**Neglect**

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**INTRODUCTION**

Unilateral spatial neglect is a common and disabling syndrome following unilateral stroke, especially after infarction of the right middle cerebral artery. The patients typically exhibit a constellation of deficits, but their tendency to ignore information towards the contralesional side of space (i.e. usually the left side) is particularly striking, especially given that this can arise even in patients who have no primary sensory or motor deficit on the affected side. Recent progress in understanding such neglect has come from relating the disorder to the underlying neural systems that are damaged or preserved, and also from relating certain aspects of neglect to ‘attentional’ phenomena in normal people, who can analogously fail to consciously perceive or respond to stimuli if they do not attend to them.

**CLINICAL SIGNS**

Although the exact pattern of deficit varies from one patient to another, the following clinical signs may be present in prototypical cases. The patients behave as if half of their spatial world were lost (usually the left side, following right hemisphere damage). They may ignore people or objects on the affected side of space, eat food from only the other side of their plate, shave or make up only one side of their face, dress only one side of their body, miss letters, words or even a whole page on the affected side when reading, and overlook or forget contralateral turns in routes. Notably, many patients with neglect often do not realize that they are missing anything on the affected side (anosognosia). If the brain damage causes paralysis of contralateral limbs, the patients may even remain unaware of this if they also suffer from spatial neglect for that side of space.

In the clinic, neglect is not only observed in daily life, but also demonstrated with a variety of simple paper-and-pencil tests. For example, when patients are required to search for and mark all target shapes on a page (cancellation task), they may mark only a few of those on the ipsilesional side and ignore the presence of the others even when given unlimited time (Figure 1a). When asked to mark the midpoint of a horizontal line (bisection task), some patients may deviate towards its ipsilesional end, as if ignoring or compressing its contralesional extent (Figure 1b). When drawing from memory or copying a picture, they may omit most details from the contralesional side (Figure 1c), even for familiar objects with important unique features on either side that have a prescribed layout (e.g. the numbers on a clock face). Such spatial biases do not arise only in visually guided behavior. Even when blindfolded and exploring objects haptically, the patients may search only for those on the ipsilesional side. When asked to point straight ahead in darkness, or to move a laser-pointer to the subjective straight ahead position, neglect patients may deviate ipsilesionally. When searching for invisible targets in darkness, their eye movement path may show an analogous bias towards the ipsilesional side. Sound localization may also be affected, with inaccurate spatial coding on the contralesional side, and/or mislocations towards the ipsilesional side.

Importantly, such failures to detect, perceive, localize, explore or act towards the affected side
of space in neglect patients are typically not attributable to primary sensory or motor loss. Many patients who do suffer from such primary losses do not exhibit neglect; conversely, other patients can exhibit neglect despite having no paralysis, no visual field cut, and no other primary sensory loss. This is further illustrated by another common component of the syndrome. Perceptual ‘extinction’ arises in patients who can detect and report a unilateral stimulus presented alone on the affected side of space, but who miss the same stimulus if presented concurrently with another detected stimulus on the ipsilesional side. The ipsilesional stimulus ‘extinguishes’ awareness of a contralesional stimulus that would otherwise be detected. Such extinction can arise within vision, touch, audition, or even smell. It can also be elicited cross-modally, as when a visual stimulus on the ipsilesional side extinguishes awareness of a touch on the contralateral hand that would otherwise have been felt. It has been suggested that extinction may reflect a pathological bias in attention, which becomes most apparent when multiple concurrent stimuli compete to attract attention. Note that multiple stimulation tends to be the rule rather than the exception in daily life; and that competition between multiple stimuli may also be involved in many other tests for neglect (e.g. cancellation tasks).

Unlike sensory deficits, neglect is often reduced if the patient’s attention is directed towards the affected side, even in the presence of competing stimuli. Moreover, neglect is often graded (becoming increasingly severe for increasingly contralateral locations), without the step-function at anatomical midlines that characterizes lower-level sensory disorders (e.g. hemianopia). Finally, unlike sensory disorders, neglect can be influenced by changes in posture. The same retinal stimulation in the contralateral visual field may be detected or neglected, depending on the current direction of the eyes in their orbits, and/or of the head on the trunk. Remarkably, neglect patients may see objects in the left visual field better when just their trunk is twisted leftwards (so that the same retinal stimulation now falls further to the right of their body). Analogously, tactile detection may improve for the contralateral hand if this is placed further towards the ipsilesional side of the body.

In some patients neglect can arise in tasks of mental imagery or of memory, again demonstrating some independence from sensory deficits. The
patients may fail to describe elements that would be situated on the contralesional side for well-known settings or imagined scenes. Moreover, when asked to adopt a different perspective in their mind’s eye (e.g. the view from the other side of a familiar city square), the previously omitted details may now be reported, while previously reported details now shifted to the neglected side become missed instead. In some cases, neglect in mental imagery can apparently arise without ostensible neglect for externally present stimuli, and vice versa.

**ANATOMICAL CONSIDERATIONS**

Neglect can arise after focal damage in a number of different brain areas, all reciprocally interconnected in a distributed network that is considered critical for the elaboration of high-level multimodal spatial representations, for the control of spatial attention, and for the spatial preparation of intentional motor responses. Although some aspects of neglect can be seen in the immediate aftermath of left hemisphere damage, neglect is more common and much more enduring after right hemisphere damage. Prototypically, severe neglect is seen after major strokes in the territory of the right middle cerebral artery, causing damage to numerous brain areas and also to underlying white matter that affects remote connections. Such large lesions (Figure 2a) may cause numerous deficits, each of which can potentially exacerbate the others to produce florid neglect symptoms. Severe neglect can also follow more focal damage centered around the sylvian fissure, involving right inferior parietal cortex (supramarginal and angular gyri, Brodmann areas 39 and 40; Figure 2b). However, even such relatively focal lesions may affect many distinct parietal areas, and also disrupt fiber connections in the paraventricular white matter. It has been suggested that the superior temporal cortex may have a critical role in spatial neglect, although this remains controversial.

Other areas implicated include the prefrontal cortex (either close to the frontal eye field or in the more ventral inferior frontal gyrus), medial frontal cortex (supplementary motor and cingulate areas), thalamus (anteromedial nuclei and posterior pulvinar) and basal ganglia. It has been suggested that subcortical lesions might produce neglect by disconnection or functional disruption of distant parietal areas. Parietal lesions themselves can cause remote dysfunction in frontal and cingulate areas, and this has been found to correlate with neglect.
severity. Even though neglect is characterized by a dramatic loss of conscious perception and of goal-directed action towards the affected side of space, the typical brain lesions are quite remote from primary sensory and motor cortices. This further underlines the point that patients can exhibit severe neglect despite not being blind, deaf, insensitive or paralyzed. For instance, patients can show severe visual neglect despite primary (striate) and secondary (extrastriate) visual cortical areas in the occipital and temporal lobe remaining structurally intact.

Some aspects of neglect have been related to neurophysiological data on parietal, premotor or prefrontal cortex, as gleaned from single cell recordings in monkeys. Particularly relevant properties of certain intraparietal neurons include the following: convergence of spatial information from different modalities; modulation of sensory responses (e.g. to stimuli at a particular point on the retina) by current posture; some ipsilateral receptive fields in addition to a predominance of contralateral receptive fields; highly selective responses to currently attended or salient stimuli; and involvement in the initial translation of sensory information into particular spatial motor responses. Computational models have shown that all of these aspects of parietal neurons may help to explain seemingly disparate aspects of neglect (specifically, its often multimodal nature; its modulation by posture; its graded nature; its attentional aspects; and the combination of perceptual and motoric biases; see below). Nevertheless, it remains controversial whether brain lesions in monkeys can produce deficits closely mimicking human neglect. Extinction-like deficits, as well as biases in search and exploration, may follow unilateral destruction of structures associated with human neglect, or reversible chemical lesions within specific intraparietal subareas. However, these deficits seem relatively short-lived and less severe than the human syndrome, perhaps reflecting the much larger size of damage in stroke patients (see Figure 2) or some laterality of function that is unique to humans.

VARIETIES OF NEGLECT: DISSOCIATIONS AND SUBCOMPONENTS

The exact pattern of deficit can differ between patients with neglect, presumably in accord with differences in the lesion. Dissociations have been reported between different tests for neglect (e.g. cancellation versus bisection or extinction); between perceptual versus motor aspects of neglect; between perceptual versus imaginal neglect; and between neglect in different spatial domains (e.g. in near within-reach space, versus far in space; or within objects versus between objects). Bisection and cancellation tasks can indeed provide contrasting measures of neglect. Difficult cancellation tests may constitute the paper-and-pencil measure correlating best (to date) with clinical severity of neglect and with function in daily life, whereas bisection tests may show substantial influences from other deficits (e.g. coexisting visual field cuts). Extinction can dissociate from neglect in some cases, although as noted earlier, there is an analogous competitive aspect to many of the standard tests for neglect.

The issue of perceptual versus motor aspects arises because many tasks in which patients show neglect not only assess perception or attention for the affected side, but also require a spatial motor response to stimuli there (as in the cancellation task). In principle, pathological neglect behavior (e.g. failures to cancel contralesional targets) could either have a perceptual/attentional basis, or instead reflect some deficit in executing movements towards the affected side (perhaps even with the ipsilesional limb), or a combination of such deficits. Some studies have sought to disentangle such components with ingenious methods for opposing the spatial direction of sensory information versus the required motor response (e.g. by means of video systems, reversing mirrors, pulley systems, or spatially reversed mouse–cursor relations in computerized studies). Such work initially suggested a relatively clear-cut distinction between ‘perceptual’ neglect after posterior lesions and ‘motor’ neglect following more anterior prefrontal lesions. However, the apparent frontal involvement may primarily be due to the unusual requirement to move away from the direction indicated by target stimuli in many of these experimental situations. Frontal lesions are known to produce general impairments in such incompatible tasks. Further work has separated perceptual and motor requirements by changing the start position and hence the direction of movement, while still reaching directly towards the same visual target. In this situation, patients with inferior-parietal (but not frontal) lesions were not only impaired at perceiving contralesional visual stimuli, but over and above this were slower to initiate movement in the contralesional direction. Such a combined perceptual-motor deficit would accord with recent views of parietal areas as sensorimotor interfaces.

Nevertheless, with appropriate tests, purely sensory and purely motor aspects of the neglect
syndrome can still be identified. For instance, tests of perceptual extinction do not require spatially directed motor responses, yet can reveal clear deficits. On the other hand, purely motor neglect may be apparent in patients who fail spontaneously to use the contralesional hand, even when this is not paretic and can be moved skillfully when prompted. ‘Motor extinction’ can be observed for tasks requiring unseen bimanual action (e.g. raising both hands, or making repeated movements with both, either in or out of phase), with deficient contralesional movements during bimanual but not unimanual actions. Note that this may reflect competitive aspects analogous to those for perceptual extinction, but possibly arising within different neural structures. Motor extinction or underuse of a nonparetic contralesional hand has been observed after unilateral lesions to frontal cortex, supplementary motor area, parietal cortex, basal ganglia or thalamus.

Pioneering lesion work in monkeys showed that unilateral damage to different areas of premotor cortex could produce phenomena resembling neglect or extinction for different spatial domains: within space close to the head following damage to area 6, sparing behavior for more distant stimuli; and vice versa following damage to area 8 instead. Human studies have reported that neglect is sometimes more severe for stimuli in near space than in far space (in bisection tasks), or conversely worse in far space than near space for other patients across a variety of tasks. This dissociation between near versus far neglect suggest that it may affect different types of spatial representation independently, rather than arising only within some single ‘master map’ of space. A similar conclusion follows from demonstrations that neglect can arise either ‘within’ visual objects, or ‘between’ visual objects. Such a dissociation may actually arise within the same patient, but affect opposite sides of space. For instance, one patient with bilateral brain damage showed neglect of the left side of individual objects (e.g. missing the initial letters in words), but neglect of whole objects on the right side of space (e.g. missing whole words on that side of a page). Importantly, this pattern was not just specific to reading, but was found across a variety of different tasks and stimuli.

The various dissociations described above indicate that neglect is a multicomponent disorder, consistent with the anatomy reviewed earlier. In addition to the different types and different domains of neglect, some further components exist that might not produce neglect in isolation, but exacerbate symptoms when combined with the other deficits. One example of this is the bias towards ‘local’ rather than ‘global’ aspects of a visual scene, associated with damage to the right temporoparietal junction. Some patients with focal damage here may exhibit local biases without neglect, whereas patients with equivalent damage in the left hemisphere contrastingly show a global bias. Because the large right hemisphere lesions in neglect will often include the temporoparietal junction, such patients are likely to suffer from local biases in addition to their perceptual, attentional and motor biases towards the ipsilesional side of space. This may greatly exacerbate their deficit: because their attention tends to lock onto local rather than global aspects of complex displays, as in cancelation tasks, they may consequently neglect a much wider area of contralesional space.

Another deficit that might apply to all locations following right hemisphere damage, yet still exacerbate spatial neglect when combined with biases towards the ipsilesional side, concerns an impairment in tonic arousal. The noradrenergic alerting system, originating in the brainstem and projecting to frontal cortex, shows greater right lateralization cortically in humans. Extensive right hemisphere damage may cause many neglect patients to be chronically underaroused, with particular difficulties in maintaining self-arousal endogenously over lengthy periods. This might in turn aggravate their neglect. In apparent support of this, phasically alerting neglect patients with warning stimuli can temporarily reduce their abnormal ipsilesional bias.

A further deficit that might apply to both sides of space, yet exacerbate contralesional neglect, concerns a general reduction in perceptual capacity following right hemisphere damage. As described earlier, perceptual extinction is a failure to detect contralesional stimuli specifically in the presence of multiple competing stimuli. This may reflect reduced processing capacity in addition to the ipsilesional bias. Neglect patients may thus exhibit a degree of simultanagnosia (a difficulty in perceiving multiple stimuli simultaneously) in addition to their lateral bias. In support of this, patients with extinction following right parietal damage may show an impaired capacity for reporting more than one target even in vertical arrays briefly presented on the ipsilesional (i.e. supposedly intact) side. Moreover, if instructed to report any contralesional item first in brief bilateral displays, they may show paradoxical extinction of items on the ipsilesional side. Abnormally prolonged attentional dwell-time has also been observed in people with right hemisphere neglect, even when...
all stimuli are presented at central fixation and in rapid succession. Finally, it has recently been proposed that, in addition to the lateral biases in attention, neglect may involve deficits in spatial working memory (or more specifically, in maintaining representations of locations already examined during search, across saccades). Spatial working memory tasks in the normal brain activate a predominantly right-lateralized network that is strikingly similar to the areas of typical lesions in neglect patients. If neglect patients fail to form a stable representation of previously searched locations across multiple saccades, then their search might return recursively to those locations most favored by their lateral attentional bias, without the patient realizing this, exaggerating the bias still further.

The possible involvement of local biases, deficits in alertness, general reductions in perceptual capacity, and impairments in spatial working memory, all as exacerbating factors, may provide some explanation for the strong association of neglect with right hemisphere damage. Further accounts for this asymmetry include proposals that in humans the right hemisphere is specialized for spatial cognition (perhaps as the flipside of left hemisphere specialization for language); or that some right hemisphere areas normally represent locations within both sides of space, while left hemisphere homologues primarily represent contralateral locations (so that a right hemisphere lesion would be more devastating in terms of the spatial locations whose representations are lost). None of these various explanations need be regarded as mutually exclusive. Analogous hemispheric specialization may not exist in other animals.

RESIDUAL UNCONSCIOUS PROCESSING

Despite escaping the patient’s awareness, neglected or extinguished stimuli can nevertheless undergo residual unconscious processing. Such findings again underscore the fact that neglect or extinction can arise despite sparing of some basic sensory and motor processes. Much of the evidence for residual processing has stemmed from analogies between the fate of neglected and extinguished stimuli in the patients, and the fate of unattended information in neurologically healthy people. While normal people can show little or no explicit awareness for stimuli that are not selectively attended, some implicit processing of these can nevertheless be revealed by indirect measures such as priming. As a first approximation, the residual unconscious processing found in patients with neglect or extinction corresponds well with that thought to take place ‘preattentively’ in the normal brain. In people with or without brain damage, this processing can determine which information will attract attention and reach awareness, and which will escape awareness instead.

Residual unconscious processing for contrale- sional stimuli can manifest in different ways. Extinguished or neglected stimuli can influence the patients’ responses to consciously detected ipsilesional stimuli (e.g. affecting the speed of such responses), revealing that the presence, color, shape, or even the semantics of a contraleisonal stimulus can sometimes be extracted despite unawareness of it. In some cases, particular relationships between concurrent contraleional and ipsilesional stimuli can influence the degree of extinction or neglect. For instance, extinction is reduced when bilateral stimuli can be linked into a single object through image-segmentation principles, connecting the stimulated spatial locations to yield a common perceptual event. Such effects imply that image-segmentation processes may operate normally on contraleional visual inputs, prior to the level at which extinction arises. Similar conclusions follow from the various manifestations of so-called ‘object-based’ neglect (i.e. neglect affecting segmented visual objects, rather than unparsed spatial regions of the retinal image). Extinction or neglect can also be influenced by the particular identity of the stimuli used, again suggesting that some residual processing occurs prior to stages where contraleional inputs become extinguished or instead detected. For instance, stimuli of particular emotional significance (e.g. angry faces) may undergo less extinction, in keeping with the fact that such stimuli can readily capture attention even in healthy people.

The anatomical basis of such residual processing has been studied using functional imaging and electrophysiological measures of neural activity in the patients’ brains, in response to extinguished or neglected stimuli. To date, functional magnetic resonance imaging (fMRI) studies have confirmed that, although escaping awareness, such stimuli can still activate anatomically intact areas in striate and extrastriate visual cortex, including category-specific areas in temporal cortex (e.g. the fusiform face area for extinguished faces), plus more remote limbic regions (e.g. amygdala and orbitofrontal cortex for extinguished fearful faces). This supports prior proposals that residual unconscious processing in neglect and extinction may reflect preserved afferents into primary visual cortex (V1), and
thence along the ventral visual system into temporal lobe (typically spared by prototypical parietal lesions). On the other hand, even early visual responses to extinguished stimuli may not be entirely normal. Visual evoked potentials have shown that components around 100 ms after stimulus onset can be attenuated for extinguished compared with perceived contralesional stimuli. Functional MRI results have also shown greater visual activation associated with conscious perception versus extinction, together with a greater covariation of striate visual cortex with parietal and frontal areas in the intact hemisphere during conscious perception. These results may accord with proposals that such parietal and frontal areas control spatial attention in the normal brain, by modulating activity in early sensory areas.

**REHABILITATION**

Neglect is disabling and carries a poor prognosis for independent living after a stroke. Spontaneous recovery occurs in some cases, but is often partial and poorly understood, though it may correlate with improved cerebral blood flow in spared areas of both the damaged and intact hemispheres. There have been some encouraging demonstrations of plasticity in the adult brain from other research areas, but rehabilitation of neglect remains a major challenge despite considerable effort and some recent progress. The evidence described above of considerable residual processing, and of factors influencing the degree of deficit, suggests a potential platform to build on.

One approach has been to train patients to direct search or attention towards the contralesional side. Neglect is improved by this in the short term, but there is little generalization to daily life. Another approach has been to modulate arousal, but again the challenge is to generalize this successfully to self-arousal during daily life. Use of the contralesional limb (in nonparetic patients) on the contralesional side of space can reduce neglect. However, many patients may not use this limb spontaneously in daily life, favoring the ipsilesional limb instead. Ipsilesional arm restraint may be considered, since this can ameliorate mild contralesional paresis, and may also reduce neglect. Patching of the whole ipsilesional eye has produced inconsistent results. More recently, patching of the ipsilesional visual hemifield in both eyes has produced some encouraging results. The logic behind this intervention is to correct the asymmetrical spatial bias by inducing a reverse bias at the input stage.

Caloric stimulation of the vestibular system (by iced water in the left ear, or warm water in the right ear, to induce vestibular signals similar to those from actually turning left) has been shown to ameliorate perceptual and exploratory neglect, plus associated deficits such as imaginal neglect, or anosognosia for hemiplegia. Again, the asymmetric stimulation may oppose the pathological bias to the ipsilesional side caused by the lesion. Vestibular signals also contribute to coding of external space relative to the body, being integrated with other sensory signals within parietal cortex. Similar principles may explain the analogous beneficial effects of vibratory neck-muscle stimulation (inducing proprioceptive signals similar to a leftwards turn of the trunk relative to the head). Both vestibular and proprioceptive manipulations produce consistent reductions in neglect, but their effects dissipate when the stimulation ends. The same applies for optokinetic stimulation.

Longer-term benefits have been reported following prism adaptation. The patients wear prisms shifting visual information towards the ipsilesional side, so that their reaches to visual targets initially err in the ipsilesional direction. Following adaptation, the hand is directed further to the contralesional side for a given retinal position. Just 10 min of this procedure has been claimed to improve neglect over several days, although the exact basis for this remains unknown. Prism adaptation in the reverse direction has no analogous impact.

Finally, drugs such as dopamine agonists have been used to increase arousal and enhance contralesional exploration, but with only mixed success to date.

Research into the processes that are impaired or spared in spatial neglect, and into the underlying neural mechanisms, has uncovered many important new findings in recent years. It is hoped that these findings will contribute to improved rehabilitation procedures in the future.

**Further Reading**


Mesulam MM (1999) Spatial attention and neglect: parietal, frontal andcingulate contributions to the


### Nervous System

*See* Autonomic Nervous System

### Neural Activity

*See* Decoding Neural Population Activity; Decoding Single Neuron Activity; Diffusion Models and Neural Activity; Rate versus Temporal Coding Models; Single Neuron Recording

### Neural Basis of Memory: Systems Level

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*Introductory article*

A systems level approach to the neuroscientific investigation of memory looks at the ways in which different areas of the brain interact and communicate to achieve this function.

**Introduction**

What did you eat for dinner two days ago? What is the name of the mouse in the story *Dumbo*? How many turns do you need to make to get from your front door to your bedroom? How are you able to understand the visual symbols in this sentence? Memory – our remarkable capacity to learn and retain information – offers the answers to these questions. Across a lifetime, we encounter, store and retrieve an enormous amount of information. We have knowledge about ourselves, about world facts, and even about things that we do not usually associate with our memory, such as habits and skills. How does