Relating unilateral neglect to the neural coding of space

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Neuropsychological findings on the human neglect syndrome after parietal damage may relate to the physiological properties of single cells that have been studied in monkey parietal cortex and in related brain areas. Human neglect may reflect partial loss or dysfunction of similar cell populations, producing a pathological gradient in the numbers of cells representing particular lateral positions in space, for particular functions. This can explain the graded deficits seen in patients. We might expect the patient deficits to cellular properties for several current issues: spatial frames-of-reference; multimodal integration; effective treatments for neglect; motor components to parietal function; and residual unconscious processing. A neural perspective may resolve traditional debates in the neglect literature and outline directions for future research.

Introduction

Unilateral neglect is a common and disabling syndrome after unilateral brain damage. Patients with unilateral neglect appear oblivious towards the side of space opposite their lesion [1–4]. After a lesion to the right side of the brain, patients may ignore people on their left side, miss food on the left of their plate, and fail to shave their lesion [1–4]. For instance, after a lesion to the right hemisphere intact [6–9]; in particular, both show a gradual decline against lateral position — rather than a step-function centred on anatomical midlines, such as a strong representation for one visual field versus none for the other — together with an off-centre peak (Figure 1). There may, however, be a quantitative difference between humans and monkeys. While the gradients within the two hemispheres are mirror images of each other in monkeys, they may be asymmetric in humans [14] such that the gradient in the right hemisphere is shallower. This could explain why neglect is more severe after right-hemisphere lesions in humans (leaving the patient with just the steep pathological gradient of the intact left hemisphere).

The pathological gradient in neglect patients becomes particularly problematic for them when several stimuli are presented simultaneously (for a review, see [15]). In this case, a more ipsilesional stimulus will usually be most salient for the patient, and may ‘extinguish’ other stimuli from awareness so that a previously detectable contralesional field. Moreover, any deficit is typically graded in nature, such that performance becomes increasingly worse for stimulus events further towards the affected contralesional side, with no sudden drop-off at anatomical midlines (such as the vertical meridian which separates right and left visual fields) [5,6]. Smania et al. [7] found that the perceptual detection rate for visual targets decreased monotonically in right-parietal neglect patients as the target was guided toward the left on the retina. Unlike normal subjects, the patients performed better for right eccentric targets than for central ones, thus showing an ‘off-centre’ peak in performance. Behrmann et al. [8] found that neglect patients made increasing numbers of saccades towards the right during visual search, with monotonically increasing fixation durations in that direction. Karnath et al. [9] found that saccades and head turns in neglect patients are biased towards the right during exploration.

Such graded impairments may be explained by a pathological gradient in the number of neurons for particular regions of space within the parietal lobe after the lesion [10,11,12]. Physiological studies in the monkey show that unlike earlier visual areas, parietal regions include some neurons with ipsilateral receptive fields, so that although the representation within one hemisphere emphasizes contralateral space overall, some ipsilateral representation is also present. More specifically (see Figure 1), the number of left-hemisphere neurons responding to a particular location decreases monotonically as one considers increasingly lateral locations, and vice versa in the right hemisphere ([13]; S. Ben-Hamed, JR Duhamel, personal communication). The number of neurons for different lateral positions in parietal areas of one monkey hemisphere thus resembles the graded performance of neglect patients with only one hemisphere intact [6–9]; in particular, both show a gradual decline against lateral position — rather than a step-function centred on anatomical midlines, such as a strong representation for one visual field versus none for the other — together with an off-centre peak (Figure 1). There may, however, be a quantitative difference between humans and monkeys. While the gradients within the two hemispheres are mirror images of each other in monkeys, they may be asymmetric in humans [14] such that the gradient in the right hemisphere is shallower. This could explain why neglect is more severe after right-hemisphere lesions in humans (leaving the patient with just the steep gradient of the intact left hemisphere).

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Spatial nature of neglect, in relation to parietal neurons

A further difference between neglect and primary sensory loss is that visual neglect does not affect just fixed positions on the retina and tactile neglect does not affect just fixed somatotopic positions on the body, whereas primary sensory losses do take these fixed forms. Whether or not a neglect patient will become aware of a particular stimulus on the retina, or on the hand, can depend on current posture. Thus, a previously neglected left visual field stimulus may become detectable [21,22] with the eye and/or head deviated to the right, or with the trunk deviated towards the left [23], even though the retinal input remains unchanged. Likewise, a previously neglected touch on the left hand can enter awareness if the hand is placed to the right of the patient’s trunk [24].

Just like neglect, the response of neurons in the parietal lobe is influenced by posture. Thus, while the majority of neurons in parietal areas LIP and 7a have retinotopic receptive fields, the amplitude (or ‘gain’) of their retinal response is modulated by postural factors such as eye position [25]. Such ‘gain modulation’ by nonretinal factors (see Figure 2) can explain why neglect arises in a mixture of egocentric coordinates, with posture having an effect in addition to retinal location [10]. Moreover, similar principles can explain examples of so-called ‘object-based’ neglect [16,26,27]. Recent physiological evidence shows that the gain-modulation principle extends to many different types of information that are combined with retinal information in parietal neurons, as illustrated below.

Multimodal issues in neglect and in the neural coding of space

Recent research has demonstrated both that many neurons in the parietal lobe (plus elsewhere in the network for spatial representation and attention) are involved in multisensory integration, and that unilateral neglect can be a multimodal deficit. For instance, visuo-auditory cells have been reported in parietal areas LIP [28,29] and PRR (the parietal reach region) [30], while visuo-tactile cells have been found in VIP (the ventral intraparietal area) [31]. Such cells typically have spatially congruent receptive fields in the different modalities that can stimulate them (i.e. stimulations from the same external location typically drive the cell, across the different modalities). Moreover, many parietal cells also integrate visual inputs with vestibular signals, as in areas 7a and VIP [32].

The convergence of multimodal inputs in posterior parietal cortex seems consistent with observations that neglect can arise crossmodally [33,34,35]. Moreover, several recent studies (e.g. [36,37]) have shown that an ipsilesional event in one sensory modality can extinguish the patients’ awareness of a contralesional event in a separate modality. Ladavas and colleagues [37] found in right-hemisphere patients that a visual event in the right hemifield extinguishes awareness of a touch on the left hand more strongly when the visual event occurs closer to the (unstimulated) right hand. It is tempting to relate such crossmodal interactions to those found at a cellular level in neurons with spatially congruent receptive fields in the modalities of vision and touch. Such neurons have recently been studied in parietal area VIP as well as in prefrontal cortex, and the visual receptive field is found to follow the tactile receptive field in space as the corresponding body part is moved [31,39]. But some forms of multimodal neglect may arise from large lesions affecting several different unimodal areas. There have been occasional reports of patients who show neglect in one modality but not another [40]. However, this issue is far from being settled. A failure to detect neglect in one modality might reflect a lack of sensitivity in the testing procedure. Ceiling
and floor effects have rarely been ruled out, and the issue merits further systematic study.

Treatments that ameliorate neglect, in relation to parietal neurons

Neglect can be transiently ameliorated by several manipulations. Caloric vestibular stimulation (via iced-water in the left ear, which stimulates the vestibular organs) has dramatic effects in the short term (e.g. [41]). Vibration of the left neck-muscles (to produce a similar afferent input to that induced by twisting the trunk leftward) can also transiently improve visual neglect [23,42]. A possible neural basis for these striking effects can now be proposed, as the principle of gain modulation for retinotopic neural responses has now been extended [33••] to include vestibular influences (e.g. in monkey parietal area 7a, but not LIP) and also neck-proprioceptive influences (in LIP but not 7a). It is thus possible that these treatments have their effect on neglect by a similar mechanism to the one we suggested earlier for the influence of postural factors [10•] (see Figure 2).

A recent study has shown that prism adaptation, implemented such that reaching responses had to be corrected by moving farther towards the contralestional direction, can subsequently ameliorate visual neglect in standard clinical tests [43•]. The neural basis of this remains poorly understood, and may involve plasticity (perhaps in brain areas that remain intact in most neglect patients, such as the cerebellum), although it is possible that the effect could also involve postural factors, as with other effective interventions in neglect.

Motor components of neglect and of parietal activity

In addition to its role in multimodal spatial integration, the posterior parietal cortex is involved in the initial stages of planning spatial movements. The role of monkey LIP in saccadic eye movements is well documented (see [44] for a recent study), consistent with the strong projections it sends to the superior colliculus and frontal eye fields. It is now clear that some parts of the parietal lobe are involved in the control of reaching rather than saccades. Cells in the

![Figure 2](image-url)
PARIETAL neurons in particular, respond before and during reaching towards visual as well as towards auditory targets [20,30,45•]. Parietal neurons can also respond during object manipulation with the hand, such as when moving a joystick [19•].

It has long been suspected that neglect in human patients may involve motoric as well as perceptual biases, although any motor components of neglect were traditionally attributed to frontal damage [46,47]. In keeping with the recent physiological reports of cellular activity related to motor initiation within the parietal lobe, some recent studies have shown that neglect patients with damage restricted to the parietal lobe have deficits in initiating movements towards their affected side, in addition to their perceptual impairments. They may be slow to direct their ‘good’ ipsilesional hand in the affected contralesional direction, and over and above their perceptual deficit for that side [46•,48], they may also show saccadic biases [49]. Such combined perceptuo-motor deficits are consistent with the physiological evidence for the parietal lobe as a sensorimotor interface.

**Spatial coordinates of motor-related activity in the parietal lobe**

Mapping of the motor fields of LIP and PRR neurons shows that these may be eye-centered, whether the animal is responding to a visual [45••] or an auditory target [30]. This corresponds to the same place on the retina when eye position is changed, although it may be gain-modulated by postural factors. The discovery of eye-centered fields is unsurprising in area LIP, given its involvement with saccades—these are already known to be specified in eye-centered coordinates in the superior colliculus. However, eye-centered motor fields for the reaches of neglect patients in PRR are a more surprising discovery, given that other stages of the motor commands for reaching (e.g., in primary motor cortex) are clearly not eye-centered. The result is particularly remarkable for unseen reaches to auditory targets [50], as these do not logically require any eye-centered coding whatsoever. The principle of eye-centered coding, in addition to their perceptual impairments, may facilitate communication between different parietal areas, each area being subject to gain-modulation by different factors, but within a common eye-centered code.

If eye-centered coordinates are used in the initial specification of reaches toward visual and auditory targets, as the physiology suggests, then one might expect that the eye-centered position of such targets could affect reaching accuracy. Humans can make systematic errors when pointing or reaching to visual targets, and the amplitude of these is related to the current eye-centered location of the target [50], even for unseen memory-guided reaches, after a delay during which eye-position is changed [51,52]. As with eye-centered coding in the motor fields of parietal neurons, this systematic error extends even to unseen memory-guided reaches to auditory targets, which do not logically require any eye-centered coding [53]. It can also be found for proprioceptively specified targets, and even for imagined targets [53].

These recent findings all lead to the prediction that many aspects of neglect after parietal damage should show strong influences of the eye-centered position of stimuli, even for nonvisual modalities [54]. However, one should not expect the patients’ deficits to be purely eye-centered, given that parietal neurons with eye-centered fields also show strong gain-modulation by noncentral factors such as postural inputs. As discussed earlier (in the section on the spatial nature of neglect), such gain modulation is consistent with the mixture of egocentric coordinates in which neglect is typically manifest for the patients. Moreover, while the recent physiological studies reveal that eye-centered fields are surprisingly common in parietal neurons, not all show this (see Figure 3). In particular, a few neurons have body-centered fields, while the majority vary within all egocentric reference frames [39,55,56]. Recent computational modelling [10•,57] shows that such body-centered fields, together with the gain modulation described earlier (see Figure 2), can provide basis functions for stimulus inputs and posture signals. This allows coding of spatial location in multiple frames-of-reference simultaneously, and so can explain why neglect is not purely eye-centered. Such coding also provides a particularly efficient representation for performing multisensory integration [57] and for solving the non-linear problem of generating spatial motor commands from sensory signals [10•].

**Residual processing in neglect**

Numerous behavioral studies have now shown that some residual, unconscious processing can take place for the information neglected by the patients [58–61]. The patients’ reaction times can be affected not only by the presence of a neglected visual stimulus, but also by its colour or shape, and even by its identity and semantics (for reviews, see [4,62]). Such residual processing presumably reflects those neural pathways that remain intact in the patients, rather than the lesioned areas of the parietal lobe and related structures. Consistent with this, primary visual areas may be structurally intact in many neglect patients, along with projections to the ventral pathway into the temporal lobe, which may subserve object identification. A recent study used fMRI [63•] to confirm that striate, extrastriate and fusiform regions could still be activated by neglected visual objects in the damaged right-hemisphere of a patient with a focal inferior parietal lesion. Event-related brain potential (ERP) methods have also been used recently to study processing for neglected stimuli. One study [64•] showed a dramatic difference in the neural response for the same visual stimulus when consciously detected versus not detected, while another study [65] showed some preserved ERP components for neglected stimuli, consistent with the fMRI data of [63•].
Can a neural perspective resolve traditional debates in the neglect literature?

A common debate in the neglect literature has been whether neglect is best explained in terms of an attentional deficit or a deficit in spatial representation [66]. From the perspective advocated here, this issue becomes moot. We suggest (see also [12]) that the deficit is caused by a loss of neurons representing particular locations in space (by means of particular combinations of spatial sensory input, and/or for particular motor plans). These neurons provide a highly selective representation of the current sensory input, even in the intact brain, corresponding to that which the person or animal is currently attending [17••]. Gradients such as the one depicted in Figure 1 might thus be considered not only to correspond to the number of neurons representing different positions in space, but also to the effective ‘attentional weight’ [67•] or ‘salience’ [17••] of those positions. (For brain areas where neurons have motor fields, any gradient also reflects the probability of directing a motor response to a particular location.)

Another controversial issue has been whether neglect has a single primary cause or whether it involves so many different components, which vary between patients, that neglect becomes ‘meaningless’ as a single entity [68]. Again, this issue becomes moot from the perspective advocated here. On the one hand, we suggest that the primary cause of all forms of neglect is selective loss of neurons coding particular locations in space, for particular functions. On the other hand, such a graded impairment can arise in many different brain areas following a diffuse lesion. The evidence from monkey physiology shows that even closely neighbouring areas of the parietal lobe are involved in subtly different functions, albeit according to similar computational principles (e.g. selecting sensory locations as targets for eye- versus hand-movements, as in LIP versus PRR; or integrating retinal information with neck-proprioception versus vestibular information, as in LIP versus area 7a). Most neglect patients have quite large lesions, which involve many brain areas, and so may show spatial biases in many domains; for instance, the lesioned areas may together affect not only perception but also eye- and hand-movements, and may be modulated by both proprioceptive and vestibular inputs. Because the exact lesion differs from patient to patient, so will the exact pattern of impairment. Indeed, it is now known that some patients with bilateral lesions can exhibit pathological gradients in one direction for performance in one class of tasks, yet in the opposite direction for other tasks (for example, see [69]); this presumably reflects different pathological gradients within different subsystems.

Future directions

In this review, we have tried to relate emerging data on the physiology of monkey parietal neurons to recent findings on neglect in human patients with parietal lesions. It
is quite a leap from single-cell data to patient performance, and explicit computational modelling [10] is required to bridge the gap. The gap may also be narrowed by functional imaging of human cell populations, and by further study of the behavioral effects of selective parietal lesions in monkeys. It remains controversial whether an exact equivalent of human neglect can be seen in animals [70,74], but it is clear that at least some aspects can be produced by appropriate lesions [72–74]; however, directly comparable tasks have rarely been used in animal and patient studies to date. The lesions in monkey studies are typically much smaller than the diffuse lesions caused by stroke in patients, so it may be unsurprising that human neglect is typically more severe and durable, comprising many components. Highly specific lesions in the monkey may advance our understanding of the function of particular parietal areas, and functional imaging may reveal homologous areas in humans. A recent study by CS Li, K Grieve and A Andersen (unpublished data) illustrates the potential of such studies. Transient unilateral de-activation of area LIP in monkeys (via muscimol) biased saccade choice in the ipsilesional area (e.g. PPR) will produce a different pattern of deficit compared to the contralateral area [72,75]. The authors report that cells in the medial superior temporal area respond primarily to the visible motion of the stimulus, whereas those in PPR respond before the joystick movements. Surprisingly, the neurons in LIP appear to respond to the internal motion of the object behind the occluder.

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34. Bisiach E:
world-referenced representations of visual space in parietal areas may similarly depend on behavioral training, although at least some of these responses have been found in naïve animals. This raises the issue of whether the other multimodal responses found in parietal areas can similarly depend on behavioral training, although at least some of these responses have been found in naïve animals.


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Rhodin J, Rods G, Piauila L, Farna A; L, Bosson D, Perenn M;


This paper reports that neglect patients show a striking and surprisingly long-lasting several hours to several days) improvement in neglect after wearing optical prisms that displace the image toward the right during reaching tasks.


41. Rubens A:
42. Karnath H:


37. Ladavas E, Di Pellegrino G, Farne A, Zeloni G:


Crossmodal extinction between a right visual event and a left tactile event in right-hemisphere patients is shown to depend on how near the visual event is to the unimpaired right hand. The authors relate this to recent single-cell findings of multimodal cells with spatially corresponding receptive fields in the ventral premotor cortex.


Karnath H: Neural encoding of space in egocentric coordinates? Evidence for and limitations of a hypothesis derived from data on patients with parietal lesions and neglect.


This study reports auditory responses in LIP neurons, but notes that these were mainly found in animals trained to make saccades towards auditory targets. The authors stress the issue of whether the other multimodal responses found in parietal areas may similarly depend on behavioral training, although at least some of these responses have been found in naïve animals.


This paper extends the principle of gain modulation in parietal neurons to reveal that area LIP shows gain-modulation by neck proprioceptive inputs but not by vestibular inputs for area 7a. This is of particular interest given the effects of such inputs on neglect patients.


This paper shows that contrary to common belief, neglect patients with parietal damage can suffer from motor deficits in addition to their visual deficits. This paper shows that contrary to common belief, neglect patients with parietal damage can suffer from motor deficits in addition to their visual deficits.

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This paper reports that neglect patients show a striking and surprisingly long-lasting several hours to several days) improvement in neglect after wearing optical prisms that displace the image toward the right during reaching tasks.


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