Chapter 14

NEGLECT I: CLINICAL AND ANATOMICAL ISSUES

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Neglect is a failure to report, respond, or orient to stimuli that are presented contralateral to a brain lesion when this failure is not due to elementary sensory or motor disorders.[1] Many subtypes of neglect have been described. A major distinction is between neglect of perceptual input, termed *sensory neglect* or *inattention*, and neglect affecting response outputs, termed *motor* or *intentional neglect*. Some further distinctions are outlined below.

Sensory neglect involves a selective deficit in awareness, which may apply to all stimuli on the affected side of space (*spatial neglect*) or be confined to stimuli impinging on the patient's body (*personal neglect*). It may even effect awareness of one side of internal mental images (*representational neglect*). The perceptual modalities affected by neglect may also vary: subtypes of sensory neglect exist for the visual, auditory, and tactile modalities. The deficit in awareness is accompanied by an abnormal attentional bias. Attention is usually biased toward the ipsilesional side (*contralateral neglect*) but in rare cases may be contralesional (*ipsilateral neglect*). Once attention is engaged on an ipsilesional stimulus, subjects may have difficulty disengaging their attention to move it to the contralesional side. If the lack of awareness and attentional bias are present only when there is a competing stimulus at a more ipsilateral location, the disorder is termed *extinction*. Many patients with neglect recover and become able to detect isolated contralesional stimuli, but they continue to manifest extinction.

Motor or *intentional neglect* involves a response failure that cannot be explained by weakness, sensory loss, or unawareness. There may be a failure to move a limb (*limb akinesia*), or the limb can be moved but only after a long delay and strong encouragement (*hypokinesia*). Patients with intentional neglect who can move may make movements of decreased amplitude (*hypometria*). They may also have an inability to maintain posture or movements (*impersistence*). Patients with motor neglect who can move their contralesional limb may fail to move this limb (or have a delay) when they are also required to move their ipsilateral limb (*motor extinction*). Limb akinesia, hypokinesia, hypometria, and motor impersistence can affect some or all parts of the body, including limbs, eyes, or head. The elements of intentional neglect discussed above can be *directional* (toward the contralesional hemispace) or *spatial* (within the contralesional hemispace). Patients with motor neglect may have intentional biases such that there is a propensity to move toward ipsilesional space. There may also be impaired ability to disengage from motor activities (*motor perseveration*).

TESTING FOR NEGLECT

In this brief review we cannot address all aspects of testing; therefore, for a complete discussion and list of references, the reader is referred to Heilman and coworkers.[1]

Inattention or Sensory Neglect

To test for inattention, the patient is presented with unilateral stimuli on either the ipsilesional or contralesional side in random order. If a patient fails to detect more stimuli on the contralesional side than the ipsilesional side, it would suggest that the patient is suffering from inattention. However, if the patient totally fails to detect any stimuli on the contralesional side, it is often difficult to tell whether or not the patient has inattention or a sensory loss. The auditory modality is the least

difficult in which to dissociate inattention and sensory loss, because sounds made on one side of the head project to both ears, and each ear projects to both the ipsilateral and the contralateral hemisphere. Therefore, if a patient is unaware of noises made on one side of his or her head, this unawareness cannot be explained by a sensory defect and suggests that the patient has inattention. In the visual modality, because unawareness may be hemispatial (body-centered) rather than retinotopic, having the patient deviate the eyes toward ipsilateral hemispace may allow him or her to become aware of stimuli projected to the contralesional portion of the retina. In regard to tactile neglect, one may have to use caloric stimulation of the ear to see if the patient can detect stimuli during such stimulation. One may also use psychophysiologic techniques such as evoked potentials or galvanic skin responses to see whether patients who are unaware of stimuli demonstrate autonomic signs of stimulus detection.[2]

Extinction

To test for extinction, one may randomly intermix the unilateral stimuli described above with bilateral simultaneous stimuli. The stimuli can be given in any modality (e.g., visual, auditory, tactile). When a subject has hemianopia, extinction may occur even within the ipsilesional visual field.

Intentional or Motor Neglect

Patients who have severe limb akinesia may appear to have a hemiparesis. An arm may flaccidly hang off the bed or wheelchair. Sometimes, with strong encouragement from the examiner, it can be demonstrated that such a patient has normal strength. Some patients, however, will still not move, and one may have to rely on brain imaging to learn whether the corticospinal tract is involved. In patients with motor neglect, the lesion should not involve the corticospinal system. Magnetic stimulation may also be helpful in demonstrating that the corticospinal tract is normal.[3] As discussed, patients with hypokinesia are reluctant to move the affected arm or only move it after delay. However, once they have moved, their strength may be normal. To test for hypometria, the arm is passively moved or the patient is shown a line and asked to make a movement of the same length. Patients with hypometria will undershoot the target. To test for impersistence, the patient is asked to sustain a posture. Patients with impersistence cannot maintain postures. As mentioned, patients can be tested for forms of motor neglect by using the limbs, eyes, or even head. They can be tested in ipsilateral versus contralateral hemispace and in an ipsilesional versus contralesional direction. For example, patients with right hemisphere lesions might have trouble spontaneously looking leftward (directional akinesia) and even have their eyes deviate to the right (gaze palsy). Other patients might be able to look leftward but make small (hypometric) saccades (directional hypometria). Patients with right hemisphere lesions who are able to look to the left might be unable to sustain gaze in this direction (directional impersistence).

Further Assessments of Spatial Neglect

A more complete assessment of neglect involves additional tests, which require the patient to perform simple tasks that go beyond the reporting of a stimulus or the movement of eyes or limbs toward a target. These tasks can nevertheless be performed at bedside without special equipment. The four most commonly used tests are described here.

In the *line bisection task,* the patient is given a long line and asked to indicate its midpoint (Fig. 14-1). Although horizontal lines are most commonly used (intersection of the coronal and axial planes), neglect has been reported in the vertical dimension (both up neglect and down neglect) and in the radial dimension (near neglect and far neglect). In general, the longer the line, the greater the percentage of error. Placing the line in contralesional hemispace can also increase the severity of the error, as can putting cues on the ipsilesional side.

In performing the *cancellation task,* a sheet of paper that contains targets is placed before the patient and the patient is asked to mark out (cancel) all the targets (Fig. 14-2). Increasing the number of targets can increase the sensitivity of this test. Increasing the difficulty with which one discriminates targets from distractors can also increase the sensitivity of this task.

In testing *drawing,* the patient should be asked to draw spontaneously as well as to copy figures (Figs. 14-3 and 14-4). Copying asymmetrical nonsense figures may be more difficult than copying well-known symmetrical figures.

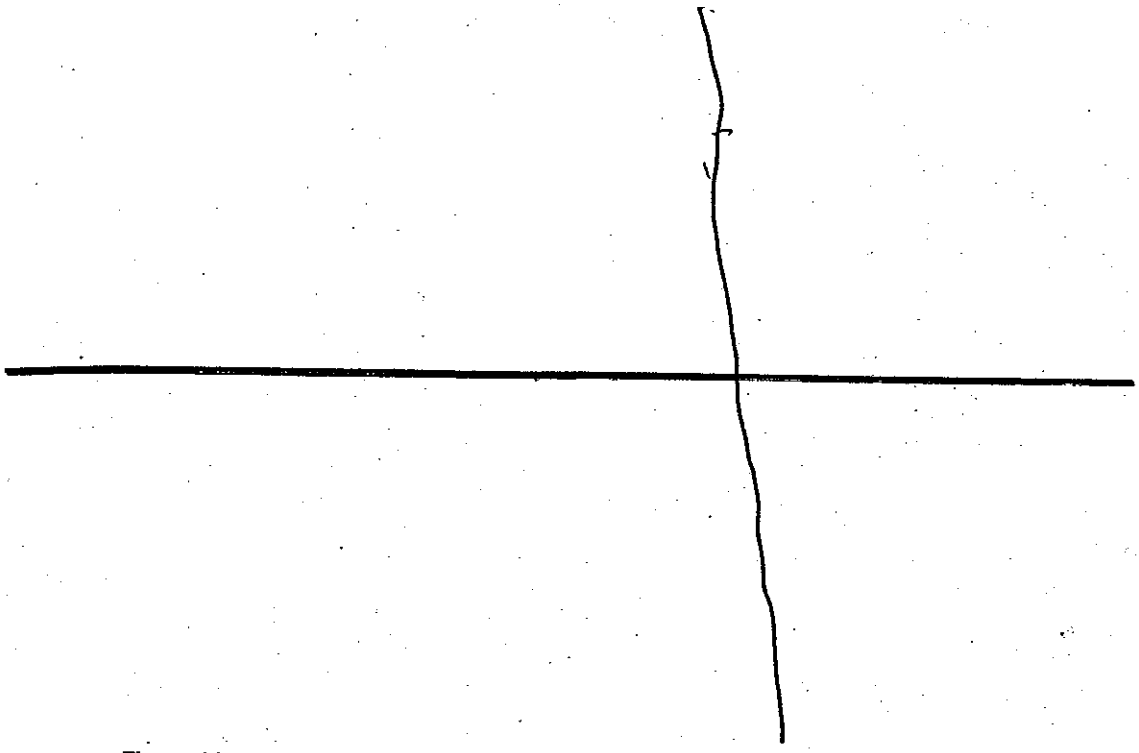

Figure 14-1
Line bisection task performed by a patient with a right hemisphere infarction and left hemispatial neglect. (Courtesy of Dr. Todd E. Feinberg.)

In testing for representational neglect, one should ask a subject to *image a familar scene* and then report what he or she sees. A patient with representational neglect will recall more objects from the ipsilesional than the contralesional part of the image.

Further testing can elucidate the underlying systems of spatial representation, attention, and intention that are affected. For example, it may be difficult to dissociate sensory attentional disorders from motor intentional disorders. In general, the best means of doing this is by performing cross-response tasks where the subject responds in one side of space to a stimulus presented on the opposite side. Video cameras, strings and pulleys, or mirrors can be used in the performance of a cross-response task.

To dissociate intentional from representational deficits one can use a fixed-aperture technique. To do this, an opaque sheet with a fixed window is placed over a sheet with targets so that only one target can be seen at a time, thereby reducing attentional demands. In one-half the trials, the subject moves the top sheet; in the other trials, the subject moves the target sheet. A failure to explore one portion of the target sheet in both conditions suggests a representational defect, and a failure to explore opposite sides of the target sheet in direct and indirect conditions suggests a motor intentional deficit.[4]

To dissociate spatial neglect of one side of the environment from neglect of one side of the person, one can ask the patient to lie down on his or her side. This decouples the environmental left and right from the body's left and right. If the patient has a right hemispheric lesion, is lying on the right side, and now fails to detect targets toward the ceiling, the neglect is body-centered. However, if the patient continues to neglect targets on the left side of the room, the neglect is environmentally centered (see Chap. 15).[5,6]

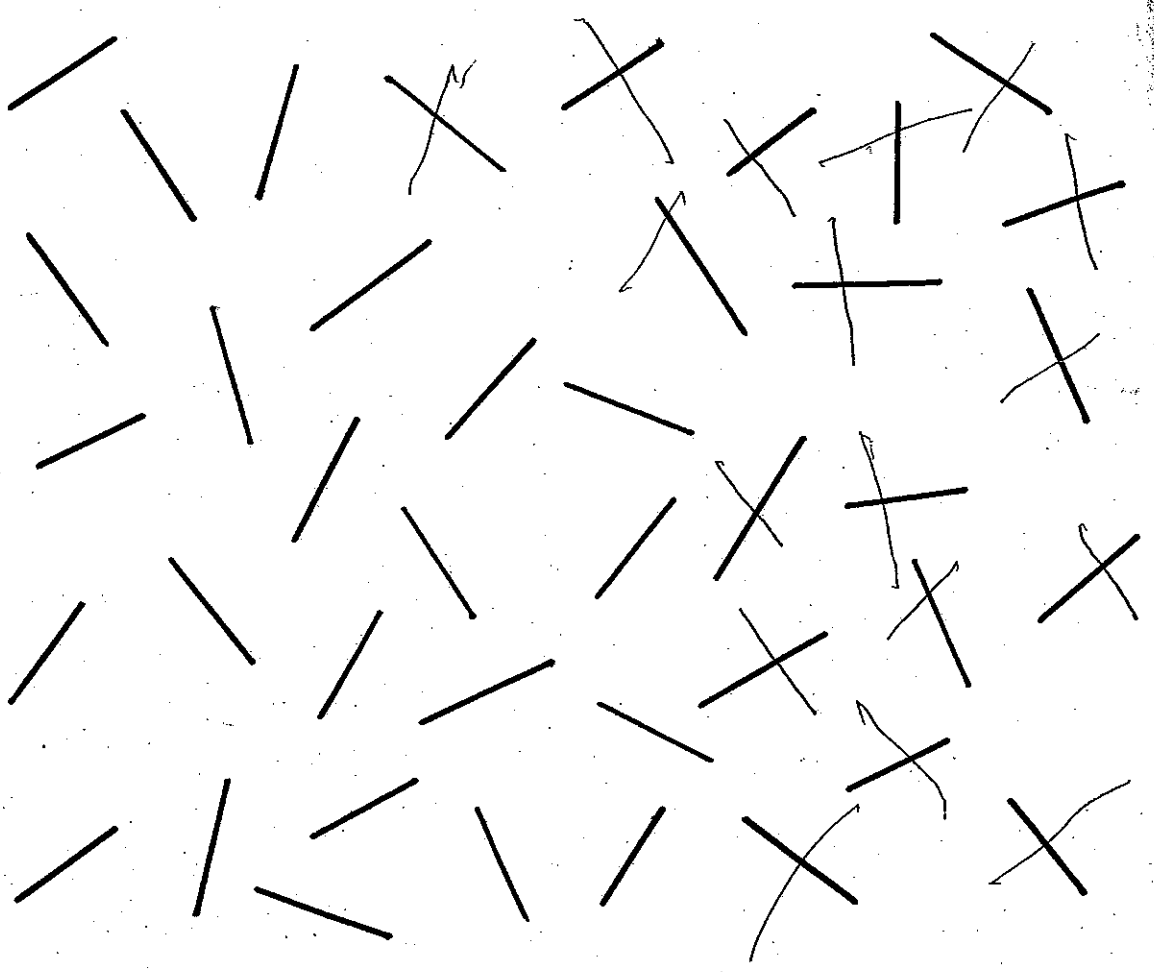

Figure 14-2
Cancellation task of same patient as in Fig. 14-1. (Courtesy of Dr. Todd E. Feinberg.)

PATHOPHYSIOLOGY

As the foregoing review suggests, neglect is not a homogeneous syndrome. The neglect syndrome has not only many manifestations but also many levels of explanation. For a more complete discussion, see Heilman and coworkers.[1] The heterogeneity of neglect is apparent on an anatomic level as well.

In humans, neglect is most often associated with lesions of the inferior parietal lobe (IPL), which includes Brodmann's areas 40 and 39. However, neglect has also been reported from dorsolateral frontal lesions, medial frontal lesions that include the cingulate gyrus, thalamic-mesencephalic lesions, basal ganglia, and white matter lesions. Because there is a limit on the anatomic, physiologic, and behavioral research that can be done in humans, much of what we know about the pathophysiology of the neglect syndrome comes from research on Old World monkeys. Monkeys also have an IPL; however, their IPL is Brodmann's area 7. In humans, the intraparietal sulcus separates the superior parietal area, Brodmann's area 7, from the inferior parietal lobule, Brodmann's areas 40 and 39. Some have thought that the IPL of monkeys is a homologue of the IPL in humans. Others, however, have thought that both banks of the superior temporal sulcus (STS)

Figure 14-3
Copies of flower demonstrate left hemispatial neglect. A *and* B *provide models on left, patient production on right. (Parts* A *and* B *courtesy of Dr. Todd E. Feinberg; part* C *courtesy of Dr. Robert Rafal:)*

are the homologue of the inferior parietal lobule in humans. We[7] have demonstrated that spatial neglect in monkeys is primarily associated with ablation of the STS region and not the IPL. These results suggest that, in regard to neglect, it is the monkeys' STS that is the homologue of the temporoparietal junction of humans.

Anatomic studies of the STS of monkeys have provided some information as to why this area produces neglect when ablated. The STS is composed of

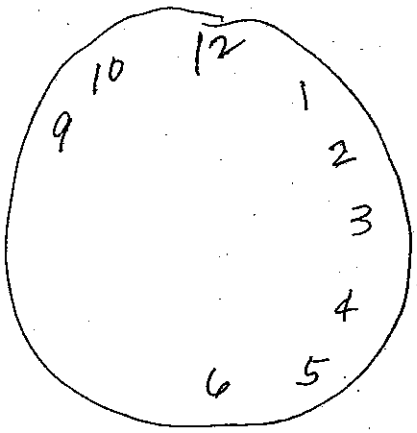

Figure 14-4
Clock drawn by a patient with left hemispatial neglect. (Courtesy of Dr. Robert Rafal.)

multiple subareas and is one of the sites of multimodal sensory convergence. Visual, auditory, and somatosensory association cortices all project to portions of the STS. In addition, the STS has reciprocal connections to other multimodal convergence areas, such as monkeys' IPL (Brodmann's area 7). Because ablation of area 7 in monkeys, a multimodal convergence area, was not associated with spatial neglect, we do not believe that ablation of a sensory convergence area alone can account for the unawareness that is seen with neglect syndrome. Therefore, we[7] have proposed a role for monkeys' STS in awareness.

Mishkin and colleagues[8] have suggested that the visual system, when presented with stimuli, performs dual parallel processes. Whereas the ventral division is important for determining the type of stimulus ("What is it?"), the dorsal system codes the spatial location of the stimulus ("Where is it?"). In monkeys the "where" system is in part mediated by the posterior portion of Brodmann's area 7 or the monkey's IPL, and the "what" system is in part being mediated by the inferior visual association cortex found in the ventral temporal lobe. It has long been recognized that bilateral ventral temporal lesions in humans and monkeys induce visual object agnosia, a deficit in the "what" system. In contrast, biparietal lesions in monkeys induce deficits of visual spatial localization but not object discrimination. We[7] have posited that these "where" and "what" systems integrate in the banks of monkeys' STS or in the inferior parietal lobule of humans. According to our research,[7] lesions of monkeys' STS and humans' temporoparietal junction induce unawareness or neglect not only because this is the area that receives polymodal sensory input but also because it is a convergence site of these perceptual-cognitive systems that deal with both the "what" and "where" aspects of environmental awareness. Both anatomic and electrophysiologic data substantiate the hypothesis that monkeys' STS is an area of convergence of these two systems (see Ref. 7). We[7] have also proposed that similar areas important for spatial localization and object identification may also exist in the auditory and tactile systems and that these modalities may also converge in the STS.

Although there is anatomic and physiologic evidence that there is convergence from the Brodmann's area 7 "where" system and the ventral temporal lobes' "what" system, this cannot account for the observation that ablation of the STS induces unawareness. The STS receives input not only from these "what" and "where" systems but also from the cingulate gyrus and the dorsolateral frontal lobe. In earlier studies, we have demonstrated that lesions in both these areas are also able to induce neglect. The dorsolateral prefrontal region is important in the mediation of goal-directed behavior and may provide the STS with information that is not directly stimulus-dependent or related to immediate drives and biological needs but rather directed at long-term goals. The cingulate gyrus is part of the limbic system and may provide the STS with information about biological needs and drives. Because monkeys' STS or humans' temporoparietal junction are supplied with "what" and "where" conative and motivational information, it may be able to make attentional computations.

Monkeys' STS has reciprocal connections with the ventral temporal "what" region and the parietal "where" region. Therefore, after the STS region performs an attentional computation, it may reciprocally influence the neurons in the ventral temporal lobe and Brodmann's area 7 regions.

Electrical stimulation of the STS is capable of activating the midbrain reticular formation more than stimulation of surrounding posterior regions. Therefore, the superior temporal sulcus appears to be important in the cortical control of arousal, and the

supermodal synthesis discussed above may also lead to neuronal activation in the ventral temporal "what" and dorsal area 7 "where" systems. Therefore, if the STS in monkeys or the temporoparietal junction in humans is dysfunctional, it not only fails to make attentional computations but also cannot arouse or activate directly or indirectly those areas that determine both location of objects and their identity. This failure of activation may prevent the monkey or human from being aware that there is a stimulus in the space opposite the lesion.

Bisiach and Luzzati[9] have demonstrated that subjects with neglect may have an inability to image those objects in scenes that would fall into contralesional hemispace, and Heilman and coworkers[10] have demonstrated a hemispatial antegrade memory deficit associated with neglect. Therefore, lesions of the IPL in humans may be associated with the inability to activate old memories or form new memories of objects that are located in contralesional hemispace. In monkeys, the STS has strong reciprocal connections with the hippocampus and the hippocampus has been posited to be important in retroactivation of sensory association areas.[11] Thus, a partial (spatial) failure of retroactivation may account for the imagery-memory deficits.

In monkeys and humans, spatial neglect can often be distinguished from deafferentation by observing exploratory behaviors. Deafferented subjects fully explore their environment. However, patients with neglect often fail to fully explore the neglected portion of space. Theoretically, if we ablated both area 7 (the "where" system) and the ventral temporal cortex (the "what" system in monkeys), we suspect that these animals would continue to be able to explore their contralateral hemispace. The failure to explore contralesional space that we observed in animals with STS lesions and humans with IPL lesions may be related to the reciprocal connections that the STS has with the frontal arcuate gyrus region. The frontal arcuate gyrus region or frontal eye field is important for the initiation of purposeful saccades to important visual targets. The periarcuate region is important for the initiation of voluntary arm movements to important visual stimuli. It has been demonstrated that lesions of this region, as well as the basal ganglia and thalamus, which are all part of an intentional functional network, may induce motor intentional neglect. However, exploratory defects may be also seen with posterior STS lesions in monkeys or IPL lesions in humans. In monkeys, the frontal arcuate area and periarcuate regions have strong connections with both area 7 and the STS. Whereas the STS may be critical in activating both periarcuate and arcuate regions, area 7 may be important for providing these frontal regions with the spatial maps needed to make purposeful exploratory limb and eye movements. In addition to the dorsolateral frontal lobe, the motor intentional network also includes the medial frontal lobes, the cingulate gyrus, the basal ganglia, and the thalamic cortical loops as well as input from the STS or IPL. Whereas the attentional and intentional networks are highly interactive, they do not entirely overlap. Therefore one may, as discussed, see neglect fractionate into motor intentional and sensory attentional components.

In humans, neglect can be associated with both right and left hemispheric lesions, but neglect is in general more severe and frequent with right than left hemispheric lesions. These asymmetries appear to be related to asymmetrical representations of space and the body. For example, whereas the left hemisphere primarily attends to the right side, the right hemisphere attends to both sides.[12,13] Similarly, while the left hemisphere prepares for right-side action, the right prepares for both.[12]

TREATMENT AND MANAGEMENT OF NEGLECT

Neglect is a sign and symptom of cerebral disease and thus it is critical to treat the underlying disease and to prevent further insults. Because patients with neglect may be unaware of stimuli, they should avoid both driving and working with tools or machines that might cause injury to themselves or others.

Many patients with neglect have anosognosia; during the acute stages when patients have anosognosia, rehabilitation is often difficult. In most patients, anosognosia is transient; but because patients with neglect remain inattentive to their left side and in general are poorly motivated, training is laborious and in many cases unrewarding. There are, however, some rehabilitation strategies that might be helpful. Diller

and Weinberg[14] were able to train patients with neglect to look to their neglected side; however, it was not clear that these top-down attentional-exploratory treatments generalized to other situations. In contrast to this top-down treatment, Butter et al.[15] used a bottom-up treatment, where they used flashing lights to attract attention to the left side and demonstrated that dynamic stimuli presented on the contralesional (left) side reduced neglect. Even patients with hemianopia improved, suggesting that these dynamic stimuli influenced brainstem structures. Robertson and North[16] demonstrated that having patients move their contralesional hand in contralesional hemispace can also reduce the severity of hemispatial neglect.

Rubens[17] induced asymmetrical vestibular activation in patients with left-sided neglect by injecting cold water into the left ear and noting that unilateral spatial neglect abated. Vestibular stimulation can also help sensory inattention.[18] Optokinetic nystagmus and cervical vibration can also reduce neglect.[19,20] Unfortunately, these procedures produce only temporary relief. Rossi et al.[21] used prisms to shift images from the neglected side toward the normal side. Although the treated group performed better than the control group in tasks such as line bisection and cancelation, activities of daily living did not improve. Rossetti et al.[22] had subjects with neglect repeatedly point straight ahead while wearing the prisms. Thereafter, on tests of neglect, these treated patients showed a reduction of their ipsilesional bias, which lasted for 2 h after the prisms had been removed, but it is uncertain how much longer this effect can last.

Some investigators have found that an ipsilesional patching procedure reduces neglect,[23] but others have found that it can make neglect more severe.[24] Thus, when using patching, each eye should be tested before deciding which eye should be patched. Neglect in rats was treated with apomorphine, a dopamine agonist; this treatment significantly reduced neglect in these animals.[25] Fleet et al.[26] treated two neglect patients with bromocriptine, a dopamine agonist. Both showed dramatic improvements. Subsequently, other investigators have also shown that dopamine agonist therapy may be helpful in the treatment of both sensory and motor neglect.[27] Barrett et al.[28] and Grujic et al.[29] found, however, that in some patients, dopamine agonist therapy increased rather than decreased the severity of neglect. Barrett et al.'s patient had striatal injury and suggested that the paradoxical effect seen in their patient may be related to involvement of the basal ganglia. In patients with striatal injury, dopamine agonists may be unable to activate the striatum on the injured side but instead activate the striatum on the uninjured side, thereby increasing the ipsilesional orientation bias.

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