Somatosensory Gating and Recovery From Stroke Involving the Thalamus

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Background and Purpose—In the undamaged brain, sensory input to the cortex is intricately controlled via sensory gating mechanisms. Given the role of corticothalamic pathways in this control, it was hypothesized that in patients recovering from thalamic stroke there would be evidence of disrupted sensory gating and that efficient control of cortical sensory inputs would emerge during recovery.

Methods—Four patients were tested serially after stroke from 1 to 24 weeks after injury. Perceptual thresholds, somatosensory evoked potential amplitudes, and functional MRI activations under specific somatosensory stimulation conditions were measured.

Results—All patients demonstrated comparable results, revealing disrupted threshold detection to vibrotactile stimuli in the presence of a concurrent competing, contralateral input. In contrast, threshold detection was comparable between the affected and unaffected sides when there were no competing stimuli. This compromised capacity to inhibit competing sensory inputs was paralleled by a reduction in the measured activation of cortical representation in the stroke-affected hemisphere (functional MRI and somatosensory evoked potential) during bilateral stimulation. After recovery, perceptual detection improvements during bilateral stimulation were paralleled by enhancements of primary somatosensory cortical activation in the stroke-affected hemisphere.

Conclusions—These results provide insight into potential mechanisms that contribute to sensory gating and suggest that the ability to control sensory input through effective gating mechanisms, in addition to primary somatosensory representation, may be important for poststroke sensory recovery. (Stroke. 2002;33:2642-2651.)

Key Words: recovery of function ■ sense ■ somatosensory evoked potentials ■ thalamus

It has become increasingly clear that the integrity of the somatosensory system is important to motor recovery after stroke.1 Traditionally, clinical determination of sensory status involves testing perceptual thresholds.2,3 Although such approaches reveal evidence of primary sensory loss, they typically do not reveal the capacity of the central nervous system to modulate afferent information. To achieve normal interaction with our environment, relevant sensory information must be identified and extracted from a vast array of concurrent inputs. Inability to do this will influence sensorimotor or perceptual ability, even if the primary sensory representation is intact.

In the somatosensory system, such extraction of sensory information is achieved through highly selective mechanisms involving both inhibition of ascending afferent paths carrying task-irrelevant information, a phenomenon often called sensory gating, and facilitation of task-relevant information.4–6 Although the precise mechanisms remain unclear, interactions between the prefrontal cortex, thalamus, and primary sensory cortex appear to play an important role in this process.7 The present study explores the specific influence that stroke-induced lesions involving the thalamus have on the capacity to extract and gate sensory information.

There are reports in the literature describing sensory deficits after thalamic lesions.8,9 However, relatively few investigate alterations in cortical representation after thalamic stroke in humans. Using PET, Remy et al10 reported 7 patients with stroke in the ventroposterior thalamic nuclei. Despite resting hypoperfusion, the primary somatosensory cortex (SI) activated normally during vibration of the hand. This characterizes primary representation but not the ability to modulate sensory inputs evident in tasks featuring multiple inputs.

The purpose of the present study was to investigate the role of somatosensory gating mechanisms in recovery from stroke involving the thalamus or its reciprocal connections with the cerebral cortex. We hypothesized that efficient task-related modulation of sensory inputs is an important factor contrib-

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utting to recovery from thalamic stroke. Specifically, deficits in the ability to detect contralesional tactile stimuli when presented bilaterally are reflected by deficiencies in sensory gating mechanisms measured at the level of SI. Noteworthy is our current approach that incorporates complementary measures (perceptual, electrophysiological, functional brain imaging) at multiple time points during recovery. Partial results have been presented in abstract form.  

### Materials and Methods

**Subjects**

Four patients were tested serially during recovery (1 week to 6 months after stroke) from thalamocortical stroke. Lesion information and demographic data are summarized in the Table. None of the patients presented with hemispatial visual neglect as assessed by the Sunnybrook Neglect Battery, which comprises 4 subtests: spontaneous drawing and copying of a clock and daisy, line cancellation, line bisection, and shape cancellation. No patient had large-artery disease as revealed by cortical Doppler or stroke location. Five control subjects were scanned on 2 separate days to ensure reproducibility of stimulus-induced functional MRI (fMRI) activations. All participants provided written, informed consent, and the experimental procedures were approved by the Sunnybrook and Women's College Health Sciences Center Ethics Committee.

**Behavioral Tests**

Perceptual thresholds were obtained to vibration (105 Hz) applied to the left and right thumbs with a biothesiometer (Phystemp). With the subject's eyes closed, the thumb was placed on the post of the biothesiometer, and the experimenter continuously increased the distance of excursion of the post until subjects detected the vibration. Perceptual thresholds were determined 3 times for both the stroke-affected and unaffected thumbs. Testing was repeated with concomitant competing vibration presented to the contralateral hand (≈100 Hz, constant-amplitude, suprathreshold). Light touch sensation was assessed with Semmes-Weinstein monofilaments.

Statistical analyses of these data were performed on a patient-by-patient basis. For the unaffected hand, 95% confidence intervals (CIs) were computed around mean differences between perceptual thresholds for the 2 conditions (with and without competing stimulation) across testing sessions. For the stroke-affected hand, perceptual threshold differences were compared with the 95% CI for the unaffected hand at each testing time.

**Somatosensory Evoked Potentials**

Somatosensory evoked potentials (SEPs) were evoked by electrical stimulation of the median nerve at the wrist (square wave pulses, 0.5 ms; Grass S88 stimulator with SIU5 stimulus isolation unit). Stimulus intensity was estimated by maintaining abductor pollicis brevis M-wave magnitudes, electromyographic (EMG) waves resulting from direct stimulation of motoneuronal axons serving the muscle, at ≈20% of maximum. SEPs were recorded from scalp electrodes positioned over CP3 and CP4, referenced to AFZ, in accordance with the modified international 10 to 20 system. Impedance at SEP and EMG recording sites was less than 5 kΩ; and 10 kΩ, respectively. SEP and EMG recordings were amplified (×40 000, ×1000; respectively), filtered (1 to 100 Hz, 3 to 300 Hz, respectively; SA Instrumentation), digitized at 1000 Hz (National Instruments), and stored on computer for subsequent analysis. Each SEP trace was obtained by averaging ≈100 artifact-free samples. The initial cortical SEP components were measured peak to peak from the N20 to the adjacent P27 (Figure 1c), which arise from activation of neurons within areas 3b and 1, respectively. Mean N20-P27 amplitude differences were computed in the presence and absence of contralateral vibration in a group of 15 control subjects for a study to establish the reliability of task-related modulation of SEP amplitudes. There were no differences in N20-P27 amplitude between the 2 conditions (mean±95% CI, 0.13±0.46 μV). Task-related differences from individual patients at each testing time were compared with the 95% CI for the control group.

**Functional MRI**

Three separate fMRI scans were performed in random order with tactile stimulation of the index finger of the stroke-affected hand, the unaffected hand, and both hands simultaneously. Tactile stimulation consisted of brushing along the entire length of the index finger with a small brush in a block design (30 seconds of stimulation, 30 seconds of rest for 5 repetitions). Total time in the scanner was ≈40 minutes.

Functional and anatomical imaging was performed on a clinical MRI scanner (1.5 T, GE Medical Systems, software version LX 8.2.5, NV/i hardware platform) with a standard head coil and a vacuum pillow (Vac Fix, Par Scientific Inc) to reduce head movements. Blood oxygenation level dependent (BOLD) functional images were acquired axially with gradient echo imaging with single-shot spiral readout (repetition time=1500 ms; echo time=40 ms; flip angle, θ=80°; acquisition matrix=64×64; field of view=20 cm; slices=18; slice thickness=3.0 mm). In addition, high-resolution T1-weighted 3-dimensional fast spoiled gradient-echo anatomical images (repetition time=12.4 ms; echo time=5.4 ms; θ=35°; acquisition matrix=256×192; slices=124; slice thickness=1.4 mm; field of view=22×16 cm) were obtained. For each fMRI scan, a time series of 210 images per slice was generated. After 3-dimensional registration to correct for residual head motions between image acquisitions, statistical analyses were performed on a voxel-by-voxel basis with Analysis of Functional Neuroimages (version 2.25) software with orthogonalized correlation, taking into account a hemodynamic lag (4.5 seconds). Voxels were deemed significant if the correlation coefficient was $P<0.05$. To compare locations of activated regions over the repeated scanning sessions, functional maps and anatomical scans from each individual subject were normalized to stereotactic Talairach coordinates. Lesion volumes were calculated by manually tracing the necrotic region on each slice of the T1 scan taken at 3 months after stroke with ANALYZE software (Mayo Clinic).

**Results**

All 4 patients had lesions involving the thalamus (the Table and Figures 1, 3, and 5) and demonstrated comparable results.
Figure 1. Patient 1. a, T1-weighted MRI scan illustrating lesion location (white arrow) in the right ventroposterolateral nucleus 3 months after stroke. Image location is 5 mm above the line adjoining the anterior and posterior commissures. b, Perceptual thresholds to vibratory stimuli applied to the pad of the thumb in the absence (open bars) or presence (filled bars) of competing vibratory stimulation (Vib) applied to the contralateral (CL) hand. Asterisks represent perceptual thresholds exceeding the 95% CI for perceptual thresholds of the unaffected hand in the presence of contralateral vibration. c, Median nerve SEPs from CP3 in the absence (thick line) and presence (thin line) of vibration of the contralateral hand at 2 weeks after stroke. Arrow indicates stimulus onset. d, N20-P27 amplitudes with contralateral vibration during recovery expressed as a percentage of the resting amplitude. Gray horizontal bar represents the 95% CI surrounding the mean task-related N20-P27 amplitude difference in control subjects (n=15).
revealing disrupted threshold detection to vibration in the presence of competing contralateral somatosensory stimuli. This compromised capacity to gate sensory inputs was paralleled by a reduction in the measured activation of cortical representation of the affected side (fMRI and SEP) during bilateral stimulation.

**Patient 1**

Patient 1 presented with mild left hemisensory loss, without evidence of tactile extinction to light touch, and with transient left homonymous hemianopia resulting from a right thalamic lacune evident on CT (National Institutes of Health Stroke Scale21 [NIHSS], 3). MRI confirmed an infarct in the right ventroposterolateral nucleus (Figure 1a). Figure 1b illustrates 2 important observations regarding perceptual thresholds tested on the stroke-affected side. At 2 weeks after stroke, the patient was equally able to perceive vibratory stimuli applied to either thumb. However, with the stroke-affected hand, there was a significant increase in threshold detection with contralateral competing stimulation. This improved markedly with recovery. At 6 months after stroke, the task-related difference no longer exceeded the 95% CI obtained from the unaffected hand. Sensitivity to light touch did not differ between the left and right hands (smallest monofilament diameter perceived: thumb, right/left, 2.83 mm/2.83 mm; palm, right/left, 3.22 mm/2.83 mm).

Electrophysiological and fMRI measures paralleled these behavioral deficits. At 2 weeks after stroke, N20-P27 SEP amplitude was attenuated in the presence of contralateral vibration compared with rest (Figure 1c, thin versus thick line). Similar to perceptual threshold differences under conditions of competing stimulation, task-related N20-P27 amplitude differences resolved with recovery. By 24 weeks after stroke, they did not differ from the 95% CI in the control group (Figure 1d, shaded area). In Figure 2, fMRI shows that early after stroke (2 weeks, top), unilateral stimulation of the stroke-affected hand significantly activated voxels in the area of contralateral SI. However, during bilateral stimulation, there were no significantly activated voxels in the ipsilesional SI. As recovery progressed, significant activation within the same spatial regions of the ipsilesional SI was observed during both unilateral and bilateral stimulation.

**Patient 2**

Patient 2 presented with right hemisensory loss and flaccid hemiparesis that made a quick recovery (NIHSS, 21 at admission, 2 by 1 week after stroke). MRI revealed a left putaminal-capsular hemorrhage that likely affected the thalamus initially by pressure from the associated edema. By 12 weeks after stroke, the blood clot had resolved, and the residual lesion involved primarily the posterior putamen and the posterior limb of the internal capsule. Patient 2 had some residual primary sensory loss to light touch (monofilaments at 3 months after stroke: thumb, right/left: 4.56 mm/2.83 mm; palm, right/left: 4.56 mm/2.44 mm). However, there was no primary sensory loss to vibration on the stroke-affected side compared with the unaffected hand. In the presence of competing contralateral stimulation, perceptual thresholds increased >200% at 1 week after stroke. By 6 months after stroke, perceptual thresholds from the affected hand no longer exceeded the 95% CI from the unaffected side during contralateral stimulation.

Paralleling perceptual threshold differences under conditions of competing stimulation, task-related differences of N20-P27 amplitudes were apparent early after stroke (17.4% reduction with competing contralateral stimulation) but dissipated with recovery so that, at 6 months after stroke, task-related SEP differences did not differ from that of control subjects. Figure 4a shows fMRI during unilateral and bilateral tactile stimulation with recovery. Early after stroke, there was a focus of significantly activated voxels in the ipsilesional SI with unilateral stimulation of the affected hand. During bilateral stimulation no voxels exceeded threshold within the ipsilesional SI. After recovery (6 months), both unilateral and bilateral stimulation significantly activated voxels within the ipsilesional SI.

**Patient 3**

Patient 3, a diabetic patient, presented with right hemiparesis referable to a left internal capsule lacune seen on CT. However, MRI showed bilateral thalamic lacunar infarcts in addition to a left internal capsule lacune (NIHSS, 4 at admission, 2 at 6 weeks after stroke, 0 by 3 months after stroke; Figure 3a). Light touch sensation did not differ between the right and left hands (thumb, right/left: 3.61 mm/3.61 mm; palm, right/left: 3.61 mm/3.61 mm) and did not change over time. Sensitivity to vibration on either hand was comparable to the unaffected side of the other patients when presented alone (Figure 3b). However, perceptual thresholds to vibration were elevated on both hands in the presence of competing contralateral stimulation (Figure 3b). This effect worsened from 3 to 6 months after stroke. In parallel with the perceptual deficits, task-related differences of N20-P27 amplitudes became more prominent over time. This was most evident with right hand stimulation (Figure 3c) for which, at 6 months after stroke, attenuation with competing stimulation fell below the 95% CI for control subjects. However, fMRI showed less task-specific attenuation of SI activation over time with bilateral tactile stimulation (Figure 4b).

**Patient 4**

Patient 4 presented with right hemiplegia and hemisensory loss resulting from a large left subcortical hemorrhage (Figure 5a and the Table) and was able to participate only in the fMRI testing (NIHSS, 12 at admission, 3 by 3 months after stroke). Similar to results for patient 2, Figure 5b shows focal activation within the ipsilesional SI during unilateral stimulation of the affected hand early after stroke. However, there were no significantly activated voxels within this region during bilateral stimulation. With stimulation of the unaffected hand, there were many activated clusters in a large network. By 3 months after stroke, unilateral stimulation of either the affected or unaffected hand significantly activated clusters of voxels within the contralateral SI. However, with bilateral stimulation, there were still no significantly activated voxels within ipsilesional SI. Unfortunately, perceptual threshold and SEP data are not available for comparison.
Five control subjects were tested on 2 days separated by a maximum of 3 weeks to ensure that the tactile stimulation produced consistent regions of activation within SI on repeated scans. Across subjects and sessions, there was very good reproducibility of activated regions in SI. The average location (±SE) of maximal BOLD signal associated with tactile stimulation of the right index finger was in the left postcentral gyrus (Talairach coordinates x, y, z: −45.8±3.60, −24.7±2.25, 50.8±2.53 mm, respectively). More importantly, the difference in maximal location between scan sessions was also reproducible. The average difference in location of maximal BOLD response (±SE) in SI between repeated scans in individual subjects was 0.8±0.86, 1.8±1.2, and 2.0±0.89 mm.

**Discussion**

The present study reports novel findings concerning the importance of sensory gating systems in recovery from stroke involving the thalamus or its cortical connections. There are 2 main findings: (1) Lesions involving the ventroposterior group of thalamic relay nuclei did not eliminate cortical activations associated with tactile stimulation of the stroke-affected hand, similar to the results of Remy et al; and (2) despite this unaffected primary representation, ipsilesional SI activation was abolished in all 4 patients with bilateral tactile stimulation early after stroke. Reversal of this attenuation was associated with recovery over time. These results provide insight into potential mechanisms that contribute to sensory gating and suggest that the ability to control sensory input...
through effective gating mechanisms, not just primary sensory representation, may be important for poststroke somatosensory recovery.

Previous studies have shown a complex relationship between cortical activation and thalamic injury from stroke. In particular, in a series of 7 thalamic stroke patients, Remy et al.\(^\text{10}\) reported a reduction in resting regional blood flow in SI but not in response to hand vibration associated with lesions in the ventroposterior nuclei. The patients reported here (except perhaps patient 4) all had small lesions affecting the ventroposterior nuclei. With tactile stimulation of the affected hand, threshold testing and SEP and fMRI data suggest that the direct relay of peripheral somatosensory input to SI was not strongly attenuated. All patients were able to detect unilateral contralesional stimuli, either light touch or vibration, at levels similar to ipsilesional stimuli. However, all had
profound deficits in detecting the same contralesional stimuli when accompanied by competitive ipsilesional stimulation early after stroke.

The deficiency in detecting contralesional somatosensory stimuli when both hands were stimulated is akin to the clinical phenomenon of tactile extinction. However, none of the patients had tactile extinction to light touch with normal clinical testing. This deficit was only apparent when the testing input was vibration. The pathophysiology of tactile extinction is not well understood but is often considered a disorder of selective attention to somatosensory stimuli. Remy et al. reported on 3 patients with pure tactile extinction and right subcortical lesions, with the overlapping region including the lenticular nucleus and the surrounding white
matter. Using PET, they showed that activation of SI in the affected hemisphere was impaired during bilateral vibration of the hands. However, unlike the patients presented here, SI activation was similarly impaired during unilateral stimulation.

If the ascending afferent signals reach the ipsilesional SI, what are potential mechanisms for the strong attenuation observed during simultaneous bilateral stimulation? The deficit appears to be in the ability to gate competing sensory information from the unaffected side and may be related to attentional dysfunction. Attention to tactile stimuli can lead to specific modulation of SI activity, enhancing responsiveness of the associated body part in contralateral SI\(^{24-26}\) while inhibiting ipsilateral SI.\(^{26}\) In the present group of patients, we

Figure 5. Patient 4. a, T1-weighted MRI scans 9 mm above the anterior and posterior commissures illustrating the left thalamic hemorrhage at 2 weeks and 3 months after stroke. b, fMRI scans (Talairach space, 50 mm above the anterior and posterior commissures) during tactile stimulation of the index finger on the right hand alone (Unaffected), stroke-affected left hand alone (Affected), or both hands simultaneously (Bilateral). Arrows as in Figure 2.
did not test systematically for deficits in somatosensation with distracting input in other sensory modalities. Patient 2 was tested for the presence of somatosensory or visual extinction over the first 5 days after stroke. There was evidence of somatosensory but not visual perceptual deficits at this very early stage. Thus, for this group of patients, it is not likely that the observed somatosensory perceptual deficits occurred as a result of general attentional dysfunction, although further work is required for confirmation.

There is a growing understanding of the network responsible for regulating cortical afferent inflow. Skinner and Yingling provided the first physiological evidence for a multimodal sensory gating system in cats that regulates sensory input to primary cortical regions, mediated by prefrontal-thalamic projections. Suppression of prefrontal cortical activity increased the amplitudes of evoked responses in primary sensory cortex. In contrast, stimulation of the thalamic reticular nucleus, a thin sheet of GABA-ergic cells surrounding the thalamic sensory relay nuclei, suppressed activity in primary sensory cortex in a modality-specific manner. The thalamic reticular nucleus is a likely candidate to influence the flow of sensory information through the thalamus because it receives excitatory collateral projections from thalamocortical afferents originating in all thalamic relay nuclei and in turn sends inhibitory projections back to the originating relay nuclei. This prefrontal-thalamic system provides a powerful mechanism for intramodality inhibition of irrelevant inputs early in the sensory processing stream relevant to the present data.

There is great advantage to using multiple measurement techniques to assess cortical changes associated with stroke recovery. The use of fMRI can be controversial because the BOLD signal is dependent on the integrity of the vascular system, the very system affected by stroke. However, by comparing tasks within patients within the same testing session, we are confident that the present observations reflect neural modulations and not simply a cardiovascular response to injury. Specifically, if a lack of activation within ipsilesional SI were due to a global reduction in blood flow, then this would be the case for both unilateral and bilateral stimulation within a session. This was clearly not the case. Furthermore, inferences raised by the fMRI are supported by changes both in cortical SEP components and in the behavioral results from individual patients.

For patients 1 through 3, attenuation of early SEP components during competing contralateral stimulation was indicative of abnormal sensory processing. SI activity is attenuated by other interfering somatosensory stimuli, but only very selectively when they occur anatomically near. For instance, stimulation of the index finger produces SI activity that is attenuated with a second competitive stimulus occurring on the same hand but not the opposite one. Interesting observations from the present data were the parallels between the early SEP components and the changes in perceptual thresholds. Specifically, as the behavioral deficit improved with recovery, the abnormal task-related changes in SEP amplitudes diminished. For patient 3, complicated by the presence of bilateral lesions, the behavioral deficits worsened over time but were still paralleled by task-related SEP changes (Figure 3). However, for patient 3, it is worth noting the dissociation between the behavioral/SEP results and the task-related fMRI changes with competitive stimulation. The presence of bilateral thalamic lesions, in addition to the left internal capsule lacune, makes interpretation difficult.

The integrity of ipsilesional thalamic circuitry in the recovery of sensorimotor function appears to be important. Severe hypometabolism in the ipsilesional thalamus has been shown in patients with poor motor recovery compared with those with good recovery, even though most patients did not have structural lesions in the thalamus. Our results support the notion that the thalamic circuitry has an important role in poststroke recovery, especially those circuits involved in controlling the flow of somatosensory information to the cortex.

The study of individual patients recovering from focal stroke affecting the posterior thalamus or its cortical connections provides insight into the importance of regulating afferent inflow to the cortex. The ability to control sensory information through effective gating mechanisms may be an important requisite for recovery from thalamic stroke and may have implications for stroke rehabilitation. Future work is required to determine whether specific training strategies can enhance the ability to either recover from or compensate for difficulty in filtering irrelevant sensory inputs during sensorimotor task performance and to determine the generalizability of these disrupted sensory gating mechanisms across patients with different lesion locations and characteristics.

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