Auditory and multisensory aspects of visuospatial neglect

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Spatial neglect is a common neurological syndrome in which awareness of contralesional space is disrupted after unilateral (typically right) stroke. Although most research has focused on visual aspects of neglect, there is increasing evidence that neglect can often be multisensory. Here we focus on auditory disturbances that can co-occur with visual neglect. Patients selected for showing visual neglect often also show deficits in localization of single sounds; and also in the detection or identification of contralesional sounds, particularly in the presence of an ipsilesional competitor. Moreover, auditory and visual aspects of neglect often correlate in their severity across patients. These results are considered in relation to recent neuroimaging findings in the normal brain, showing that the brain regions typically damaged in neglect patients might contain multimodal representations of space.

Unilateral neglect is one of the most intriguing neurological conditions that arises after a brain lesion, and it commonly occurs after right perisylvian damage (Fig. 1a). Patients with unilateral neglect typically behave as if the region of space contralateral to their brain lesion no longer existed [1–4]. They might ignore objects or people on their left side, omit words on the left side of a page when reading, omit left-sided details when drawing from memory or copying (Fig. 1b), often fail to mark contralesional targets in search-and-cancel clinical tests (Fig. 1c), and so on. Neglect patients might also fail to groom the left side of their own face, ignore touches on the left side of their body, and/or fail to respond when addressed verbally from the left side of space. It is now increasingly recognized that neglect symptoms typically reflect a constellation of component deficits, which can differ from one patient to another (e.g. [1,4,5]; see [3] for a recent comprehensive overview of the neglect syndrome). Impairments in spatial attention [6] and/or spatial representation [7] have often been considered crucial causes of neglect. Primary sensory or motor deficits need not be present, but can contribute [8,9]. In some cases, neglect can arise in imagery [8] or spatial memory tasks [9] also, and this can apparently dissociate from perceptual neglect for some patients [10].

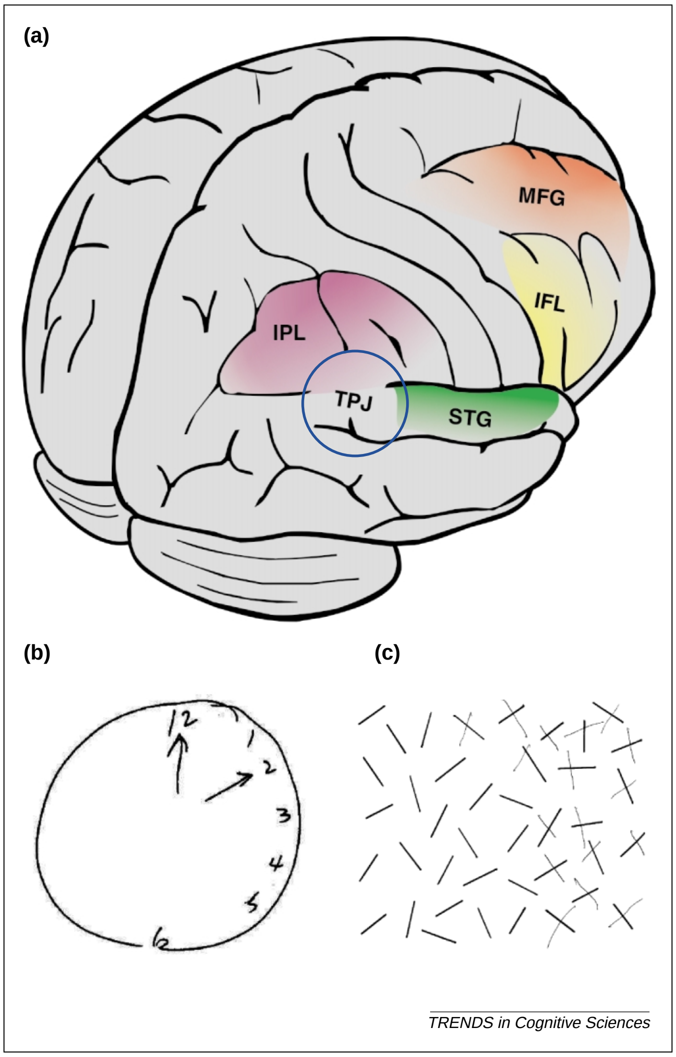

Fig. 1. (a) Cortical areas of the right hemisphere that have been implicated in neglect lesions (illustration kindly supplied by Dr Chris Rorden). IPL, inferior parietal lobe; IFL, inferior frontal lobe; MFG, medial frontal gyrus; STG, superior temporal gyrus. Such lesions can be very large, but are typically centred on perisylvian cortex and underlying white matter, and particularly on the temporo-parietal junction (TPJ; blue circle). Crucially, all of the implicated areas are broadly considered to be *multisensory* association cortex. **(b,c)** Illustrations of visuospatial neglect as manifest on simple paper-and-pen tests. **(b)** When asked to draw from memory or to copy, patients with left neglect (following right-hemisphere damage) characteristically fail to produce left-sided information. **(c)** When asked to cancel all the visual targets on a page, neglect patients typically miss those on the contralesional (left) side.

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Despite this acknowledged complexity of the neglect syndrome, until recently most research on perceptual aspects of neglect has focused on the visual domain only. However, there is now increasing interest in multisensory manifestations of neglect [11–14], consistent with the burgeoning literature on multisensory spatial processing in the normal brain (see [15,16] for reviews). Here we focus on possible auditory deficits in patients diagnosed with visuospatial neglect, and where possible, we relate this to recent neuroimaging findings on multisensory spatial processing in the normal human brain. When patients are selected for study because they show visual manifestations of neglect, they often exhibit characteristic auditory pathologies also.

Auditory localization in neglect patients

When addressed verbally from the left in the clinic, right-hemisphere neglect patients might either fail to respond, or more commonly, behave as if they heard the voice originating from their right (so-called 'alloacusis' [17]). Apparent rightward shifts in sound localization have also been observed experimentally (e.g. [18–21]) when neglect patients were asked to point to a sound presented either in free-field (from an external source; see Fig. 2a), or over headphones (pointing to a location on their head). 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 relative to the centre of the head or body midline [19,22–24]. 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. [19,24]).

However, systematic rightward biases in sound localization have not always been found when using a pointing task [25] or an auditory midline task [26]. Moreover, when auditory midline tasks have been performed with free-field sounds, 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) [22,23]. We recently proposed [15] that 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 [13]. Motor or visuo-motor biases in pointing tasks (e.g. [13,20]), or pathological distortions of perceived head/body midline in auditory-midline tasks [27], could in principle affect performance. Other tasks have recently been developed to study auditory localization, that require neither a directional motor response, nor any comparison with the head/body midline. As described below, these new tasks suggest that systematic lateral shifts in one direction are unlikely to explain all auditory spatial disturbances in neglect patients.

Increased uncertainty for contralesional sounds

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. [24,28]; Fig. 2b). In addition, their electrophysiological brain response to sudden changes in sound localization (i.e. the mismatch negativity response observed in scalp recordings of event-related potentials) is pathologically reduced for contralesional vs. ipsilesional free-field sounds [29]. This reduced discrimination for different free-field sound locations within the contralesional side of space (compared with discrimination within the ipsilesional side) might in principle be reconciled with an erroneous but systematic shift in sound location as discussed above, provided one assumed any lateral shift was non-linear (any strictly linear shift of sound position should still maintain the relative differences in location for auditory targets). Alternatively, the deficits in same/different discriminations [24,28] might indicate increased spatial uncertainty for sound position, especially for contralesional

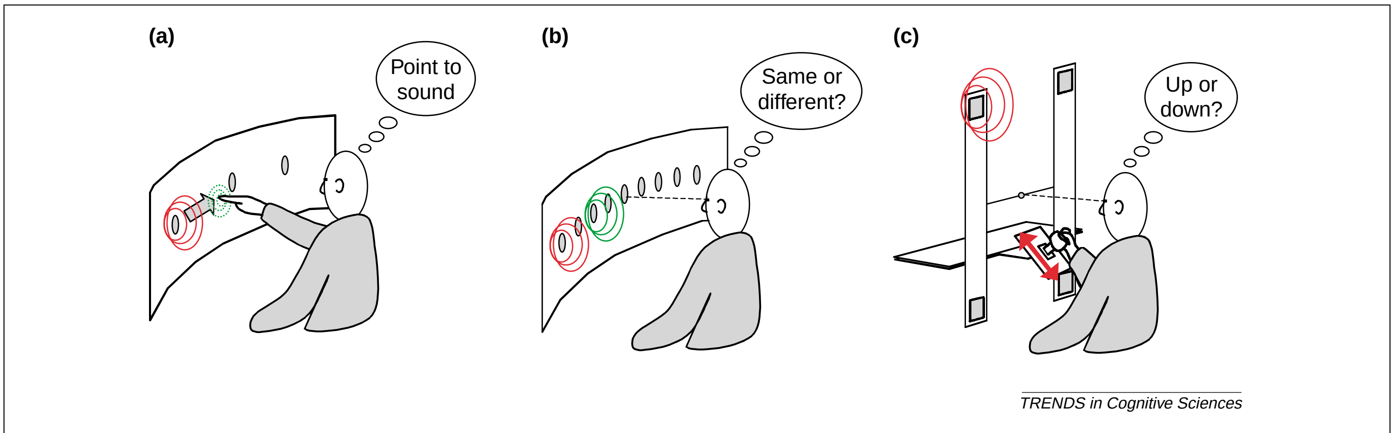

Fig. 2. Deficits for contralesional targets can also be revealed in the auditory modality for neglect patients. **(a)** In pointing tasks, neglect patients often mislocalize sound positions to the right of the actual location (e.g. [20,21]); here the red concentric circles depict actual sound position, dotted green circle depicts the apparent position indicated by pointing responses. **(b)** Neglect patients also have difficulty identifying the relative spatial location of contralesional auditory targets, as revealed by their poor performance in judging the relative azimuth (i.e. lateral position) of two successive sounds with respect to each other ('same/different' task) [28]. **(c)** Finally, localization deficits have recently been shown [30] for free-field sounds, particularly in contralesional space, when judging their elevation (i.e. up versus down), suggesting that the auditory localization deficits might involve increased uncertainty concerning the spatial source of contralesional sounds, rather than just systematic lateral shifts.

stimuli, instead of a strictly systematic shift in heard azimuth.

We examined this by studying performance in a speeded discrimination task that concerned the vertical position of contralesional or ipsilesional free-field sounds [30] (Fig. 2c). In such a task, any systematic pathological shift in heard azimuth alone should presumably not affect patients' performance, because any purely horizontal shift should not affect the relative vertical position of sounds. In fact, we found that vertical discrimination by neglect patients was slower and less accurate compared with control right-hemisphere patients without neglect, especially for sounds from contralesional space (note that worse performance in neglect patients emerged for ipsilesional sounds as well, but to a lesser degree). This finding, together with the evidence from impaired discrimination of azimuth for successive contralesional sounds [24,28], suggests that neglect patients might suffer increased spatial uncertainty in their coding of sound locations, for both the horizontal and vertical dimensions, and particularly in the contralesional hemispace, rather than just systematic horizontal shifts in localization.

Poor detection or identification of contralesional sounds in the presence of concurrent ipsilesional sounds

Although deficits in localizing single contralesional sounds have often been reported in neglect patients (see previous two sections), the patients usually *detect* these single sounds with apparent ease in most localization studies (e.g. [19–22,24,28,30]). 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. This finding has classically been related to the different 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. However, it should be noted that whereas visual environments often present multiple concurrent stimuli (as do many tests used to assess visual neglect; Fig. 1c), auditory testing of neglect patients often proceeds with a single strong sound presented against silence. Thus, the apparent discrepancy between detection failures in neglect for vision vs. hearing might also relate

Box 1. High-level spatial disturbances in auditory neglect; not just suppression of the contralesional ear

Although 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), it has become clear that the auditory deficits observed in neglect patients cannot all be explained solely in terms of poor processing (or suppression) for auditory information entering the contralesional ear [34,52]. Instead, higher-level spatial disturbances are likely to be involved, as revealed by the crucial role of subtle spatial factors in modulating auditory neglect. One striking example is 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 instead [53].

A direct investigation of the role of apparent sound location with respect to which ear the information enters was recently conducted by Bellman *et al.* [34]. They asked neglect patients to identify concurrent pairs of heard words. Either each word was presented to one ear only ('dichotic'; Fig. Ia), or each word was presented binaurally but with interaural time difference serving as the only lateralization cue ('diotic' or 'stereophonic' presentation method; Fig. Ib). With the latter presentation method, a person with normal hearing would still hear two words that each appeared lateralized to opposite sides of space (left or right), but each word now enters both ears with equivalent intensity. Among four neglect patients, two 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*).

Although the prevalence of the particular outcome described by Bellman *et al.* remains to be determined, converging evidence from other experimental paradigms also suggests that auditory spatial deficits in neglect patients are unlikely to be explained solely in terms of suppression of the auditory input at the contralesional ear. For instance, a recent study by Carlyon *et al.* [54] suggests that deficits for left-ear targets during dichotic presentation over headphones might relate more to attentional factors than to sensory factors.

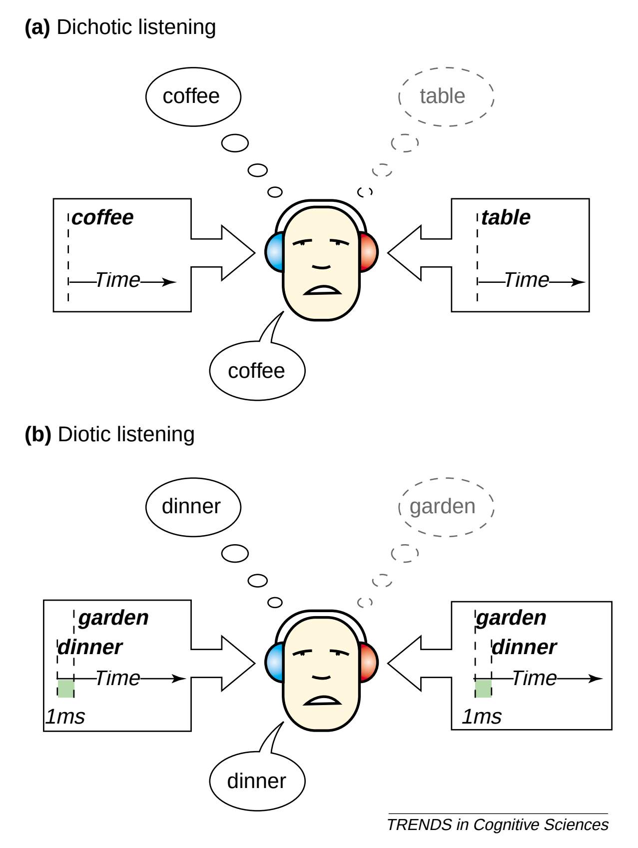

Fig. I. When asked to report concurrent words presented over headphones, neglect patients often repeat only the word lateralized on their right side. This phenomenon has typically been observed with **(a)** 'dichotic' presentation (i.e. each word reaching one ear only), but has also been observed in some cases with **(b)** 'diotic' or 'stereophonic' presentation (i.e. each word reaching both ears with equivalent intensity, but lateralized in space owing to brief interaural delays).

to the presence vs. absence of competing stimuli for the two modalities.

When two concurrent sounds are presented (thus producing the minimal version of concurrent competing stimulation), typically with one sound on each side, a consistent failure to *detect* contralesional sounds has often been reported in patients with visuospatial neglect, for both free-field sounds [17] and headphone stimuli [31]. Similarly, identification deficits for contralesional sounds in neglect patients have most commonly been observed [32–34] during concurrent presentation of two sounds, one on each side, rather than for a single sound presented in isolation (but see [32] for poor identification of unilateral left syllables presented free-field). Such effects with two concurrent competing sounds (see Box 1) might be considered the auditory equivalent of visual or tactile ‘extinction’, in which the deficit for a contralesional stimulus becomes more pronounced in the presence of a competing ipsilesional stimulus [35]. Whether auditory extinction is a deficit distinct from the impaired localization for single sounds that can also be observed in neglect patients awaits systematic investigation.

Non-spatial auditory deficits in neglect

Although the results reviewed so far suggest that auditory deficits in neglect patients often affect one side of space more than the other (i.e. with poorest performance for contralesional sounds), some non-spatially-lateralized auditory deficits have also been documented [36,37]. This appears to be in broad agreement with a growing body of evidence suggesting that ‘non-spatial’ deficits might also contribute to visual neglect (e.g. [38,39]; see [2] for a recent review).

Non-spatial auditory deficits in neglect patients were first observed in a task that required counting of the number of occurrences of a particular auditory target among a stream of sounds, of variable length, all presented centrally [37]. This might reflect a general difficulty in sustaining attention and maintaining arousal, rather than a specifically auditory deficit. 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 [36]. Despite the auditory stimuli always being presented centrally, and the patients being able to detect

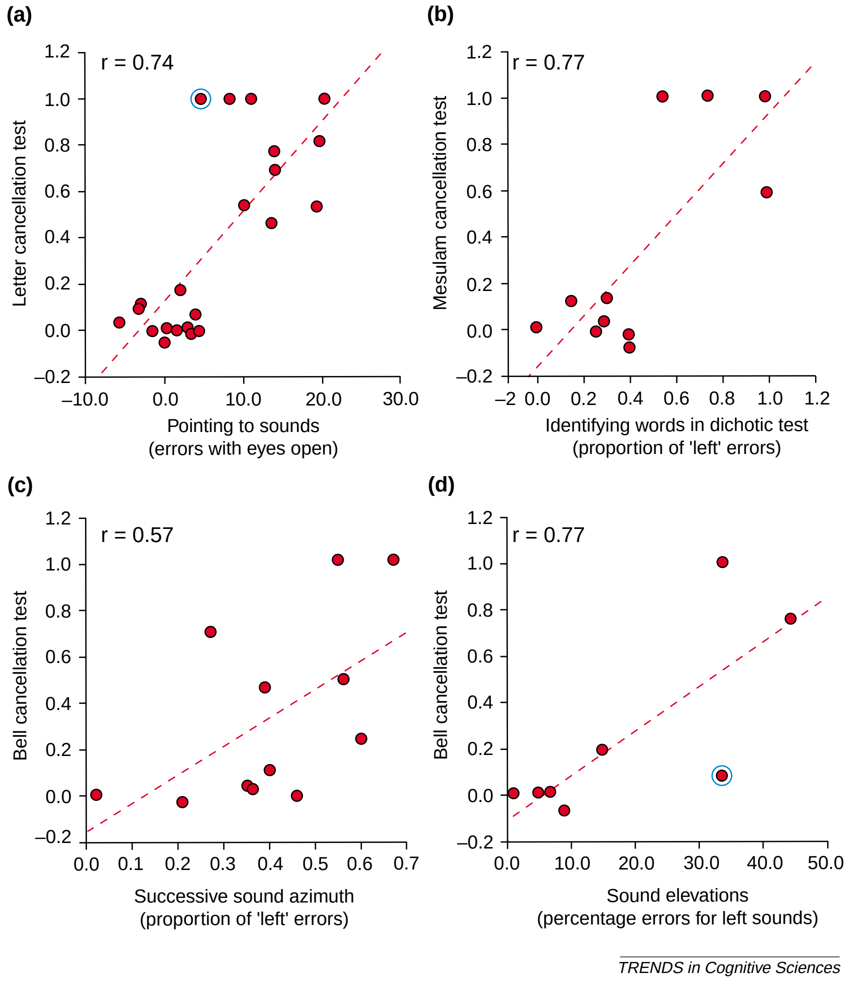

Fig. 3. Scatterplots for correlations between clinical tests of visual neglect and several dependent auditory variables. Each point represents performance for one patient. Higher values on y-axis indicate more omissions for left targets in visual cancellation tests (i.e. stronger visual neglect). There is a consistent relation overall between the severity of clinical visual neglect (y-axis) and the extent of the auditory deficit on experimental measures (x-axis); (a) is the task shown in Fig. 2a; (c) the task in Fig. 2b; (d) the task in Fig. 2c. Note that some datapoints (i.e. some individual patients) provide exceptions to this (e.g. the points circled in blue; see also Box 3).

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.

Neglect-related auditory and visual deficits often correlate in severity

The evidence reviewed above shows that many neglect patients can exhibit auditory as well as visual deficits. Moreover, many of these auditory deficits cannot merely reflect peripheral sensory impairments (see Box 1). Having established this, an important question is whether auditory and visual deficits in neglect might reflect a common multimodal disruption. One approach to this issue is correlational. In a recent meta-analysis [13], we examined how the severity of visual neglect on various standard clinical measures (e.g. cancellation tests; Fig. 1c) might relate to the severity of auditory neglect as revealed by experimental measures of the types described above. We specifically considered measures of auditory localization using either pointing (Fig. 2a); successive same/different discrimination (Fig. 2b); or speeded vertical (up/down) judgments (Fig. 2c); plus measures of auditory 'extinction' in an identification task for concurrently presented words (see Fig. I in Box 1). Remarkably, a significant correlation between the severity of clinical visual neglect and the experimental measure of auditory neglect was found for the vast majority of the possible relationships examined, thus suggesting that a relationship is consistently found across many neglect patients between several different visual and auditory measures (see Fig. 3).

It is one thing to establish a consistent correlative relationship (Fig. 3) but quite another to develop a conclusive explanation for its existence. Potential intervening variables such as lesion size and vintage still need to be fully factored out by further research. Nevertheless, the existing data (described more fully in [13]), already provide a compelling case that visual and auditory neglect are consistently correlated in severity in neglect groups (although they might be dissociated in some rare individual patients, despite being associated in most; see below). Our working hypothesis concerning this empirical relationship is that neglect can often be caused by damage to brain regions containing multisensory representations of space, with the deficit consequently manifesting across

Box 2. Functional neuroimaging of auditory space perception

The notion that brain areas well beyond auditory cortex might play a role in auditory space perception has arisen from both single-cell recording studies in animals (e.g. [55]) and from neuropsychological evidence in humans (e.g. [19]). Recently, functional neuroimaging techniques (PET and fMRI) have contributed further to knowledge about the cortical network of brain areas involved in auditory space processing in the intact human brain. Activation in parietal and frontal cortex has been observed in imaging studies that required participants to compare the azimuthal position of two sequential sounds [49,56–58], as well as in studies in which subjects were presented with sound objects moving in azimuth [48,59–62]. The latter approach also showed bilateral activations in the planum temporale, a region of the superior temporal plane posterior to primary auditory regions [60–62]. Moreover, Pavani and colleagues [61] recently demonstrated a common bilateral network of brain areas (again involving planum temporale, parietal cortex and premotor cortex) that was activated in response to both horizontal and vertical sound movement, in analogy with the existence of neglect-related disturbances for auditory processing of both azimuthal and vertical sound location (see Fig. 2b,c in main text). The network activated in neuroimaging studies of auditory spatial processing has been considered by some to reflect a 'dorsal' processing stream for auditory space perception (e.g. [56,57,63], but see [64]).

Although some of these activations are found bilaterally (in apparent contrast to the association of spatial neglect in humans with right-hemisphere lesions in particular; Fig. Ia), stronger activation of the right hemisphere has been reported (Fig. Ib), especially for the inferior parietal lobule (e.g. [58,59]), which has often been highlighted for the lesions that produce neglect. Converging evidence from magnetoencephalography also confirms a potentially special role for right parietal regions [65,66].

Two further aspect of Fig. I are notable. First, the brain areas that show right lateralized activation in functional neuroimaging studies of auditory space perception (Fig. Ib,c) have some rough correspondence with the typical lesion of neglect patients (Fig. Ia here; see also Fig. 1a in main text). This might explain the emergence of auditory spatial difficulties in neglect patients. Second, many of the areas activated by auditory spatial processing have also been shown to activate multimodally, for visual or tactile, as well as auditory, stimuli and tasks (e.g. [47,49,51]).

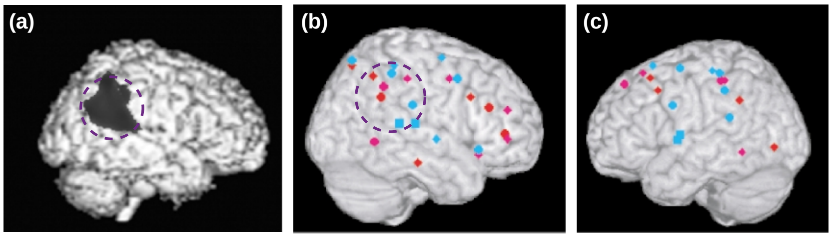

Fig. I. **(a)** Example of a lesion in a neglect patient. The damage is centred on right inferior parietal cortex (circled), but also affects superior temporal cortex and white matter. This patient has enduring visual neglect despite intact visual fields and no hemiparesis. **(b,c)** Activation peaks from PET and fMRI studies in normal subjects of auditory spatial processing superimposed on surface rendering of normalized right (b) and left (c) hemispheres, using the free-ware software MRIcro (www.mricro.com). Activation peaks are colour-coded according to the contrast shown: delayed auditory-spatial matching vs. passive listening of central sounds (red; [49,58]), delayed auditory-spatial matching vs. recognition of central sounds (violet; [56,57]), sound movement vs. stationary sounds (blue; [59–61]). The crucial point for present purposes is that many of the areas implicated in neglect are activated in these auditory spatial tasks in the normal brain. Moreover, although much of the network is bilaterally activated, some right laterality is apparent around the inferior parietal regions upon which neglect lesions are often centred (compare circled regions).

Box 3. Dissociations versus associations in neuropsychology

Traditionally, neuropsychologists have based their conclusions on dissociations between deficits (e.g. auditory neglect without visual neglect, or vice versa), rather than on associations [31,67]. This has been the conventional rule even when the dissociations are only observed in rare, atypical cases, whereas an association between deficits is frequently found, as we have observed for the correlated auditory and visual deficits in neglect patients. The dissociative approach in neuropsychology was widely adopted because any association might in principle reflect damage to separate but neighbouring subsystems in the brain. Note that on this traditional approach, the only informative patients in scatterplots are those rare cases who fall off the main regression line relating two deficits (here, those showing severe visual neglect but little or no auditory neglect; or vice versa; e.g. see circled points in Fig. 3 in main text). The fact that the vast majority of patients show a clear relationship between auditory and visual neglect would be deemed irrelevant.

However, this seems both potentially wasteful of data (most patients showing deficits are rejected as uninformative), and potentially capable of leading to overly strong conclusions about separability. Thus, dissociations between auditory and visual neglect in just a few cases might be taken (erroneously) to indicate that auditory and visual spatial processing is entirely separable at all stages. But in fact there might be multimodal stages of spatial processing, with the lesions in the rare dissociative cases simply arising at earlier unimodal stages, before multimodal convergence (see also [68] for a related argument concerning neuropsychological deficits in semantic memory).

We suggest that a complete neuropsychological explanation should ideally account for both the overall pattern (here, a clear associative relationship between visual and auditory neglect), and also for the occasional exceptions to that pattern (i.e. the rare cases showing dissociations between auditory and visual neglect). Although it remains true in principle that any association might still reflect damage to separate but neighbouring unimodal neural populations, in practice high-resolution structural and functional neuroimaging could now allow this concern to be put to empirical test. On our testable working hypothesis, the empirical correlation observed between the severity of visual and auditory neglect (that most patients obey) should be the result of damage affecting brain areas that are multimodal; whereas the rare dissociative exceptions should have damage affecting only unimodal brain structures.

multiple sensory modalities, with correlated severity. Recent functional imaging results from the normal human brain provide evidence that could be relevant to this hypothesis.

Multisensory brain areas for spatial processing

The typical brain injuries resulting in hemispatial neglect for humans are centred on the right perisylvian region, including inferior parietal [40], superior temporal [41] and inferior frontal lobes [42] (see Fig. 1a). Such brain areas are known to respond to multiple sensory modalities based on single-cell recording studies in monkeys and other animals [43–45]. Recent neuroimaging studies likewise indicate the multisensory nature of areas here in the human brain (see [15,46] for recent reviews). For instance, multimodal activation in the intraparietal sulcus, inferior parietal lobule and ventral premotor cortex has been found in response to visual, auditory and tactile stimuli [47,48]. These brain areas have also been implicated in delayed match-to-sample tasks for both auditory and visual stimuli [49], and in audio-visual binding [50]. In addition, a growing body of evidence suggests that some of these brain regions (i.e. superior and inferior parietal lobe, frontal premotor cortex) are implicated in multisensory spatial attention to peripheral locations (see [51] for review).

These recent neuroimaging findings indicate that some of the brain areas associated with neglect (e.g. in right inferior parietal lobule) are multisensory, thus providing one potential explanation for the correlatively-associated auditory and visual deficits observed in neglect patients, as described above (see Box 2). However, some functional imaging data suggest that other 'unimodal' areas nearby might be activated in auditory but not visual localization tasks; or vice versa (e.g. see [47–49]). Damage to one or other of these areas might explain why, in rare cases, severe visual neglect can be seen in the absence of auditory neglect, or vice versa. Note that in providing exceptions to the usual correlative rule, the lesions in such dissociative patients could provide important data for delineating unimodal vs. multimodal brain areas, which might converge with functional imaging results (see Box 3 for further discussion).

Box 4. Questions for future research

- Do the rare patients in whom auditory and visual neglect dissociate show systematically different lesions from the more common patients in whom neglect has multimodal manifestations that are associated in severity across the senses?
- Does any such difference in lesions correspond with functional imaging data on unimodal vs. multimodal spatial representations in the normal human brain?
- Can spared unimodal structures compensate for selective damage to multimodal structures (and vice versa)? Does their interplay change during recovery?
- Are multimodal structures normally used routinely even in apparently 'unimodal' localization tasks, perhaps because they can provide representations of space that are more stable than those tied to a single sense, such as retinotopic location in vision, somatopic in touch, and cranotopic in audition? Multisensory representations of space might include postural factors.
- Do treatment interventions that ameliorate visual neglect have corresponding effects on auditory neglect?
- How do visual and auditory neglect relate to tactile and proprioceptive aspects of neglect, and even to representational (e.g. imagery) or motor components?
- Do non-spatial aspects of neglect exacerbate spatial aspects, and vice versa?
- The cortical network activated for auditory spatial processing (see Box 2) has bilateral components, despite some right laterality around the inferior parietal lobe. Hence some aspects of this network should remain anatomically intact in neglect patients with unilateral right-hemisphere lesions. Does this imply the existence of some residual sound-localization abilities in neglect patients (which might be implicit rather than explicit)? Or does right inferior parietal cortex play the cardinal role in coordinating remote components of the network, so that the functioning of the whole network (including structurally intact left-hemisphere regions) is disrupted after lesions there?

Concluding remarks

Although research with neglect patients has usually focused on their visual deficits, it is now well established that most neglect patients have auditory as well visual deficits; and we have found that these are usually correlated in severity. Auditory localization is disrupted, especially for contralesional sounds, and such sounds can fail to be identified or even detected, especially in the presence of competing ipsilesional sounds. Although some of these effects might involve deficits to sensory auditory pathways from the contralesional ear, this cannot explain all of the auditory deficits seen (Box 1), nor their association with the severity of visual neglect (Fig. 3). Functional imaging evidence from the normal human brain suggests that the regions typically lesioned in neglect patients are involved in multimodal spatial processing, providing one natural explanation for why neglect frequently has multisensory manifestations (see Box 4).

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