

EXPERIMENTAL STUDY

A Rodent Model for Investigating the Neurobiology of Contralateral Neglect

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Background: Contralateral neglect is a common and disabling sequela of right hemisphere strokes. Neglect involves attentional and cognitive deficits, including distortions of contralateral spatial and personal awareness. There are no established successful therapies for neglect, and treatment is often complicated by anosognosia. The disturbances associated with neglect are debilitating to patients and their families, and presence of neglect is a strong predictor of poor prognosis for recovery.

Objective: The present report reviews findings from 20 years of research using a rat model of neglect. In the rat, 2 cortical areas that are linked by corticocortical connections have been identified as having a major role in neglect, and these correspond to frontal and parietal fields in primates. These 2 cortical areas also have convergent projections to the dorsocentral striatum, which has been implicated as a crucial subcortical component of the cortical-striatal-thalamic circuitry involved in directed attention and neglect. We discuss the role of the dorsocentral striatum in neglect and recovery and present evidence that induced axonal sprouting may promote functional recovery following cortical lesions that produce neglect.

Conclusions: The rodent model of neglect captures some of the essential behavioral and anatomic features of neglect in humans. This model has helped reveal the pathophysiology of neglect, has suggested a crucial role of the striatum in recovery from neglect, and is being used to investigate potential therapeutic approaches.

Key Words: contralateral neglect, rodent model, recovery

(*Cog Behav Neurol* 2004;17:191–194)

Neglect is a complex, severely disabling human neuropsychological disorder characterized by a failure to attend or be aware of novel or meaningful stimuli presented to the side contralateral to a brain lesion, when these deficits can

not be attributed to a primary sensory or motor deficit. Some manifestations of the neglect syndrome can be found in approximately 40% of all patients with cortical strokes and is most frequently associated with right hemisphere damage. Most (80%–90%) neglect cases result from destruction of 1 of 3 cortical regions: the parietotemporal junction, dorsolateral prefrontal cortex, or the cingulate cortex.^{1,2}

In addition to a lack of responsiveness to contralesional stimuli (limb, hemispacial, and directional akinesia), the neglect syndrome includes dramatic attentional and cognitive spatial deficits. Lateralized deficits include lack of a cognitive representation of the contralesional hemispace, contralesional memory defects, and disorders of personal awareness (allegnesia, asomatognosia, anosognosia).³ Milder forms of inattention can be observed with bilateral simultaneous stimulation (extinction). Nonlateralized deficits often involve attention and memory.⁴

The cognitive-representational, attentional, arousal, and motor-intentional disturbances that comprise the neglect syndrome are often debilitating to the patients' capacity for independent daily living and are a burden to their families.⁵ The presence of neglect in stroke patients is the most significant predictor of a poor prognosis for recovery.^{6–8}

Spontaneous recovery, when it occurs, takes weeks to months but is often incomplete. Many neglect patients continue to fail to interact with contralesional stimuli for months or years postlesion.^{8–10} The anosognosia or anosodiaphoria associated with neglect interferes with early stroke treatment and successful physical and occupational rehabilitation.⁵ Although there are several behavioral treatments, these rarely generalize outside of the therapeutic context or across tasks within the same therapeutic context.^{5,11} Drug therapies, such as dopamine agonists, are rarely initiated, in part because there has been no rational framework for understanding the mechanisms that might lead to a therapeutic effect. Typically, drugs have been given only to patients with chronic neglect and stable behavioral baselines because of the concern that drug effects may interfere with ongoing recovery.^{12–14} Unfortunately, in some patients with cortical strokes that also involve the basal ganglia, dopaminergic treatment increases the severity of neglect.¹⁵

A RAT MODEL OF NEGLECT

Cortical Substrates and Behavioral Characteristics

The poor prognosis and absence of proven therapies for neglect have led to the development of animal models.^{16,17}

Received for publication April 21, 2004; revised August 18, 2004; accepted September 30, 2004.

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This research was supported by NIMH grant MH60399 and the Veterans Affairs Research Service.

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Although nonhuman primates have been used to study neglect, we have developed a rat model to examine the basic mechanisms of neglect and the potential for recovery of function. A rodent model offers several practical advantages over many of the primate models, and we have found striking behavioral, pharmacological, and anatomic similarities in the systems related to neglect in rodents and primates.¹⁸

In the rat, unilateral lesions of the prefrontal medial agranular cortex (AGm, the homologue of Brodmann area 8 in primates), posterior parietal cortex (PPC, which corresponds to area 7 in primates), or the dorsocentral striatum (DCS, a subcortical convergence zone of AGm and PPC) produce manifestations of neglect in rodents that are similar to those found in human patients. Unilateral AGm lesions result in severe multimodal neglect of visual, tactile, and auditory stimuli presented in the hemisphere contralateral to the lesion, in the absence of primary motor or sensory deficits. Rats also exhibit significant allesthesia by demonstrating ipsilesional orienting in response to stimulation presented in the contralateral hemisphere. Further, as in primates, lesions of AGm or PPC result in severe egocentric or allocentric spatial deficits, respectively.¹⁸⁻²³ Rats also exhibit dissociations among the major manifestations of the neglect syndrome. For example, extinction deficits are found after unilateral lesions of AGm or PPC but not DCS.

Areas AGm and PPC are interconnected, and each has extensive multimodal cortical connections. Area AGm has extensive cortical connections with visual, somatic sensory, posterior parietal, and orbital areas.²⁴ The pattern of cortical connections of AGm, together with its known subcortical connections and known functional properties, suggests that all of AGm constitutes a multimodal frontal eye field involved in head orientation responses, with caudal AGm having more involvement in visual processing and rostral AGm directing motor output to the brainstem and spinal cord. The cortical connections of area PPC involve AGm, orbital, somatic sensory, visual association, auditory, and retrosplenial cortices.²⁵ Electrophysiological evidence indicates that the rat PPC has multimodal functions and is one component of a larger neural system concerned with spatial relationships and directed orientation.^{26,27}

The rodent model allows us to test some hypotheses that cannot be tested in primates. For example, it has been hypothesized that prefrontal and parietal areas function together as an integrated circuit for directed attention.^{1,28,29} Corticocortical axons linking prefrontal and parietal areas travel in the white matter in primates, making them inaccessible to experimental manipulation. However, in rodents these axons travel in the deep gray matter.³⁰ This allowed us to perform selective disconnection experiments, which demonstrated that disconnection alone produced severe neglect, thus supporting the hypothesis that AGm and PPC function together as a cortical network for spatial attention and spatial learning.³¹ These findings support the notion that fundamental aspects of frontoparietal circuitry are organized similarly in rodents and primates. Studies using the rodent model indicate that neglect and extinction are experimentally dissociable. Unlike cortical lesions, unilateral DCS lesions do not produce extinction or allesthesia.³² Because these symptoms of neglect appear to be

pharmacologically dissociable, it may be possible to target prospective behavioral or pharmacological treatments to deal with specific individual deficits.³³ These considerations are clinically relevant because extinction deficits often persist in patients who have recovered spontaneously from unilateral spatial neglect.⁸

Recovery from Neglect and the Dorsocentral Striatum

Studies of recovery from neglect in the rodent model indicate that recovery occurs in 3 conditions: limited spontaneous recovery, which may occur over the course of weeks to months^{20,23,34}; acute recovery induced by dopamine (DA) agonists^{12-14,20,34,35}; and dramatic, permanent recovery after 48 hours of light deprivation (LD) beginning 4 hours postlesion.^{19,36,37}

Recent findings indicate that the DCS, the main projection zone of AGm within the dorsal striatum, is a crucial component of the network for neglect and recovery in all 3 of the above contexts. Vargo and Marshall^{38,39} found that dynamic changes in NMDA and kainate receptors in the ipsilesional dorsolateral striatum (which includes DCS) were correlated with AGm-induced neglect and spontaneous recovery. We have shown that spontaneous recovery is prevented by axon-sparing unilateral DCS lesions,²¹ that the integrity of DCS is necessary for the therapeutic effects of systemic administration of apomorphine in rats with unilateral lesion of AGm,²¹ and that apomorphine infusion into DCS produces dramatic dose-dependent recovery from multimodal neglect in rats with unilateral lesions of AGm.³⁵ Further, an intact DCS is also necessary for the therapeutic effects of light deprivation.³⁷

The DCS receives inputs from several cortical and thalamic areas that are themselves linked by corticocortical and thalamocortical connections.⁴⁰ Most notable are those from AGm, PPC, and thalamic nuclei that project to them. Other cortical areas providing input to DCS include visual association area Oc2M, lateral agranular cortex, and orbital cortex. All of these cortical areas have reciprocal connections with AGm and PPC. The projection from AGm to DCS is widespread and dense throughout DCS, whereas projections from other cortical areas are mainly situated around the periphery of DCS.⁴¹ Thalamic afferents to DCS were found to be prominent from LD, LP, MD, VL, and the intralaminar nuclei.⁴⁰ Collectively, these nuclei constitute the sources of thalamic input to cortical areas AGm and PPC. In addition, they provide input to the other cortical areas mentioned above.

Collectively, the above behavioral and anatomic findings support the view that DCS is an integral component of a network of cortical, striatal, and thalamic regions involved in spatially directed attention and/or action-intention, is the site of multimodal integration of spatial stimuli, and is the critical substrate for recovery from neglect produced by cortical lesions.

Induced Plasticity in DCS and Recovery from Neglect

The evidence reviewed above suggests that the anatomic basis for recovery from neglect in rats involves dynamic

compensatory changes in DCS. Given the crucial role of DCS in recovery, we wondered if induced plasticity in DCS would produce recovery. Sprouting of corticostriatal projections and recovery of motor function are induced by treatment with an antibody (IN-1) to myelin-associated neurite growth inhibitors,^{42,43} administered following unilateral lesions of rat sensorimotor cortex.

We directly examined whether IN-1 would induce plasticity and recovery in rats with neglect. When the left AGm is lesioned to produce neglect, significant denervation of left DCS occurs, and this may allow sprouting to occur. Our preliminary findings indicate that IN-1 treatment results in behavioral recovery that is associated with sprouting of axons from contralesional AGm and ipsilesional PPC within DCS.⁴⁴ Subjects received lesions of left AGm, and injection of hybridoma cells producing the IN-1 antibody or a control antibody. All subjects were tested for neglect for 4–7 weeks, injected with an axonal tracer in the right (contralesional) AGm, and assessed for axonal sprouting by measuring axon density in DCS. In unoperated controls, axon density contralateral to the injection was less than half the density ipsilateral to the injection (contralateral/ipsilateral ratios < 0.5). Control antibody cases exhibited similar ratios. However, in IN-1 experimental cases that had recovered from severe neglect, the contralateral density was increased by over 100%, resulting in densities equivalent to those ipsilaterally and ratios of ~1.0. Our preliminary findings also indicate that sprouting induced by IN-1 is localized to the denervated territory in DCS and occurs in axons originating in ipsilesional PPC as well as contralesional AGm. Further, axons from cortical regions that do not normally project to DCS are not induced to sprout into the denervated territory. These results extend the potential therapeutic use of induced plasticity to the treatment of cognitive spatial disorders.

CLINICAL SIGNIFICANCE

Neglect is a severe and prevalent clinical disorder, and at present there are no generally accepted therapies for treatment. We have developed a rodent model to study neglect and behavioral recovery, and these rats exhibit many of the same fundamental types of deficits found in human patients with neglect. Our findings indicate that the DCS is part of the cortico-striatal-thalamic circuitry mediating directed attention and action-intention. The DCS plays a pivotal role in neglect induced by cortical lesions and may be the crucial site for the mechanisms leading to recovery. Our anatomic findings have shown that the DCS receives converging inputs from the AGm and the PPC and suggest that DCS constitutes an associative region of striatum. This has laid the foundation for our most dramatic recent finding, that extensive plasticity can be induced in the DCS afferents from the contralesional AGm and the ipsilesional PPC using IN-1 and that recovery from neglect is correlated with this plasticity. This extends the potential use of factors that induce axonal sprouting into the treatment of cognitive deficits resulting from brain damage and raises the exciting possibility that induced plasticity might eventually be used to treat neglect in humans.

ACKNOWLEDGMENTS

This research was supported by NIMH grant MH60399 and the Veterans Affairs Research Service. We appreciate the technical assistance of Maggie Stoll and Steve Wagner. Plasticity experiments were made possible through the generosity and encouragement of Drs. Gwendolyn Kartje and Martin Schwab.

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