a physiological correlate of extinction in early visual areas. Furthermore, one should consider that, in contrast to Rees et al.'s parietal patient, our patient (see [48]) has a frontal and temporal lesion as well, which is likely to have specifically disrupted the top-down facilitatory bias which normally would enhance extrastriate responses to visual stimuli.

As mentioned above, the exact neural (and cognitive) locus of extinction depends upon the task used. Thus, in a simple detection task that can presumably be carried out at early visual levels, extinction might strike early while in a face or object identification task it might strike later on in the visual processing stream. However, the general picture emerging is that extinction occurs at the perceptual level and at relatively early stages of processing although probably beyond the primary visual cortex.

6. Is temporal asynchrony sufficient to cause extinction?

In normal people the stimuli in a pair reach a putative left hemisphere decision centre more or less simultaneously (apart from a small delay of left hemifield stimuli related to the need of interhemispheric transfer) and with approximately the same perceptual clarity. A similar small temporal asynchrony occurs during within-hemifield presentations because centrally presented stimuli are relayed more quickly to higher-level centres than peripheral stimuli, as is well known from studies of reaction time (RT) to visual stimuli presented to different retinal eccentricities [8,45]. This of course depends on the distribution of ganglion cells in the retina, which show a density decrement from central to periphery and on the cortical magnification factor also. This temporal asymmetry has perceptual consequences on temporal order judgements (TOJs) as has been demonstrated by authors [10,56] who found that during simultaneous presentations of foveal and peripheral stimuli the former appear to occur first. Thus, in normal observers, in both the inter- and the intra-hemispheric condition, the difference in arrival time between the two stimuli in a pair is small, and their numerosity is correctly estimated. A similar reasoning can be applied to the intensity of the signal, as brighter stimuli are processed faster [52] and appear to arrive before simultaneously presented darker stimuli (but see [33]). In contrast, in patients with extinction, the stimulus presented to the left (contralesional) hemifield is relayed to the decision centre with a much higher latency than the ipsilesional stimulus as indicated by RT [39,47,58,59] and TOJ studies [55] in such patients. Rorden et al. [55] found that in extinction patients contralesional stimuli had to be presented 200 ms before ipsilesional stimuli to be judged as simultaneous. This suggests a prior entry explanation of extinction whereby the stimulus that gets first to the processing centre leaves no room for the tardy competitor. Rorden et al. [55] did not specify whether their patient did in fact show extinction in addition to an abnormal TOJ in their task. However, in principle the prior entry mechanism can be convincingly used to explain extinction under more demanding conditions, i.e. with shorter stimulus exposure duration and in a task that specifically tested extinction rather than TOJs. Our hypothesis proposes that contralesional stimuli may be extinguished because by the time they reach the decision centre the pathologically reduced processing resources are all committed to the ipsilesional stimuli, a phenomenon broadly similar to that shown to occur in neglect patients by Husain et al. [32] for central vision. These authors found that neglect patients with right parietal, frontal or basal ganglia strokes had an extremely protracted 'attentional blink'. When they identified a letter in central vision, their conscious experience of a subsequent letter at the same location in a rapid stream was diminished for a time duration three times as long as for controls. This longer dwell time can reasonably explain extinction of contralesional stimuli during bilateral presentations, given the delay with which they are relayed to the processing centre relative to ipsilesional stimuli. Evidence in broad keeping with the idea of a temporal impairment of visual processing can be found in Di Pellegrino et al.'s study [16]. These authors tested single letter discrimination for unilateral versus bilateral asynchronous presentations and found that their subject could not discriminate the contralesional stimulus not only with simultaneous presentations, but also when it preceded or followed the ipsilesional stimulus by an interval up to approximately half a second. These data were considered as supportive of a competition model of extinction whereby temporal proximity rather than order of entry is important in determining extinction. When attention is attracted by ipsilesional stimuli, processing of contralesional stimuli is impaired because the former occupies all the restricted attentional capacity of the patient. In contrast, when stimuli are separated in time, processing resources become available for contralesional stimuli as well and extinction fades away. Further evidence in favour of the idea that temporal factors play a key role in extinction has been provided by a recent study by Cate and Behrman [7]. These authors asked an extinction patient to name letters presented unilaterally or bilaterally with various temporal asynchronies and found that extinction of contralesional stimuli was greatest when ipsile- sional stimuli were presented 300–500 ms in advance (see Exp. 1). This again suggests an abnormal dwell time in these patients.

The results of the Di Pellegrino et al. [16] and Cate and Behrman studies [7] may initially seem at odds with our model which posits that it is temporal asynchrony of arrival to a critical centre which determines extinction. However, there are two important sets of differences between the results of these two studies and the assump-

tions of our model. First, our model makes reference to stimuli presented simultaneously which, by virtue of an abnormal contralesional stimulus, get to the decision centre asynchronously. In contrast, in Di Pellegrino et al.'s [16] and in Cate and Behrman's [7] studies asynchrony of arrival to the centres is determined not only by unilateral brain damage but also by different onset asynchronies. It is interesting to point out that in the Di Pellegrino et al.'s study [16] the condition of highest extinction rate is with simultaneous bilateral stimulus presentation. There may be centres which compare the temporal asynchrony of stimuli at different stages of the visual system. If bilateral stimuli activate simultaneously subcortical centres (e.g. the superior colliculus responsible for reflex saccades or the pretectal nuclei responsible for pupillary reflexes) and then activate higher-level perceptual centres asynchronously, this may lead to a suppression of the tardy stimulus to preserve perceptual continuity. This is not the case when stimuli are presented in temporal succession from the very beginning and the perceptual centres are set for an asynchronous arrival of the information from the two sides. This is clearly an issue that deserves further study. A second difference concerns the task used to test extinction: our model is based on simple detection while both Di Pellegrino et al. [16] and Cate and Behrmann [7] used letter identification. While the simple numerosity judgement postulated by our model operates optimally with simultaneous stimuli, letter identification may be compromised by simultaneous distractors and therefore extinction vanishes when the distractor has been presented either much earlier or much later.

The present model of extinction postulates that the numerosity decision whether the display comprises one or two stimuli is made in a left hemisphere centre which must receive information from both visual hemifields. Information about the entire visual field has typically been associated with the posterior parietal lobe where several neurones show large receptive fields often including the ipsilateral as well as the contralateral hemifield or hemispace. It is likely that the callosal connections between posterior parietal areas are lost in extinction, as documented by our ERP studies (see above) and therefore bilateral receptive fields cannot be built up in one parietal lobe. In particular, our data have shown that the left hemisphere in extinction patients has lost the (transcallosal) representation of the ipsilateral (left) hemifield. Therefore a correct numerosity judgement with bilateral stimuli cannot be reliably made.

Our model can also account for extinction occurring within one hemifield on the basis of the pattern of distribution of attention across the visual field in extinction patients [59]. While all studies that tested within-hemifield extinction found extinction of the leftmost stimulus within the contralesional hemifield, the results are discordant for the ipsilesional hemifield where Cate and Behrmann [7] found extinction of the leftmost stimulus while others did not find extinction in further cases [15,58]. Evidence of extinction in contralesional but not in ipsilesional space is in line with the idea expressed above that in order to have extinction one needs a degradation of one of the competitor inputs. This is the case particularly for the contralesional hemifield, as demonstrated by the sharp increase in RT as one goes from central to peripheral locations (see Fig. 5) which has

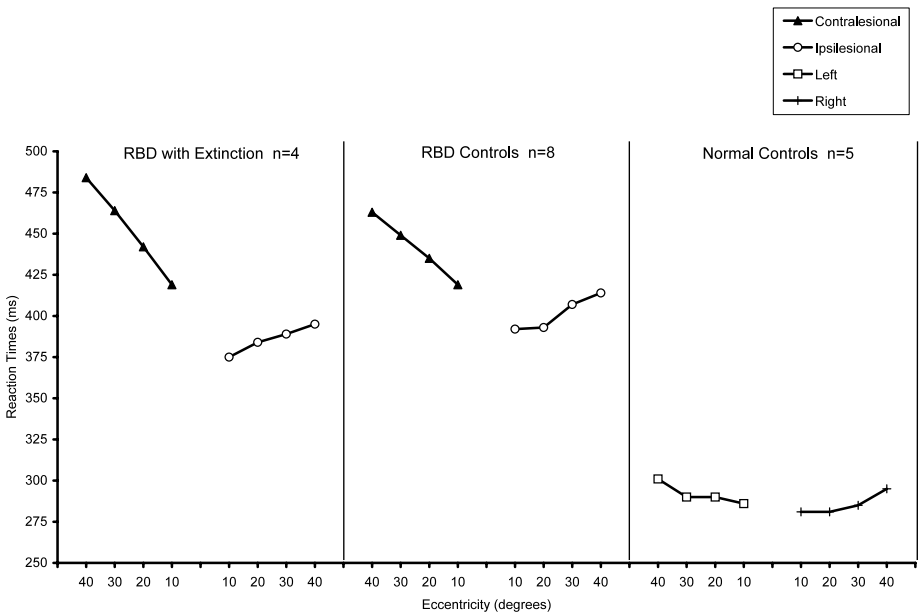

Fig. 5. Speed of reaction time across various positions in the contralesional and ipsilesional hemifled of right brain damaged (RBD) patients with extinction, RBD patients without extinction and normal controls. Clearly, in the contralesional hemifield of extinction patients (and to a lesser extent) of RBD controls, the curve relating reaction time and eccentricity is much steeper than in the ipsilesional hemifield (data from Smania et al. [59]).

been redrawn from Smania et al.'s study [59]. In contrast, in the ipsilesional hemifield, the slope of the RT increase from centre to periphery is typically much shallower. Therefore competition is likely to affect the ipsilesional much less than the contralesional hemifield and this explains the most common results obtained on extinction patients.

7. Conclusions

In conclusion, we have outlined a simple model of extinction that refers specifically to extinction as tested with a stimulus detection task. The model draws upon two main empirical findings: a degradation of the contralesional signal and a block or severe impairment of callosal transmission. Contralesional degradation is a result of an impairment in stimulus-driven attention which in neglect patients, and to a lesser extent in extinction patients, shows a left-to-right gradient from a maximum of impairment in the contralesional periphery to a minimum in the ipsilesional side [58]. This asymmetric distribution can explain why extinction sometimes occurs not only across the vertical meridian but also within the contralesional hemifield, while it is usually absent within the ipsilesional hemifield. Another factor which plays an important role is a deficit of callosal transmission. This accounts for the worsening of extinction when stimuli are presented to different hemifields across the vertical meridian [7,58]. The hypothesis of a competition between signals to access a decision centre in a system with pathologically limited processing capacity can also account for the common observation that extinction may be partial rather than an all-or-none phenomenon [7,48,70]. Of course, a race model alone cannot account for extinction entirely because in normal subjects bilateral stimuli presented with different temporal asynchronies do not yield unilateral extinction. However, there is sufficiently convincing evidence, as pointed out above, that extinction patients have a limited processing capacity as well as a forceful bias to direct attention ipsilesionally.

Whatever mechanism might be responsible for unilateral extinction, one thing is certain: that in many patients extinguished stimuli are not completely lost but may be shown to implicitly influence behaviour. These implicit effects can occur in a wide range of cognitive abilities, from simple spatial summation or gestalt completion to categorisation [5,19,47]. Marzi et al. [47] found that extinction patients show a redundant target effect, i.e. a speeding up of simple RT for two versus one visual stimuli, despite the fact that one of the bilateral stimuli was presented to the contralesional side and was therefore extinguished. Thus, spatial summation across the vertical meridian can take place independently from conscious awareness and therefore one can conclude that extinction excludes a stimulus from consciousness but not from all other neural operations. This result is not necessarily in contradiction with the idea proposed by Marzi et al. [48] that extinction occurs rather early on the cortical processing route. Tomaiuolo et al. [63] found an implicit redundant target effect even in hemispherectomised patients in whom one stimulus in a bilateral pair was presented to the hemifield, which as a result of hemispherectomy, was hemianopic. This strongly suggests that the implicit redundant target effect can be subcortically mediated and therefore it is not surprising that it can occur in extinction patients despite their impairment affecting early visual cortical processing stages. Needless to say, the systematic study of the neural and cognitive levels at which implicit–explicit dissociations occur in extinction may help us enormously in trying to understand the neural basis of conscious experience.

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