

# Neglect and extinction: Within and between sensory modalities

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**Abstract.** *Purpose:* The interest in human conscious awareness has increasingly propelled the study of neglect, the most striking occurrence of an acquired lack of conscious experience of space. Neglect syndromes commonly arise after unilateral brain damage that spares primary sensory areas nonetheless leading to a lack of conscious stimulus perception. Because of the central role of vision in our everyday life and motor behaviour, most research on neglect has been carried out in the visual domain. Here, we suggest that a comprehensive perspective on neglect should examine in parallel evidence from all sensory modalities.

*Methods:* We critically reviewed relevant literature on neglect within and between sensory modalities.

*Results:* A number of studies have investigated manifestations of neglect in the tactile and auditory modalities, as well as in the chemical senses, supporting the idea that neglect can arise in various sensory modalities, either separately or concurrently. Moreover, studies on extinction (i.e., failure to report the contralesional stimulus only when this is delivered together with a concurrent one in the ipsilesional side), a deficit to some extent related to neglect, showed strong interactions between sensory modality for the conscious perception of stimuli and representation of space.

*Conclusions:* Examining neglect and extinction by taking into account evidence from all sensory modalities in parallel can provide deeper comprehension of the neglect syndrome mechanisms and possibly more effective multi-sensory based rehabilitation approaches.

## 1. Introduction

Unilateral spatial neglect is a relatively common deficit that most frequently arises after right brain damage (RBD). Its main characteristic is a lack of awareness for sensory events located in the contralesional side of space (towards the left side space following a right lesion) and a loss of exploratory search and other actions normally directed toward that side. Most read-

ers would be familiar with some of the classic presentation (and descriptions) of neglect patients: they typically behave as if the left half of their world no longer existed, so that in daily life they may only eat from one side of their plate, shave or make-up only one side of their face [50,89], draw or verbally describe only the right side of a remembered image or place [22,136]. This shortened version of a commonly used description of what neglect is, already conveys the equally common (though often implicit) assumption that neglect is mainly a visual disturbance. This probably relies on the well-funded argument that visually-guided behaviour entails most of our daily living activities. As such, visual neglect certainly gained most of the scholars' at-

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tention over the expression of this syndrome in other modalities and, accordingly, the main visually-centred aspects of neglect will be first briefly reviewed here.

However, there is now large consensus that neglect and extinction<sup>1</sup> can virtually affect all of the other sensory modalities (separately or jointly), as well as the motor domain. We will address such a diversity of the neglect symptomatology to provide an up-to-date multisensory-motor framework. In addition, we will argue that the multisensory nature of neglect is most likely to have profound implications for rehabilitation of this cognitive deficit. Accordingly, we will conclude by reviewing some recent multisensory-based approaches to neglect rehabilitation.

## 2. Visual neglect and extinction

The last “decade of the brain” studies have brought convergent and definite evidence that neglect is a protean disorder, whose definition escapes from the boundaries of any theoretical unifying attempt [75]. Despite its heterogeneity, several core aspects of visual spatial neglect have been identified and, although they might be present at different levels in different patients, they are quite widely acknowledged to represent main aspects of this multifaceted syndrome. It is beyond the scope of this work to provide a comprehensive review of visual neglect and its theoretical accounts (see [107]). What follows is instead a brief list of examples with two purposes. First, to show how deeply the study of visual neglect has contributed to the understanding of the anatomo-functional structure of human conscious experience. Second, to recall the core aspects of the syndrome that should be taken into account when examining the literature on non-visual manifestations of neglect and extinction.

The diagnosis of visual neglect typically requires a comparison of performance on the left-side of a display with that on the right-side in tasks such as line bisection, cancellation, drawing (from model or memory). These tasks commonly reveal the presence of a spatial bias towards the ipsilesional side, in terms of rightward deviation and/or omissions of left-sided items. The presence of abnormal biases across hemispaces, in absence

of contralateral primary sensorimotor loss, highlights neglect as a higher-order deficit of spatial cognition. This defective behaviour has been alternatively taken as evidence of patients’ defective spatial attention and/or representation, or altered computation of an egocentric reference frame (for review, see [149]).

Indeed, neglect patients suffer from reduced visual spatial attention [49], especially in its exogenous component ([95] for review, see [6]). Not only simple reaction time (RT), but also search times for contralesional target are lengthened, increasing with the number of ipsilesional distractors, thereby indicating a difficulty in disengaging attention from ipsilesional stimuli [11, 127]. Despite the presence of attentional deficits, preattentive processing has been shown to be relatively preserved in visual neglect and extinction, proceeding up to the level of the extraction of the meaning of contralesional “neglected” items [19,50,97], thus confirming that implicit visual processing can influence explicit visuo-motor performance.

Problems of attentional orienting towards the left side of space are compelling when observing neglect patients’ behaviour. An interesting debate in the recent past has concerned what should be intended as “left” in left visual neglect and extinction. When asked to copy, for example, neglect patients typically draw the right side of a perceptual scene, omitting several details, or even leaving incomplete the left part of centrally located, single element of the scene. This behaviour is most likely responsible for the word “hemispacial” neglect, as implicitly referring to a corporeal midline that should represent the vertical cleavage line with respect to which conscious perception is preserved (to the right), or more or less absent (to the left). Although the trunk is one of the most important egocentric reference frames’ origin [85], visual neglect and extinction can also be manifest according to other reference frames. For example, neglect patients have been reported to miss out the respective left part of two objects present in a scene (object-based neglect), instead of missing the leftmost one (space-based neglect), and vice-versa [48, 74]. Moreover, visual neglect can be selectively present for the vertical, not the horizontal dimension [123,128].

Dissociations of this kind have largely contributed to thinking of visual neglect as an increasingly fractionating entity [73,107]. Along the same line, patients may show left visual neglect for a limited sector of space around their body, the peripersonal/reaching space [20, 72]. On the contrary, neglect can affect selectively a farther sector of the extrapersonal space [5,157]. Neglect for near space can also be “transferred” into far

<sup>1</sup>The issue of whether (and to what extent) neglect and extinction should be conceived of as separate deficits is outside the scope of this work (for review, see [106]; see also [64]). Nonetheless, throughout this review we will clearly specify whether the reported studies concerned extinction or neglect patients.

space when using tools as physical extensions of the body for bisecting lines of constant visual angle [20]. Visual neglect can even be confined to either internally generated representations of visual images or perceptually presented scenes [70].

The role potentially played by non lateralised deficits of sustained attention and arousal on the genesis of visual neglect has been recently stressed [83,135]. By studying sustained attention through the use of an auditory target detection test, Hjaltason and colleagues [80] found a strong relationship between the presence of sustained attention deficits and visual neglect severity. Similarly, neglect patients may show a significantly longer “dwell time” for a secondary visual target being detected after presentation of a first target (attentional blink [82]). However, the degree of impairment on tasks for sustained attention does not always differentiate between RBD patients populations with and without visual neglect, although neglect patients are certainly affected by non lateralised attentional deficits when compared with age-matched healthy subjects [55]. Indeed, neglect seems to be mainly characterised by spatial deficits, though non lateralised attentional deficits are also present, without being specifically responsible for the major manifestations of the syndrome.

Another non-lateralised aspect of visual neglect that has recently raised great interest is the possible involvement of a spatial working memory deficit in the genesis of the syndrome. When invited to ocularly explore a scene to report targets amidst distractors, neglect patients do not only avoid exploring left-sided elements, but also produce a high number of rightwards saccades bringing their eyes to re-fixate items on their ipsilesional side that had already been “visited” [100]. Most important, many of these re-fixations were associated with a failure to keep track of spatial locations across saccades, the patients being unaware of revisiting previously visited locations. The presence of spatial working memory deficits should not be conceived of as an alternative account for visual neglect, but could certainly contribute to exacerbating omission of left sided items, especially in patients with lateral parietal involvement [100].

A different approach has been undertaken by Pisella and Mattingley [122], whose arguments propose that the origin of some re-visiting behavioural deficits in neglect might not be due to the proposed spatial working memory disorder. They suggest that the manifestations of visual neglect that are hardly grasped by more traditional accounts solely based upon deficits of spatial attention, representation, or working memory can actu-

ally be accounted for by an additional underlying disorder of spatial remapping due to parietal dysfunction (for another alternative account, see [139]).

One important issue that is currently the object of a very lively debate is the fine-grained anatomy of visual neglect. There is controversy as to whether lesions of the inferior posterior parietal cortex are still to be considered as the crucial anatomo-pathological counterpart of visual neglect [150], or whether and to what extent the mid-temporal gyrus may also play a role in the genesis of neglect [86,137]. Most of the recent studies, although employing different techniques, seem to confirm the crucial involvement of the inferior parietal lobule and the temporo-parietal junction [27,55,75,109], as well as the crucial contribution of parieto-frontal connections [44,46]. It is out of the scope of this review to fully address this topic, but the interested reader can also refer to neurointerference studies using TMS in healthy participants [58,111], although it is worth noting that the criteria used for defining neglect are becoming important for comparing anatomical lesions studies [107].

As noted by Halligan and colleagues [75, p. 125], “Deficits of attention, intention, global-local processing, spatial memory and mental representation can all contribute to the clinical picture of neglect, which accordingly cannot be traced back to the disruption of a single supramodal process.” More recently, the neglect literature has actually seen some attempts to provide a re-unifying interpretation, not by referring to a unique feature of the syndrome, as was the tendency in the past three decades, but by advocating the need of the joint presence of (some) deficits of lateralised and non-lateralised attention, eye movement, and manual exploratory behaviour, spatial working memory and remapping to fully account for the puzzling lack of awareness for contralesional events that is the hallmark of neglect (see [35,83,122]).

From this brief review, it is apparent how much the study of visual neglect has contributed to the refinement of our understanding of human conscious awareness. Although this supremacy of vision studies over the other sensory modalities can be explained, at least in part, by the fact that the appropriate technology has been made available for vision well before than for touch, audition or the chemical senses, it is quite surprising that relatively few(er) studies have addressed neglect and extinction in the other senses, or even in the motor domain [77,102]. In the following sections, we will review the current knowledge for non-visual manifestations of neglect and extinctions.

### 3. Tactile neglect & extinction

Generally, neglect is less evident and usually less strong in the tactile domain than for the visual modality. Many authors [30,62,79] failed to demonstrate tactile neglect in right brain damaged patients with visual neglect, when using tasks such as rod tactile bisection or haptic exploration. Fuji and colleagues asked visual neglect patients to bisect a tactually presented stick. The examiner placed the blindfolded patients' index finger on the centre of the stick and asked him to move the finger and stop it at the estimated midpoint of the stimulus. Although the patients showed rightward errors on a visual bisection task, they performed normally on the tactile test. Similar findings were described by Hjaltason and colleagues in an analogous study, where RBD patients were asked to perform the visual and tactile bisection, as well as a visuo-tactile variant of the same task. In the latter task, patients had to indicate the midpoint of a rod in the same way as in the tactile version, but in a free vision condition. Rightward bias was present only in the visual task and no difference was found between the tactile and the visuo-tactile rod bisection.

Evidence for tactile neglect comes from studies that employed spatial exploration tasks like in the maze test [41], whereby RBD patients were asked to move their forefinger along the alleys of a maze hidden behind a curtain, in order to search marbles placed at the end of one of its four lateral arms. Failure to find the targets in the contralesional part of the maze was taken as evidence of tactile neglect. Following this criterion, RBD patients with visual neglect showed more "tactile neglect" than control groups. Although these results have been replicated [21], Villardita [154] reported that patients with left visual neglect engaged at the same test preferred to explore the left part of the maze, thus suggesting an inconsistency between the phenomena described for vision and touch. Other studies have concentrated on the weak relationships between visual and tactile neglect, which seem to be double dissociable [21, 30,33]. One of the possible reasons for the paucity of tactile neglect studies may derive from its definition, most often diverging from the classical "omission" of left-sided targets that is so clearly and astonishingly present in the visual modality. Strictly speaking, one may ask the question of whether pure tactile neglect exists at all. Indeed, the difficulties in describing tactile neglect might be overcome if one admits that some cases of apparent hemisensory loss are, at least partially, mimicked by tactile neglect ([25], see also [108]).

Several studies have shown that vestibular stimulation (cold water in the left ear) may induce a transient remission of diverse neglect symptoms in RBD patients. However, a contralesional supposedly somatosensory deficit may also be ameliorated by vestibular stimulation [25,151], thus revealing a higher order problem and suggesting that tactile neglect may be mistaken for a mere sensory deficit. In this respect, it would be interesting to establish which proportion of RBD patients seemingly affected by hemisensory loss is, in fact, affected by unisensory tactile neglect.

While tactile neglect has been rarely documented, tactile extinction is much more frequently reported [113], even when assessed by simple confrontation methods. Extinction patients are able to detect a single stimulus presented alone either to the ipsi- or the contralesional side of space, but fail to report the same contralesional stimulus when this is delivered concurrently to a second one in the ipsilesional side of space (for review, see [103]). In the tactile domain, extinction has been reported to occur at the level of the hands, the face-neck, the arms-legs, both in case of symmetrical and asymmetrical stimulation [7,15,56], or between the two sides of a single body-part [110,147].

To some extent, both neglect and extinction show a similar lack of awareness for tactile inputs delivered in the side of the body opposite to the brain lesion, despite relatively intact primary sensory pathways, such that extinction has long been considered as a residual form of spatial neglect [50]. However, they also differ in some respects and double dissociations have been documented [31,64,134,153], suggesting that the underlying neural mechanism of extinction and neglect might differ [87].

Both "tactile neglect" and tactile extinction may manifest according to different reference frames. For example, they can be modulated by body posture and by the relative position of the stimulated body parts. Left tactile extinction is reduced when the left hand crosses the body midline and lies in the right hemisphere, or even occupies a relative left location as compared to the right hand in the same hemisphere [1,7,141]. Moreover, a single-case study of a RBD patient [148] illustrated that right hand touches may also be extinguished by a concurrent ipsilesional elbow stimulus (see [15,63]) when the right hand lies on the left and the elbow on the right of the patient's body midline. Similar effects of posture arise in neglect patients [109], whereby detection of single contralesional tactile stimuli increases when the stimulated hand lies in the ipsilesional hemisphere, whereas touches delivered to the ipsilesional "good"

hand are omitted to a variable degree when the right hand lies in the contralesional affected hemispace [1, 7]. Similar to what has been reported for visual neglect [124], improvements in tactile neglect and extinction have been observed following a reduction of gravitational inputs, obtained by placing the subjects in a supine position [120].

Moreover, in the visual domain it is typically assumed that extinction is maximal under conditions in which competing stimuli occur simultaneously [95]. One may ask whether, in addition to posture, time (e.g., asynchronous stimulation) could also modulate tactile extinction in a similar fashion. The more a stimulus is temporally tied apart from another, the more reliably contralesional events should be perceived [26]. In this respect, Mattingley et al. [103] examined tactile detection in a RBD patient with tactile extinction, introducing a variable stimulus onset asynchrony (SOA) between bilateral stimulations. The occurrence of a right-sided competitor interfered with detection of left targets across a range of asynchrony from  $-400$  to  $1200$  ms (minus means that left leads), showing an asymmetry in the effect. The point of subjective simultaneity appears thus to be biased in favour of ipsilesional stimuli. These results suggest that sensory timing problems might be present in both visual and somatosensory neglect [10].

In the case of tactile extinction considerable processing can still take place prior to the level at which loss of awareness arises. Although the extinguished tactile stimulus does not access consciousness, it may interfere with perception of the ipsilesional one [2]. More direct evidence comes from measures of patients' neural activity through functional imaging or event-related potentials. Some studies in the visual domain observed that the relatively early components of visual processing may be abnormal for contralesional stimuli in visual extinction [101]. Similarly, it is possible to examine the fate of extinguished tactile stimuli in those bilateral conditions where extinction arises, by comparing correct unilateral ERPs with incorrect ones in case of extinction [52]. In a single RBD patient study, bilateral trials with extinction still revealed residual early components (P60 & N110) over the right hemisphere in response to the extinguished left touches. These components were completely absent in the right hemisphere after a single right hand stimulation, although these kind of stimuli have the same conscious report of the other ones. However, the somatosensory neural activity in the right hemisphere was reduced in amplitude when compared to the one elicited by right hand stimulation on the left hemisphere. This suggests that, although

tactile extinction is not a pure sensory deficit and is defined in conditions of bilateral stimulation, there may be an underlying pathology for the contralesional unilateral stimulation too, in agreement to what has been suggested for visual extinction [101]. Finally, these results demonstrate that somatosensory cortex activity is not sufficient for tactile inputs to reach awareness. In the same vein, a PET study [129] revealed that tactile extinction is associated with reduced activity in the secondary somatosensory cortex, but not in the primary one, suggesting that processing of bilateral tactile stimuli takes place at a "higher" stage and that extinction arises at a high level of tactile input processing.

#### 4. Chemical neglect & extinction

To date, only a limited number of investigations concerning the suppression of (or competition among) spatial information processed through the so-called 'chemical senses' (i.e., olfaction and taste) have been reported [12,13,16,18,105]. A number of various different reasons may account for this lack of research. First, the distinction between pure chemical versus somatosensory information is often problematic (e.g. [18]). Second, it is widely assumed that olfaction and taste are senses that are not specialized for conveying spatial information (e.g. [92]). In olfaction, in particular, it is still unclear whether humans can localize at all the source of the olfactory stimulation by distinguishing between odours that are processed through the right versus the left nostril. This is particularly true when the stimulus is a pure odorant rather than trigeminal, that is when the odour does not cause any somatosensory stimulation that is known to be encoded by the trigeminal system (see [47]).

##### 4.1. Olfaction

With respect to olfaction, Mesulam [105] first described a case of left-sided olfactory extinction revealed under double simultaneous stimulation of both nostrils in a patient with a brain lesion localized in the right parietal cortex. A few years later, Bellas and colleagues [12,13] assessed the ability of a group of fifteen RBD patients who were affected by left tactile extinction on the hand to identify and localize a series of bilaterally presented olfactory stimuli. On each trial, patients were presented with two stimuli (one in each nostril) using squeezing bottles and their task was to name each of the odours that were perceived. Partic-

ipants could receive either the same pure odorant in both nostrils, or different odorants in each nostril, or else an odorant in one nostril and a trigeminal odour (vinegar) in the other. As the authors could not find another appropriate trigeminal odour, the vinegar odour was only presented singularly to one of the two nostrils while the other nostril was stimulated with a pure odorant. Bellas and colleagues [12] reported the presence of an extinction-like phenomenon in the patients' performance. Specifically, when two different stimuli (being either two pure odorants or an odorant and the trigeminal odour) were delivered to each nostril, RBD patients consistently failed to report the stimulus delivered to the left nostril. As the olfactory system would predominantly project its fibres ipsilaterally while the trigeminal system would be a contralaterally innervated system, the authors considered these results as evidence supporting the representational theory of neglect (see [22]). Indeed, if the sensory theory (see [37]) was responsible for the olfactory and trigeminal extinction, the pure odorants presented to the right nostril rather than those presented to the left nostril should have been extinguished. Bellas et al. [13] also reported that the patients affected by olfactory extinction showed a large number of displacements in that the correctly-identified stimuli presented to the left nostril were described as being in the right nostril.

The studies conducted by Bellas and colleagues represent a first step in the investigation of phenomena such as extinction and neglect in the olfactory modality. Nevertheless, it is not completely possible to determine the exact influence exerted by the nasal somatosensation in the olfactory extinction reported, since one of the odours considered as being pure odorants was later found to be processed probably also by the trigeminal system (i.e., a soap odour; see [13]). Finally, the possibility of highlighting deficits related to the localization of stimuli in the olfactory sensory modality should be interpreted within a much wider debate regarding whether the olfactory system could extract spatial information from pure odorants (i.e., without any interventions of the trigeminal system; e.g., see [47,92]; though see [126,155]).

Kobal and colleagues [92], for instance, claimed that the human olfactory system appears to be able to localize the source of the olfactory stimulation only when the odour elicits also a trigeminal response. This would appear to be in contradiction with the pioneering work of von Békésy [155] who showed that trained participants localized both trigeminal stimuli and pure odorants between the two nostrils. Moreover, Porter et

al. [126] showed recently that naive participants were able to reliably localize pure odorants between the two nostrils in a setting in which olfactory stimuli were delivered by a computer-controlled air-dilution olfactometer that controlled for the exact timing in stimuli presentation. The stimuli were presented to the nose through a compartmentalized nasal mask that allowed for mono-rhinal odour presentation and the sniff flow-rate was controlled in real-time. Clearly, if the ability of the olfactory system to extract spatial information from non-trigeminal stimuli turns out to be true, new light could be shed on the extinction phenomena described for odours. In fact, the relative contribution of pure odorant and somatosensory information to olfactory localization could be disentangled using experimental methods similar to those described by Porter and colleagues.

#### 4.2. Taste

The existence of neglect and/or extinction in taste has been even less explored than in olfaction, even though in humans the ability to localize taste stimuli presented on the tongue has been previously described (e.g. [140, 156]). Bender and Feldman [17] first reported a single case of a patient with a wide parietal-occipital tumor and tactile extinction on the upper limbs who also showed extinction of taste sensations on the left part of the tongue when two tastes were presented simultaneously on each hemi-tongue. Taste stimuli were applied on the tongue surface by means of cotton buds and they were all accurately identified and localized by the patient when presented singularly. The results of the assessment revealed that the patient was not only affected by unimodal taste extinction, but that he also displaced taste sensations under crossmodal taste-tactile stimulation. In particular, when a touch or a pinprick was delivered to the right hemi-tongue and a taste was applied on the left hemi-tongue, the patient repeatedly reported bilateral taste stimulation, thus surprisingly extinguishing the right touch and partially misplacing the left taste stimulus. Unfortunately, Bender and Feldman did not describe in detail the method that was used to generate the tactile sensations.

More recently, Berlucchi and colleagues [18] described a study carried on two groups of patients (i.e., having a right or left brain lesion) and a control group. The RBD patients were affected by tactile (on the hands), visual, and/or auditory extinction with different degrees. By using a highly controlled stimulus presentation (e.g., use of micro-pipettes and controlled wa-

ter temperature), Berlucchi and colleagues could disentangle (contrary to [17]) between the presence of taste and/or tactile extinction on the tongue. A sub-group of the RBD patients showed tactile extinction under bilateral simultaneous stimulation of the tongue. However, the authors failed to find any significant presence of taste extinction even among these tactile extinguishing patients, thus highlighting for the first time the existence of dissociations between extinction phenomena occurring in somatosensory or in purely chemical information processing. There also appeared not to be any consistent correlations between the presence of tactile extinction on the tongue and that of tactile (on the hands), visual, and auditory extinction. Berlucchi and colleagues suggested that a distributed taste representation could account for the existence of such dissociation. Namely, the processing of somatosensory information coming from the tongue would be predominantly contralateral, whereas the taste stimulation would activate the brain areas ipsilateral to the hemitongue being stimulated (e.g., see [3,114]). Moreover, according to Berlucchi and colleagues, the fact that a dissociation between gustatory and tactile extinction could be highlighted would suggest that gustatory extinction occurs consequently to a severe tactile extinction (see [17]). The patients involved in their study would have been affected by a mild tactile extinction, thus allowing the gustatory information to be processed by the preserved left hemisphere.

To date, thus, there is still no clear evidence of the existence of purely taste extinction and/or neglect, while few studies provided evidence about the presence of tactile extinction on the tongue or inside the mouth following a right brain lesion [4,18]. In the study of extinction and neglect, a wide number of questions related to the chemical senses are still waiting for answers. Today, it would appear to be possible to devise studies where information conveyed by the chemosensory modalities and by the collateral somatosensory modality could finally be investigated separately [18, 126,140]. Therefore, future research will be in charge of furthering our understanding about odours and tastes and their links with spatial representations.

## 5. Auditory neglect & extinction

Patients with focal brain lesions can also suffer a number of disturbances in the auditory modality that can be characterised as auditory manifestations of the neglect syndrome. Patients with right hemispheric le-

sions might either fail to respond when addressed verbally from the left, or more commonly behave as if they heard the voice originating from their right (e.g. [16, 38]). This suggested a deficit in detection and localisation of auditory stimuli, especially when they originate in contralesional space, which could emerge for hearing as well as for vision. Although this clinical observation has generally been confirmed, a number of recent evidence has now highlighted important differences between the manifestations of neglect in hearing and vision.

### 5.1. Deficits of sound localisation

The disturbance for sound localisation, originally described as ‘alloacusic’ [16], has been the topic of several experimental works in the last two decades (see [118] for review). A first aspect that emerged from these systematic investigations is that auditory spatial disturbances in neglect patients might reflect increased spatial uncertainty for sound position, especially for contralesional stimuli, instead of a strictly systematic shift in heard azimuth towards the ipsilesional side. For instance, when asked to discriminate verbally the relative position (same vs. different) of two sounds in close succession, neglect patients typically perform worse for pairs of sounds originating from the contralesional side (e.g. [117,146]; see also [40] for evidence of reduced mismatch negativity response in scalp recordings of event-related potentials for contralesional vs. ipsilesional free-field sounds). In addition, it has recently been shown that patients with neglect perform less efficiently than control right-hemisphere patients without neglect in a discrimination task that concerns the vertical position free-field sounds [116,119]. Thus, a disturbance in auditory space perception emerges even when localisation involved the vertical dimension, orthogonal to any potential horizontal shift.

Horizontal bias in sound localisation have instead been typically documented when neglect patients are asked to point to a sound presented in free-field (i.e., from an external source [115,121]; but see [138]), or over headphones (pointing to a location on their head; e.g. [23]). In addition, deficits have been observed when using ‘auditory midline’ tasks, in which patients adjust a continuous sound (or make judgments on a discrete sound) to locate it relatively to the centre of the head or body midline (e.g. [23,90,146,152]; but see [34]). For sounds presented over headphones (with either varied intensity at the two ears, or varied interaural timing cues to sound localization), neglect patients

typically report a sound to be central when it is actually lateralized towards the left (i.e. more intense or arriving earlier at the left ear), as if there were a rightward shift in perceived location (e.g. [23,146]). By contrast, for sounds presented free-field, neglect patients often reported that an external sound seemed aligned with their head/body midline when it was actually presented to the right (thus implying a leftward shift in sound localization if one assumes that perceived head/body midline is veridical, which it might not be in neglect patients [90, 152]). As proposed recently [115], some of these discrepancies concerning the direction of lateral shifts in sound localization for neglect patients might actually relate to non-auditory aspects of the task. Specifically, motor or visuo-motor biases in pointing tasks [115], or pathological distortions of perceived head/body midline in auditory-midline tasks [57] could in principle affect performance.

### 5.2. *Detection and identification deficits*

Although auditory spatial deficits have often been reported in neglect patients for single auditory stimuli, especially when they originate in contralesional space, the patients usually detect these single sounds with apparent ease in most localization studies (e.g. [23,115–119,121,146]). This might appear to contrast with characteristic clinical deficits affecting the visual modality in neglect patients, where complete failures to detect or respond to contralesional visual events are commonly noted, rather than merely failures in localization. Two critical differences between hearing and vision may account for this discrepancy. First, the anatomical organization of the auditory system, which is less crossed than for other senses, with some ipsilateral as well as major contralateral cortical projections of the input reaching each ear. Second, the typical reduced complexity of the auditory environment in experimental setups. Unlike experiments in vision, in which targets are often embedded among many distracters, the typical experiment in the auditory domain presents a single strong sound against silence [115]. Indeed, when even a minimal version of concurrent competing stimulation is produced, usually by presenting one sound on each side of the head, a consistent failure to detect and/or identify contralesional sounds emerged, for both free-field sounds [39,142] and headphone stimuli [14,42]. Strictly speaking, however, such effects with two concurrent competing sounds might be considered the auditory equivalent of visual or tactile extinction, rather than manifestations of neglect.

A long standing debate in relation to detection and/or identification deficits under double simultaneous auditory stimulation has been whether poor detection of sounds at the contralesional ear could be related to neglect of contralesional auditory space [81], or instead should be ascribed solely to poor processing (or suppression) of the auditory information entering the contralesional ear [8,9]. Indeed, free-field sounds presented from a contralesional location will tend to be more intense at the contralesional ear, and if presented monaurally over headphones, will only reach that ear. However, there is now mounting evidence suggesting a role for higher-level spatial factors (e.g., perceived external position, spatial attention, relation to visual neglect) in the contralesional detection/identification deficits for auditory stimuli observed for neglect patients (e.g. [14,29,142]). For instance, it has been shown that identification of left free-field sounds can sometimes improve in the presence of a fictitious visible sound source (a ‘dummy’ loudspeaker) on the right, which reportedly made it seem that the sounds originated from the right side [142]. In addition, a direct investigation of the role of apparent sound location with respect to which ear the information enters was recently conducted by Bellman and colleagues [14], presenting each auditory stimulus (heard words) either to one ear only (‘dichotic’ stimulation), or binaurally but with interaural time difference serving as the only lateralization cue (‘diotic’ stimulation). Under double simultaneous presentation, two out of four neglect patients tested in the study showed poorer performance for left than right words only with dichotic presentation (consistent with a deficit for sounds entering the contralesional ear), whereas the other two patients were impaired in reporting left words for both methods of lateralized presentation (consistent with an identification deficit for sounds perceived as originating from contralesional space).

### 5.3. *Non spatial auditory deficits*

A final aspect that merits attention is the description of non-spatially-lateralized auditory deficits in patients with visual neglect [34,80,135]. Robertson and colleagues, for instance, documented a non-spatial difficulty in sustaining attention and maintaining arousal in the auditory modality, in a task where neglect patients were required to count the number of occurrences of a particular auditory target among a stream of sounds, of variable length, all presented centrally. Non-spatial auditory deficits have also emerged when patients with

visual neglect were asked to listen to a short rapid sequence of auditory stimuli over headphones, to detect which of the stimuli had a higher pitch [34]. Despite auditory stimuli were always presented centrally, and patients were able to detect subtle pitch modulation for single auditory objects, they were severely impaired at any comparison between two sounds in a rapid sequence, possibly as a result of pathologically limited attentional capacity.

## 6. Multisensory neglect and extinction

The previous sections on non-visual manifestations of neglect and extinction clearly showed that in many circumstances neglect and extinction can emerge for a single sensory modality, or for multiple sensory modalities in a given patient [43,153]. Note however that all the works reviewed so far were concerned with stimulation delivered within a single sensory modality at a time. We now turn to examine how neglect and extinction affecting a unimodal sensory system can be influenced (enhanced or degraded further) by the concurrent activation of another modality.

A number of evidence has now systematically shown that extinction in particular can emerge even when concurrent stimuli are presented in different sensory modalities, i.e., different sensory inputs delivered to the ipsi- and contra-lateral side of the patient's body [17, 45]. Tactile extinction, for example, can be modulated by visual events simultaneously presented in the space region near the tactile stimulation, increasing or reducing tactile perception, depending upon the spatial arrangement of the stimuli. In particular, the visual stimulation in the ipsilesional side exacerbates contralesional tactile extinction, whereby the presentation of visual and tactile stimuli on the same contralesional side can reduce the deficit [96]. Moreover, the modulation described is most consistently manifest when visual-tactile interaction occurs in the space close to the body than when the space far from the body is visually stimulated.

In a similar way, visual and tactile information are integrated in other peripersonal space regions, such as around the face [56,99]. In this case, extinction patients were presented with unilateral and bilateral tactile stimulation on both cheeks and, in addition, visual stimuli were concurrently presented in the contralesional or ipsilesional side. As for the hand, exacerbation of the deficit was found in the ipsilesional visual condition, whereby the visual stimulus enhanced tactile detection

when delivered in the contralesional side. The modulation, again, is more evident when the visual stimulus is presented in a near-body region of space rather than in a farther region, thus implying that sensory integration arising from the same near-the-body location allows for the tactile input to reach awareness.

Similar modulations of tactile extinction have been reported following another kind of multisensory interaction, between audition and touch [98]. When sounds are concurrently presented with single touches delivered at the level of the neck in tactile extinction patients, their contralesional tactile detection is most likely to be hampered by proximal, as compared to far loudspeakers. Interestingly, such a multisensory effect observed in the front space with respect to the patients' head was even stronger when cross-modal auditory-tactile extinction was assessed in the patients' back space, thus suggesting that different degrees of multisensory integration may occur depending upon the functional relevance of a given modality for that particular sector of space [54].

These results support the existence of a peripersonal multisensory space in humans, akin to that described in animals studies [94]. Evidence from animal studies [51,68,69,131,132] revealed a dissociation between a space far from the body that can not be reached by a simple arm movement, and a near peripersonal space, a region of space extending only a few centimetres out from the body surface. Indeed, a strong multisensory integration takes place at single neuron level in this region of space: the same neurons activated by tactile stimuli delivered on a given body-part are also activated by visual or auditory stimuli delivered in the space near that body-part. In this respect, the selectivity of visual-tactile extinction for the proximal sector of space is reminding of the spatial bias observed in unimodal visual neglect, which may selectively arise in the near peripersonal space [32,72].

An interesting characteristic of the space region surrounding the body is its plasticity. Through tool-use, for example, it is possible to remap the space so that "far becomes near" [20]. When asked to use a long stick to bisect distant horizontal lines the neglect patients' selective bias, formerly present only in the near space, was transferred to the far space. Similar results have been described in extinction patients who, after tool-use, showed increased contralesional tactile extinction when a visual stimulus was presented far from the body at the extremity of a hand-held tool. Therefore, using a tool to retrieve distant objects increases the strength of visual-tactile integrative effects in a region of space

far from the patients' body. Such a phenomenon has been ascribed to a tool-use dependent size-change of the peri-hand multisensory space [53].

Altogether, these results show that the expression of cross-modal interaction seems to be a rather frequent occurrence, which can be selectively modulated by several parameters relative to the relationship between the stimulus and the body: like distance, spatial location, auditory complexity, spatial and temporal coincidence. Therefore, these findings are in good agreement with a modular organization of space in which several neuronal structures are devoted to the processing of different space sectors, in different co-ordinates, across different modalities, most probably for different behavioral purposes [143]. Among these structures, the representation of near and far peripersonal space in humans parallels the functioning of the circuit of multisensory areas that has been well documented in monkeys, which is similarly sensitive to the same parameters listed above.

## 7. Multisensory-based rehabilitation approaches

The reported frequency of hemispatial neglect varies widely from 13% to 81% of patients who have had right hemisphere stroke [145]. The presence of neglect has been associated with poor outcome measures on functional activities following a stroke [55,65,67]. Patients with neglect<sup>2</sup> have been found to have longer lengths of stay in rehabilitation facilities and lower scores on the Functional Independence Measure (FIM) [71] and thus require more assistance at discharge than patients without neglect [36,88]. Neglect severity also predicts the degree of family burden more accurately than the extent of brain damage [27].

These are the main reasons why it is important to know whether or not neglect spontaneous pattern of evolution tends towards recovery, in which proportion of patients and to which degree. In this respect, a recent study [55] has shown that only 43% of neglect patients improved spontaneously during a two-week long assessment in the acute phase (up to six weeks post-stroke) and only 9% of patients showed complete recovery. When a subset of this patient population was

re-assessed during the chronic phase, the proportion of patients who recovered increased up to 63%, although recovery was complete only in 25% of them. Since spontaneous recovery in the acute and chronic phase of the disease is not axiomatic and, when present, does not allow for complete remission of neglect symptoms in most patients, it is very important to individuate efficient treatment strategies to improve recovery of patients with chronic and persistent unilateral neglect.

Neglect rehabilitation approaches have been classically divided into two classes: rehabilitation procedures based on a voluntary reorientation of attention toward the contralesional space and rehabilitation procedures based on the sensory stimulation of the affected (contralesional) field, or sensory deprivation of the good (ipsilesional) field. The second class of rehabilitation procedures are based on an interpretation of neglect as an attentional-representational deficit due to the competition between left and right space representations. After a right brain damage, the contralateral space representation is weak and, as a consequence, the competition with intact ipsilesional space representation induces neglect in that sector of space. The antagonism between left and right space representation may be reduced by sensory stimulating the contralesional hemispace (i.e. vestibular, optokinetic, left-sided transcutaneous mechanical vibration, left-sided electrical nervous stimulation and left-limb proprioceptive stimulation), or by suppressing sensory inputs from the ipsilesional hemispace (i.e., hemiblinding technique). Needless to say, most of the studies focussed on the visual components of neglect, although several non-visual aspects of neglect and associated disorders may also benefit from some of these approaches [104,149].

More recently, many studies have outlined that space representation is based not only on input and output responses, that is on sensory and motor information, but on the integration of these information from multiple sensory modalities. As reviewed above, neuropsychological findings have shown the existence of multisensory systems devoted to the integrated coding of spatial information, e.g., a visuotactile system [96,99], an auditory – tactile system [54,98], and an auditory-visual system [59,61]. These integrated systems can offer a unique opportunity to improve the performance of patients with spatial representational deficit, such as patients with visual neglect. As a consequence, potential therapeutic implications could derive from the integration of visual and proprioceptive information, and visual and auditory information; for example, a multisensory based approach to neglect rehabilitation may

<sup>2</sup>To date, rehabilitation studies have focussed on neglect rather than extinction, most likely because extinction is not known to have such a negative impact on patients' everyday life as neglect, although some approaches have nonetheless proved to ameliorate extinction, for example in the tactile modality [76,112].

enable patients to detect “bimodal” stimuli for which unimodal components are below behavioural threshold. Concerning the integration of proprioceptive and visual information it has been shown that passive movements of the contralesional arm in the contralesional space may improve visual neglect. As far as the integration of visual and auditory integration, bimodal audiovisual stimulation of the affected field can improve perception of the visual events in the neglected hemisphere [59]. This amelioration of visual detection was observed only when the two simultaneous stimuli were spatially coincident, or when they were located near one another in space (at a distance of  $16^\circ$ ). In contrast, when the spatial disparity between the two sensory stimuli was larger than  $16^\circ$ , patients’ visual performance remained unvaried. Moreover, multisensory enhancement was greater when visual stimuli were presented in the most peripheral positions of the affected visual field where the impairment was more severe. This is in keeping with the functional properties of multisensory neurons described in animal studies [144]: a greater enhancement of bimodal neurons’ response is observed when visual and auditory stimuli originate at the same time (temporal rule) and from the same position and, as a consequence, fall within the excitatory receptive fields of a visual-auditory multisensory neuron (spatial rule), and when two weaker, rather than two strong stimuli are combined (inverse effectiveness rule). These functional integrative properties are well suited to explain the amelioration of visual neglect patients following multisensory stimulation, thus providing a potential neuronal substrate for a multisensory based treatment of neglect.

Beyond the existence of beneficial effects of audiovisual stimulation, showing that a sound can ameliorate visual detection in neglect patients, the characteristics of patients who can benefit from audio-visual integration effects would be important to establish. It is well known that sensory deficits, such as visual field deficit (e.g. hemianopia), are frequently associated with neglect and may represent a negative predictive factor for cross-modal audiovisual integration in neglect patients [61]. Moreover, since it has been shown that, not only the superior colliculus [144], but also “heteromodal” [66] and “sensory-specific” [28,66] cortices are involved in cross-modal integration, it is possible that the site of cerebral lesions may affect audio-visual integration. The presence of cross-modal audio-visual integration effects has been recently investigated in patients with either neglect or hemianopia and in patients with both hemianopia and neglect [61]. Patients were

asked to detect visual stimuli presented alone or in combination with auditory stimuli that could be spatially aligned or not with the visual ones. As in the previously reported study, an enhancement of visual detection was found when a sound was presented in the same position of the visual one, but only in patients affected either by neglect or hemianopia; by contrast, enhancement dependent upon the multisensory integration did not occur when patients presented with both deficits. Moreover, a different influence of the site of the cortical lesion on multisensory integration has been found. When patients’ lesion was mainly confined to fronto-temporo-parietal areas (neglect patients), or to the occipital areas (hemianopic patients), the visual and auditory stimuli were effectively integrated, whereas when the lesion involved all the previous lobes, although to different degrees in different patients, the effects of multisensory integration were no longer present (neglect patients with hemianopia).

The results of these studies underline the relevance of cross-modal integration in enhancing visual processing in neglect patients and in patients with visual field deficits. The possibility of a sound improving the detection of visual stimuli is very promising with respect to the possibility to take advantage of the brain’s multisensory capabilities for a rehabilitation approach of visual attention deficit and visual field defects [24,61]. In this respect, one question which needs to be addressed in the future is whether a systematic bimodal stimulation, by affecting orientation towards the neglected/blind hemifield and modulating the processing of visual events, can improve visual exploration, perhaps with long-lasting effects. A cross-modal training might reinforce the innate ability of our brain to perceive multisensory events, hidden in the normal condition in which unimodal processes are usually at work on unisensory events that are sufficiently salient to be perceived. This possibility is particularly relevant in terms of rehabilitation perspectives because it is non-invasive, as compared with other rehabilitative procedures, and does not require the voluntary displacement of the patients’ attention to the affected side, which can be particularly difficult for neglect patients.

## 8. Summary and conclusions

As it results from the experimental evidences reviewed above, some core aspects of neglect and extinction are observed across different modalities. Whatever explanation is proposed for the lack of perceptual

awareness, the deficits can not be solely attributed to early sensory problems. For example, patients' performance in visual and tactile detection may strongly vary according to different reference frames and postural changes. In addition, Pavani and colleagues [119] recently showed that discrimination performance for auditory stimuli presented in the contralesional auditory hemifield of visual neglect patients can actually improve when patients gaze towards the left. A pure sensory deficit would imply a complete loss of perception irrespective of spatial relationship between body-parts or gaze direction. However, the presence of subtle sensory dysfunctions has been recently consistently reported in visual, tactile, and auditory studies of neglect and extinction. Although still unclear, the role possibly played by early sensory deficits can no longer be excluded, as degradation or slowing of sensory inputs processing may concur to the difficulty in perceiving contralesional events.

Other features of neglect and extinction studies recently gained considerable interest, such as the presence of non lateralised deficits and their contribution to the syndrome. However, the latter have been mainly reported in vision and audition, whereas their potential role in the chemical and tactile modalities has not been systematically explored. In the same vein, clear evidence of processing without awareness is mainly available for the visual and tactile modality.

Although we did not intend to provide an exhaustive critical review of what the multisensory approach tells us about the current neurocognitive models of neglect and extinction, we believe the study of unisensory and multisensory neglect and extinction is both theoretically and clinically relevant. The within- and between-modality approach would hopefully proceed in parallel, the other senses possibly filling the gap with vision, which is still dominant. We undertook this direction as it may provide a wider framework within which multisensory-based rehabilitation approaches may be devised. An increasing attention devoted to non-visual manifestations of neglect may be of great interest for deepening our knowledge of human spatial awareness.

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