

plasmly in members of both families, including the 2 mothers. Single mtDNA deletions, occurring in a mother and her son, were previously reported [13], but they differed in the 2 patients by size and localization, making direct transmission of the mutation unlikely.

Since in all our patients deletions were present in different tissues, the origin of heteroplasmy must be traced back to a somatic mutation occurring at a stage earlier than organogenesis. In mouse [14] and *Xenopus laevis* [15] embryos, mtDNA content increases tremendously during organogenesis. As a result, enormous amplification could occur even of a single deleted mtDNA, which because of its smaller size, replicates faster than wild-type mtDNA. Furthermore, the rapid cell proliferation will promote mitotic segregation, "loss" of mutant mtDNAs in the extrafetal structures, and negative selection of respiratory-deficient cells. These can be important clues to understanding the variability in the quantitative distribution of the heteroplasmic mtDNAs in different clinical phenotypes.

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Dissociated Neglect Behavior Following Sequential Strokes in the Right Hemisphere

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A 42-year-old woman suffered two focal right hemisphere strokes, sequentially damaging different components of a proposed cerebral network for the spatial distribution of attention. Her first stroke was centered in the right frontal lobe and resulted in left hemispatial neglect but only for tasks that emphasize exploratory-motor components of directed attention. A second stroke occurred 20 days later in the parietal lobe and led to the emergence of perceptual-sensory aspects of neglect. This case strongly supports the existence of a distributed anatomic-functional network subserving directed attention.

Daffner KR, Ahern GL, Weintraub S, Mesulam M-M. Dissociated neglect behavior following sequential strokes in the right hemisphere. *Ann Neurol* 1990;28:97-101

Unilateral neglect is a common and dramatic sequel of right hemisphere injury. It reflects a fundamental disruption in the distribution of directed attention and manifests itself clinically as a failure to recognize, respond to, and explore stimuli located within the left hemispace [1-3]. While the occurrence of neglect was originally believed to reflect parietal lobe disease [4, 5], subsequent reports have clearly shown that lesions elsewhere in the right hemisphere may result in a similar clinical picture [6-12].

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Several authors have accounted for the various behavioral components of neglect and the multiplicity of underlying lesion sites on the basis of a distributed cerebral network [1, 2, 13, 14]. According to one of these theories, directed spatial attention is subserved by a distributed cerebral network with three cortical components [1, 2]. The relationship between the anatomical site of the lesion within this network and the clinical features of the resultant neglect behavior is incompletely understood. We recently had the opportunity to investigate a patient who had had two sequential right hemisphere strokes involving separate anatomical components of the attention network. Each stroke resulted in different behavioral deficits that were in keeping with the proposed organization of this network.

Case Report

A 42-year-old right-handed woman with a history of severe hypertension and thrombotic thrombocytopenic purpura (in remission) developed acute neurological deficits. She had full visual fields, normal extraocular movements, a left facial palsy, and mild left upper-extremity weakness. The left plantar response was extensor. Pin prick and light touch sensations were intact. There were mild and inconsistent deficits in position sense, graphesthesia, and stereognosis in the left upper extremity.

The patient was alert, oriented, and appropriately motivated. Judgment, insight, and abstract reasoning were intact. Digit span was 6 forward and 5 in reverse. Tasks requiring sustained vigilance, divided attention, memory, language, and analogical reasoning were done well.

The major abnormalities on mental state testing were noted in tasks of directed attention and complex perceptual processing. She was given two types of spatial attention tasks, emphasizing either perceptual-sensory or exploratory-motor processes. The perceptual components were assessed by tests for sensory extinction. The patient was presented with multiple trials of sensory stimulation in each of the three major modalities. Six stimuli were right sided, 6 were left sided, and 6 were bilateral and simultaneous, presented randomly. She was errorless in the tactile modality, and exhibited left-sided extinction in only 1 of the 6 trials of bilateral auditory stimulation. There was no visual extinction, but she exhibited allesthesia, by mislocating the stimulus to the right in 1 of 6 unilateral left-sided visual stimulation trials. In summary, after the first stroke, the degree of sensory neglect for the left hemispace was minimal.

The exploratory-motor components were tested by two instruments. On a random letter cancellation task [15, 16], using her unaffected and preferred right hand, she marked only stimuli located within the right margin of the test sheet (Fig 1). The second test to assess the exploratory-motor aspects of neglect was based on a manual spatial exploration task [16]. The patient was blindfolded and asked to search by palpation for a small plastic pin fixed to a cork-covered board. There were 9 trials conducted in each hemispace, using each hand. The patient took significantly longer to locate a target in the left hemispace than in the right. Using her unaffected right hand, she required a mean of 18 seconds

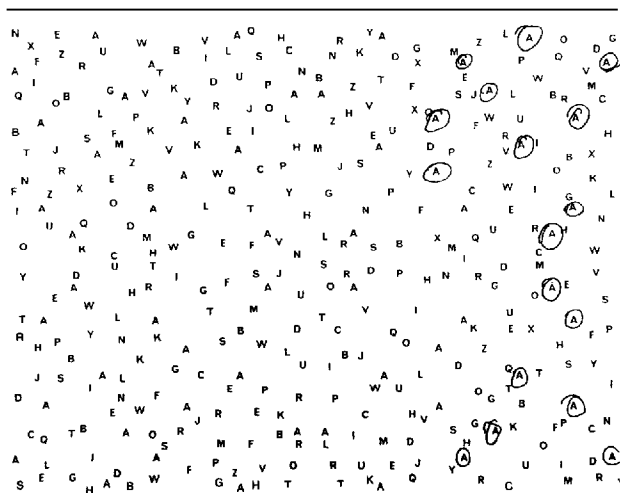


Fig 1. Performance on a visual exploratory task, the random letter cancellation test, demonstrating dramatic neglect of the left side of the page.

in the left hemispace versus 10 seconds in the right hemispace ($p < 0.05$, one-tailed Wilcoxon signed ranks test). Even when using her modestly paretic left upper extremity, she consistently crossed over the midline to begin her search on the right side of the board, and required 47 seconds to locate a target on the left side versus 26 seconds on the right ($p < 0.05$). The severity of exploratory-motor neglect revealed by these two tests contrasted sharply with the very mild tendency for sensory extinction.

Other tests of complex perceptual function revealed salient deficits. For example, she performed in the severely impaired range (7/30) on the Judgment of Line Orientation Test [17], the Block Designs subtest of the Wechsler Adult Intelligence Scale-Revised (raw score, 17; scaled score, 6) [18], the Facial Recognition Test (35/54) [19], and the Mental Rotation subtest of the Luria-Nebraska Neuropsychological Battery (6/10) [20].

A cranial computed tomographic scan revealed an infarction in the right frontal lobe within the distribution of the middle cerebral artery, largely involving the middle frontal gyrus and including the frontal eye fields (Fig 2). Extensive vascular, cardiac, and hematological tests failed to reveal a specific cause for the stroke.

Examination 1 week later demonstrated mild improvement of motor strength. Repetitive trials of sensory stimulation revealed no extinction in any modality. On the random letter cancellation task, she exhibited some improvement but still missed about half (12/30) of the targets on the left side of the test sheet. At this stage of partial recovery, the dissociation between the exploratory-motor and perceptual-sensory components of neglect became even more obvious.

Two weeks after discharge, she came to the emergency room complaining of a right frontal headache and an episode of visual clouding of her right eye. Her elementary neurological examination revealed a left facial palsy and weakness of the left upper extremity. There was no hemianopsia. Pin, temperature, light touch, and vibratory sensations were intact. She exhibited marked astereognosis and agraphesthesia in the left hand.

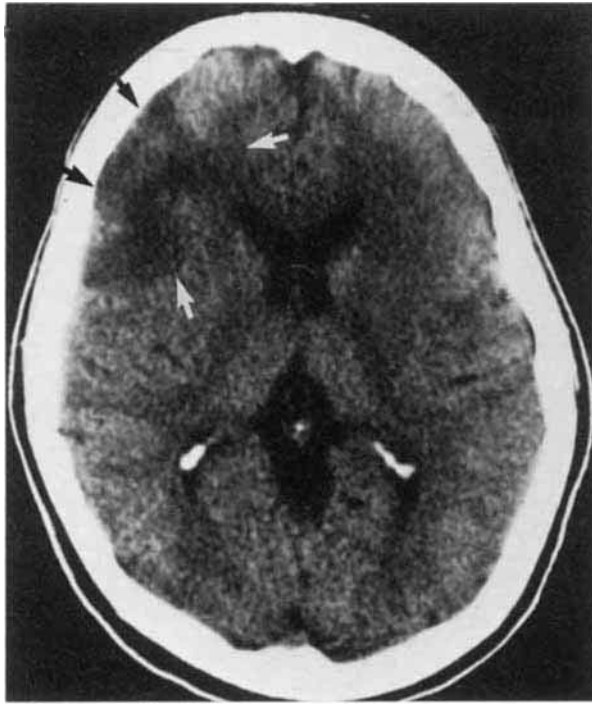


Fig 2. Axial computed tomographic scan after the first stroke, demonstrating an infarction in the right frontal lobe (demarcated by arrows), largely involving the middle frontal gyrus and including the frontal eye fields. The right side of the head is on the left side of the scan.

Repeat administration of the sensory stimulation trials revealed prominent neglect and alliesthesia. In the visual and auditory modalities, she made no mistakes when presented unilateral stimuli; however, she exhibited left-sided extinction on bilateral simultaneous stimulation in 4 of 6 trials in the visual modality and in all 6 trials in the auditory modality. She made no errors when given unilateral right-sided and bilateral simultaneous tactile stimuli but exhibited alliesthesia by mislocating to the right side 3 of 6 tactile stimuli presented on the left side. Thus, extinction was particularly prominent in the two modalities, auditory and visual, which are most closely associated with the extrapersonal space. In comparison with the first stroke that yielded left-sided extinction in only 8% of the bilateral simultaneous stimulation trials in the visual and auditory modalities, the second stroke increased the frequency of these errors to 83%.

Repeat administration of the two exploratory-motor tasks demonstrated the reemergence of severe deficits. For example, on the random letter cancellation test, she missed all 30 stimuli on the left. Performance on the Judgment of Line Orientation Test (8/30) and Block Designs (raw score, 6; scaled score, 4) remained severely impaired.

A computed tomographic scan revealed a new right posterior parietal stroke with a hemorrhagic component. The infarct included the inferior parietal lobule and was confirmed by a follow-up magnetic resonance imaging scan (Fig 3).

Discussion

Many theories have been proposed to account for neglect. Some have emphasized its sensory manifesta-

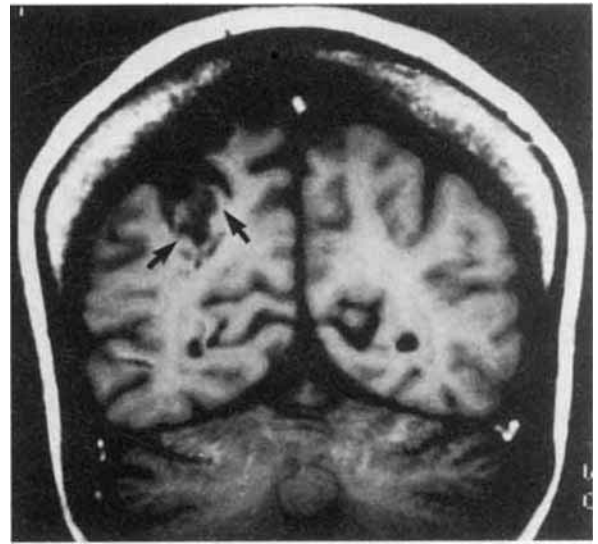


Fig 3. Coronal magnetic resonance imaging MRI (T1-weighted image) revealing the second stroke in the right posterior parietal lobe, including the inferior parietal lobule. The right side of the head is on the left side of the scan. Arrows demarcate the infarct.

tions. For example, Denny-Brown [21] argued that parietal lobe damage leads to deficits in sensory integration (amorphosynthesis), resulting in neglect of the contralateral hemispace. Bender [22] invoked a process of perceptual rivalry through which sensory input to a lesioned hemisphere is degraded and "extinguished" when competing with simultaneous input to the intact hemisphere. Others have argued that neglect reflects distortion of the internal mental representation of extrapersonal space [23, 24]. Heilman and colleagues [13, 14, 25] have described a neuroanatomical system involving cortical-limbic-thalamic-reticular components that lead to preparatory activation or arousal toward meaningful stimuli in the contralateral hemispace.

A review of neglect syndromes in monkeys and humans suggested that several cerebral regions provide an integrated network for the mediation of directed attention [1, 2]. The three cortical components of this network are the posterior parietal lobe, frontal eye fields, and the cingulate gyrus. In addition to delineating these anatomical regions, three major behavioral components of attention were also identified as follows: (1) A sensory component provides an internal representation of extrapersonal space. Dysfunction of this component yields extinction, alliesthesia, and perceptual misrepresentations. (2) A motor component coordinates scanning and exploratory behavior. Dysfunction of this component is manifested as impaired scanning, searching, and orienting. (3) A limbic component regulates the spatial distribution of motivational valence. Dysfunction of this component can lead to an emotional devaluation of events occurring in the opposite hemispace.

It was hypothesized that specific parts of the anatomical network provided the underlying substrate for the different behavioral aspects of directed attention. The parietal component was linked with the perceptual-sensory aspects, the frontal component with the exploratory-motor aspects, and the cingulate component with the motivational aspects. Although studies with experimental animals have tended to support these relationships, pertinent evidence has been difficult to gather in humans. The special nature of our patient's clinical course allowed us to address this issue. Sequential and relatively selective damage to two components of the attention network created the appropriate circumstances for a dissociation of her neglect behavior.

The first stroke sustained by our patient yielded an infarction in the frontal lobe including the frontal eye fields. At that time, the patient demonstrated severe left-sided neglect on two tasks that emphasize the exploratory-motor components of directed attention but not on tasks that emphasize its perceptual-sensory components. The patient's second stroke involved the right posterior parietal lobe, including the inferior parietal lobule. At that time, the patient developed marked sensory-perceptual aspects of neglect in the form of multimodal extinction. Even this patient, however, demonstrates the existence of a strong physiological linkage among the various components of this network, since the exploratory-motor deficits reemerged with increased intensity after her second stroke in the parietal lobe.

Consideration of the different components of neglect is important when evaluating patients. Our patient's performance after the first stroke (severe exploratory neglect with minimal sensory extinction) demonstrates that sensory extinction cannot be viewed simply as a subtle form of neglect as some have claimed. Tests that emphasize one component of directed attention may be normal in the face of marked abnormalities in tasks that emphasize other components [3, 9, 16, 26, 27]. The absence of primary visual and auditory sensory loss or oculomotor deficits illustrates that neglect does not result from a combination of elementary sensory-motor deficits but reflects a disorder of complex attention.

Even after the first stroke, the neuropsychological deficits exhibited by our patient were not limited to hemispatial neglect. She did poorly on visual-perceptual and spatial rotational tasks. The existence of such additional deficits is in keeping with the network approach to the localization of complex behavior. This approach suggests that cortical areas subserving a complicated behavior such as attention are also components of intersecting networks subserving other complex neuropsychological functions. The unique circumstances of this patient's clinical history further support the conclusion that directed spatial attention is

subserved by a cerebral network containing several anatomically distributed but neurally interconnected components, each specializing in a different aspect of this behavior.

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Positron Emission Tomography in Shy-Drager Syndrome

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We studied the nigrostriatal dopaminergic pathway in 3 patients with Shy-Drager syndrome, by using positron emission tomography and [¹⁸F]6-fluoro-1-dopa to determine whether their parkinsonism correlated with impaired functional integrity of the presynaptic nigrostriatal pathway. One patient had short duration of disease, mild parkinsonism, and a normal positron emission tomographic scan, suggesting pathological changes functionally distal to the nigrostriatal pathway. Two patients with longer duration of disease had more severe parkinsonism and reduced [¹⁸F]6-fluoro-1-dopa uptake, suggesting impaired nigrostriatal dopaminergic function with progression of Shy-Drager syndrome.

Bhatt MH, Snow BJ, Martin WRW, Cooper S,
Calne DB. Positron emission tomography
in Shy-Drager syndrome.
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Shy-Drager Syndrome (SDS) is characterized by autonomic failure with any combination of parkinsonism, pyramidal dysfunction, cerebellar ataxia, and lower

motor neuron deficits [1]. Parkinsonism is an important manifestation of SDS [1-3]. With the availability of [¹⁸F]6-fluoro-1-dopa (6-FD) and positron emission tomography (PET), the functional integrity of the nigrostriatal pathway can be studied in vivo. Striatal 6-FD uptake has been shown to be depressed in presynaptic nigrostriatal dopaminergic disorders such as idiopathic parkinsonism [4-7]. The purpose of this study was to evaluate presynaptic nigrostriatal function in parkinsonism of SDS by using 6-FD PET.

Patients and Methods

Patient 1

A 52-year-old man had a 4-year history of limb rigidity, impotence, incontinence of urine, chronic constipation, and multiple syncopal attacks. On examination he had postural hypotension (220/130 supine, 70/50 standing). Rigidity, bradykinesia, hypomimia, and hand tremor were present. His voice was monotonous and hypophonic. He had brisk tendon reflexes and bilateral extensor plantar responses. He scored 35 on the Columbia scale, which measures overall motor deficits in parkinsonian patients. Head computed tomographic (CT) scan was normal. Levodopa/carbidopa (250/25 mg four times daily) and bromocriptine (20 mg/day) did not improve his parkinsonism.

Patient 2

A 52-year-old woman had a 4-year history of unclear speech and bradykinesia. She suffered multiple syncopal attacks. Two years after the onset of her disease she developed incontinence of urine and feces. On examination there was a postural drop in blood pressure (130/90 supine, 80/60 standing). She had rigidity, marked bradykinesia, hypomimia, and a fine postural hand tremor. Her Columbia score was 53. She had emotional lability, an active jaw jerk, brisk tendon reflexes, and bilateral extensor plantar responses. Head CT scan and magnetic resonance imaging were normal. Levodopa/carbidopa (250/25 mg four times daily) and bromocriptine (15 mg/day) did not help her.

Patient 3

A 72-year-old woman had a 6-month history of unsteady gait, multiple syncopal attacks, and incontinence of urine and feces. On examination, she had a postural drop in blood pressure (180/110 supine, 55/30 standing) with hypomimia, cogwheel rigidity, bradykinesia, and bilateral spasticity. Her Columbia score was 28. She could not walk tandem. Rectal examination revealed a gaping, patulous anus. Head CT scan was normal. Levodopa/carbidopa (250/25 mg three times daily) was not helpful.

There were 14 normal control subjects (age range, 22-80 yr; mean, 45.5 yr). They were asymptomatic, neurological examination was normal, and none was taking medication. The data collection scheme for both groups (control subjects and patients) was identical, and a standard protocol for PET scanning approved by the University of British Columbia Ethics Committee was followed.

Methods

PET studies were performed with the University of British Columbia/TRIUMF positron emission transaxial tomog-

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