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Amount but Not Pattern of Protective Sensory Stimulation Alters Recovery After Permanent Middle Cerebral Artery Occlusion

Melissa F. Davis, BS*; Christopher C. Lay, BS*; Cynthia H. Chen-Bee, MS; Ron D. Frostig, PhD

Background and Purpose—Using a rodent model of ischemia (permanent middle cerebral artery occlusion), our laboratory previously demonstrated that 4.27 minutes of patterned single-whisker stimulation delivered over 120 minutes can fully protect from impending damage when initiated within 2 hours of permanent middle cerebral artery occlusion (“early”). When initiated 3 hours postpermanent middle cerebral artery occlusion (“late”), stimulation resulted in irreversible damage. Here we investigate the effect of altering pattern, distribution, or amount of stimulation in this model.

Methods—We assessed the cortex using functional imaging and histological analysis with altered stimulation treatment protocols. In 2 groups of animals we administered the same number of whisker deflections but in a random rather than patterned fashion distributed either over 120 minutes or condensed into 10 minutes postpermanent middle cerebral artery occlusion. We also tested increased (full-whisker array versus single-whisker) stimulation.

Results—Early random whisker stimulation (condensed or dispersed) resulted in protection equivalent to early patterned stimulation. Early full-whisker array patterned stimulation also resulted in complete protection but promoted faster recovery. Late full-whisker array patterned stimulation, however, resulted in loss of evoked function and infarct volumes larger than those sustained by single-whisker counterparts.

Conclusions—When induced early on after ischemic insult, stimulus-evoked cortical activity, irrespective of the parameters of peripheral stimulation that induced it, seems to be the important variable for neuroprotection. (Stroke. 2011;42:792-798.)

Key Words: animal models ■ basic science ■ brain ischemia ■ brain recovery ■ imaging ■ neuroprotection

Middle cerebral artery occlusion is used to model the most clinically relevant type and location of stroke in humans: ischemic stroke in the middle cerebral artery.1 We have previously shown that, if initiated within 1 and in most cases 2 hours after permanent middle cerebral artery occlusion (pMCAO) in a rat model, single-whisker stimulation completely protects against the expected stroke-related structural and functional damage and behavioral deficits according to a host of techniques. Treatment consisted of 4.27 minutes of patterned (5-Hz) stimulation of a single whisker delivered over 120 minutes.2 Animals that did not receive the same stimulation until 3 hours postpMCAO not only had eliminated function, behavioral deficits, and large infarcts, but had larger infarcts than animals that never received postpMCAO stimulation.2 These results led us to ask the following questions: (1) Given that patterns are generally important in terms of experience and learning, is random stimulation as protective as patterned? (2) The 120-minute stimulation period overlaps the 2-hour window for protection; if we condense the stimulation into 10 minutes, can it still protect? (3) Does increased cortical activity (resulting from full-whisker array versus single-whisker stimulation) alter the early protective or late damaging effects of stimulation?

To determine whether patterned stimulation was critical for protection, we administered the same number of whisker deflections as in the previous +0 hour group (stimulation delivered immediately after pMCAO), but in a random rather than 5-Hz (patterned) fashion. To address the distribution question, this random stimulation was either spread out over the first 120 minutes after pMCAO (“dispersed +0 hours group”; Figure 1A) or condensed into the first 10 minutes (“condensed +0 hours group”; Figure 1B). To determine whether more cortical activity would alter results, we ran a +0 hours group (Figure 1C) and a +3 hours (stimulation delivered starting at 3 hours postpMCAO; Figure 1D) group using the patterned stimulation protocol from the previous article except that single-whisker stimulation was replaced with full-whisker array stimulation: “+0 hours full-whisker array” and “+3 hours full-whisker array” (see “Methods” for stimulation protocol details).
Figure 1. Experimental group stimulation and assessment. Representative (A) dispersed and (B) condensed +0 hours single-whisker subjects' and full-whisker array (C) +0 hours and (D) +3 hours subjects' initial dip and overshoot before and 24 hours postpMCAO.
Using Intrinsic Signal Optical Imaging and 2,3,5-triphenyltetrazolium chloride staining, we found that changes in pattern or distribution of stimulation did not diminish protection. Full-whisker array stimulation resulted in a faster recovery in +0 hours animals and increased infarct volume in +3 hours group compared with single-whisker counterparts. Thus, it appears that once the window of opportunity to protect the cortex has closed, the more stimulation given, the worse the damage. On the other hand, when given early, alterations in pattern or distribution still lead to complete protection and more stimulation accelerates recovery.

**Methods**

All procedures are in compliance with the University of California Irvine Animal Care and Use Committee. For detailed descriptions, see Lay et al.2

**Subjects and Surgical Preparation**

Experimental subjects, 295- to 400-g male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA), were individually housed in standard cages. Animals were injected with a sodium pentobarbital bolus (55 mg/kg body weight) and supplemental injections (27.5 mg/kg body weight) were given as necessary. An approximate 5-mm×6-mm “imaging” area of skull over the left somatosensory cortex was thinned. Five percent dextrose (3 mL) and atropine (0.05 mg/kg, body weight) were administered initially and every 6 hours throughout the experiment. Body temperature was maintained at 37°C. Baseline data collection was followed by pMCAO: double ligature and transection of the stem (M1 segment; just distal to lenticulostriate branch) of the left proximal middle cerebral artery.3-5

**Stimulation Protocols**

Random Dispersed

A total of 1280 whisker deflections was delivered individually at varying intervals of 4.8±3.6 seconds between onsets of consecutive deflections. This stimulation was distributed over approximately 120 minutes (Figure 1A).

Random Condensed

A total of 1280 whisker deflections was delivered individually at varying intervals of 0.5±0.25 seconds between onsets of consecutive deflections. This stimulation was distributed over approximately 10 minutes (Figure 1B).

Patterned (Single- [Previous Study] or Full-Whisker Array [Current Study])

A total of 1280 whisker deflections was delivered in 256 events (5 whisker deflections per event in a 5-Hz pattern) at varying intervals of 21.5±5 seconds between onsets of consecutive events. This stimulation was distributed over approximately 120 minutes (Figure 1C).

**Histology (2,3,5-Triphenyltetrazolium Chloride Staining for Infarct)**

Twenty-four hours postpMCAO, the brain was removed, sectioned into 2-mm coronal slices, and incubated in 2% 2,3,5-triphenyltetrazolium chloride at 37°C for 20 minutes in the dark.6 Infarct volume was determined by an observer blind to experimental condition. A value of zero indicates no response. Asterisks indicate significant differences between baseline and 24-hours values. Right, representative 2,3,5-triphenyltetrazolium chloride-stained coronal sections. Arrow indicates approximate region vulnerable to pMCAO infarct. Scale bars indicate 5 mm.

**Intrinsic Signal Optical Imaging and Analysis**

We used Intrinsic Signal Optical Imaging to assess evoked functional response to single-whisker stimulation (whisker functional representation [WFR]) or full-whisker array stimulation (whisker array functional representation [WAFR]). For a recent review of Intrinsic Signal Optical Imaging, see Frostit and Chen-Bee.7 A detailed description of Intrinsic Signal Optical Imaging8–10 data acquisition and analysis can be found elsewhere.11,12 Briefly, a charge-coupled device camera was used for imaging with red light illumination. Poststimulus ratio images were created by calculating fractional change values relative to intrinsic activity collected immediately before stimulus onset. The first 2 phases of evoked functional representation, the “initial dip” and “overshoot,” were analyzed. The ratio image containing the maximum areal extent was quantified at a threshold level of 2.5×10−4 away from zero. Peak amplitude was quantified in fractional change units from the pixel with peak activity within the maximum areal extent for each of the 2 phases.

**Statistical Analysis**

Two-sample t tests were run on raw baseline imaging values to ensure no significant differences before pMCAO between condensed and dispersed stimulation groups or between +0 hours and +3 hours full-whisker array groups existed.

For the randomized stimulation groups, paired sample t tests were used to compare between baseline and 24-hour whisker functional representations. Because there were no responses to quantify in +3 hours full-whisker array animals, postpMCAO imaging evoked area and amplitude were converted to difference score values (postocclusion−baseline) with values away from 0 signifying a change from baseline. A constant was added to difference values, which were then transformed with a natural log function to better satisfy the assumptions of an analysis of variance (ANOVA) and inferential statistics were performed on the transformed data. After the repeated-measures ANOVA, specific contrasts were performed to identify at which postpMCAO time points WAFRs differed from baseline. Separate analyses of variance followed by respective contrasts were performed for the 2 phases of the WAFR. The α level was set to 0.05 and Bonferroni adjustment applied to account for the 5 contrasts (P=0.05/5=0.01).

Finally, infarct volume comparisons were performed by using 2-sample t tests.

**Results**

**Random Single-Whisker Stimulation**

Before pMCAO and random stimulation treatment, there were no differences between groups in area or peak amplitude of initial dip (area: t[12]=0.76, P>0.05; amplitude: t[12]=1.00, P>0.05) or overshoot (area: t[12]=−0.02, P>0.05; amplitude: t[12]=0.34, P>0.05). Twenty-four hours postpMCAO, both dispersed (n=7) and condensed (n=7) groups maintained whisker functional representation at or above baseline (Figure 1A–B). Specifically, initial dip area was equivalent to baseline (dispersed: t[6]=−2.16, P>0.05; condensed: t[6]=−2.03, P>0.05), whereas initial dip amplitude increased (dispersed: t[6]=−5.02, P<0.01; condensed: t[6]=−5.48, P<0.01). The increased whisker functional representation at 24 hours postpMCAO matches our previous findings for patterned stimulation +0 hours animals and may be evidence of changes in the system that facilitated protection.2

**Figure 1 (Continued).** Linear gray scale bar indicates intrinsic signal strength ×10−4 fractional change. Streaks correspond to large surface vessels. Illustration depicts timing, location, and number of whiskers stimulated during treatment (temporal axis not to scale). Group baseline and +24-hour data are plotted in each graph. Means and SEs are provided for the area (left) and amplitude (right) of the initial dip (first row) and overshoot (second row). A value of zero indicates no response. Asterisks indicate significant differences between baseline and 24-hours values. Right, representative 2,3,5-triphenyltetrazolium chloride-stained coronal sections. Arrow indicates approximate region vulnerable to pMCAO infarct. Scale bars indicate 5 mm.
For both groups, overshoot area (dispersed: $t_{6}=-2.37$, $P>0.05$; condensed: $t_{6}=-0.003$, $P>0.05$) and amplitude (dispersed: $t_{6}=-0.05$, $P>0.05$; condensed: $t_{6}=0.31$, $P>0.05$) maintained baseline levels. Finally, there was no sign of infarct in any subject in either group.

**Full-Whisker Array Stimulation**

When the full-whisker array was stimulated immediately after pMCAO (+0 hours full-whisker array; $n=7$), the corresponding WAFRs regained baseline level cortical function by 90 minutes of stimulation and sustained no infarct, whereas all +3 hours animals permanently lost cortical activity and sustained infarct. Linear scale bar indicates intrinsic signal strength $10^{-4}$ fractional change. Scale bar indicates 5 mm. B-C, Graphs of group baseline and postocclusion data. Means and SEs are provided for the area (left) and amplitude (right) of the initial dip (B) and overshoot (C). A value of zero indicates no response. For +0 hours animals, asterisks indicate values significantly below and daggers indicate values significantly above baseline. For +3 hours animals, all postpMCAO values are unmarked and were zero.

Figure 2. +0 hours and +3 hours full-whisker array stimulation data. A, Initial dip images from representative +0 hours and +3 hours full-whisker array animals. Illustration depicts whiskers stimulated during treatment. All +0 hours animals regained baseline level cortical function by 90 minutes of stimulation and sustained no infarct, whereas all +3 hours animals permanently lost cortical activity and sustained infarct. Linear scale bar indicates intrinsic signal strength $10^{-4}$ fractional change. Streaks correspond to large surface vessels. Scale bar indicates 5 mm. B–C, Graphs of group baseline and postocclusion data. Means and SEs are provided for the area (left) and amplitude (right) of the initial dip (B) and overshoot (C). A value of zero indicates no response. For +0 hours animals, asterisks indicate values significantly below and daggers indicate values significantly above baseline. For +3 hours animals, all postpMCAO values are unmarked and were zero.

To further characterize the effect of full-whisker array stimulation, initial dip and overshoot phases of WAFRs were examined quantitatively at 4 points during stimulation treatment in addition to the 24-hour time point (Figures 1C–D and 2). Before pMCAO, no differences between groups in initial dip (area: $F_{1,12}=0.347$, $P>0.05$; amplitude: $F_{1,12}=0.344$, $P>0.05$) and overshoot (area: $F_{1,12}=0.310$, $P>0.05$; amplitude: $F_{1,12}=0.692$, $P>0.05$) were observed. PostpMCAO, however, an interaction between assessment time point and experimental group was found for both area ($F_{4,48}=22.66$, $P<0.001$, ANOVA) and amplitude ($F_{4,48}=13.13$, $P<0.001$, ANOVA) of the initial dip. In the +0 hours subjects, both were reduced at 0 to 30 minutes of treatment (area: $F_{1,12}=22.53$, $P<0.001$; amplitude: $F_{1,12}=16.76$, $P<0.001$), but by 60 minutes, the area surpassed ($F_{1,12}=11.87$, $P<0.01$) and the amplitude reached baseline level (amplitude: $F_{1,12}=5.27$, $P>0.05$). The area of the initial dip continued to increase and remained above baseline the next day (60 to 90 minutes: $F_{1,12}=71.97$, $P<0.001$; next day: $F_{1,12}=112.58$,
whereas the amplitude remained at the baseline level (Figure 2, grey bars).

Similar to the initial dip data, there was also an interaction between assessment time point and experimental group for both the area (F_{4,48} = 26.47, P < 0.01, ANOVA) and amplitude (F_{4,48} = 43.49, P < 0.01, ANOVA) of the overshoot. In +0 hours full-whisker array subjects, overshoot was reduced for the first 60 minutes of treatment (area: 0 to 30 minutes: F_{1,12} = 17.71, P < 0.01; 30 to 60 minutes: F_{1,12} = 7.39, P < 0.05; amplitude: 0 to 30 minutes: F_{1,12} = 51.6, P < 0.01; 30 to 60 minutes: F_{1,12} = 23.47, P < 0.01) but regained baseline level area by 90 minutes (Figure 2, grey bars).

Current work in our laboratory (Davis et al, unpublished data) shows that +0 hours animals demonstrated complete recovery of initial dip before the overshoot. Although the +0 hours full-whisker array group in the present study recovered earlier than their previously mentioned single-whisker counterparts, the sequence of recovery of the phases replicate the earlier finding: the initial dip recovers before the overshoot.

**Single- Versus Full-Whisker Array +0 Hours Groups**

To study the effect of increased stimulation, we compared the rate of recovery of cortical function in the present study’s +0 hours full-whisker array animals with their single-whisker counterparts (+0 hours single-whisker group: data from a previous study; Davis et al, unpublished data). By 90 minutes of treatment in single-whisker +0 hours animals, initial dip area and amplitude and overshoot area had regained baseline values, whereas overshoot amplitude required 120 minutes (Figure 3, black bars). In the present study, the initial dip area (F_{1,12} = 11.87, P < 0.05) and amplitude (F_{1,12} = 5.27, P > 0.05) of full-whisker array +0 hours subjects recovered prepMCAO baseline values or greater by 60 minutes of stimulation treatment, and overshoot area (F_{1,12} = 1.41, P > 0.05) and amplitude (F_{1,12} = 6.96, P > 0.05) recovered prepMCAO baseline values by 90 minutes of stimulation treatment (see previous “Results” section for detailed statistical analysis of the full-whisker array group). Thus, full-whisker array treatment resulted in full recovery 30 minutes faster than single-whisker stimulation (Figure 3, grey bars).
Increased evoked cortical activity in the brain, spinal cord, or peripheral nerves can temper impending stroke damage. It has been suggested that stimulation of the brain, spinal cord, or peripheral nerves can also be protective.

Although still debated, the initial dip is generally associated with evoked neuronal activity and the overshoot with blood flow response; in any case, the recovery of both phases, and their underlying signal sources, have the same profile whether single- or full-whisker array stimulation is delivered. This similar progress of recovery of the initial dip and overshoot in both groups further supports this idea that activating the cortex early on is of more importance than the type of stimulation administered. Not all parameters of stimulation were explored, however, and it is possible that other, untested variables of whisker deflection might alter the outcome. Furthermore, it remains to be determined whether generating cortical activity in nonanesthetized animals could also be protective.

Previous research has demonstrated that direct electric stimulation of the brain, spinal cord, or peripheral nerves can temper impending stroke damage. It has been suggested that this stimulation may help maintain neurovascular coupling under ischemic conditions through collateral flow and that this is an important potential avenue for future stroke therapy. Targeting this coupling mechanism has also been suggested as a strategy more likely to succeed in translation to humans.

In the current study, we attempted to identify important aspects of protective whisker stimulation by altering components we thought might affect our results: pattern and distribution of stimulation and number of whiskers stimulated. Based on our previous work, we suspected that cortical activity was the critical factor in producing protection but were unsure whether an increase resulting from stimulating the full-whisker array would alter our results. Additionally, we considered the possibility that a patterned stimulus might be more salient to the rat cortex and also wondered whether condensing the stimulation (previously spread out over 120 minutes) into 10 minutes might alter our results.

It appears that neither the pattern nor the distribution of stimulation is an important factor for protection but that the amount of cortical activation can augment the speed of recovery (or exacerbate injury when delivered late). Thus, early administration seems to be critical. This fits with current research, which suggests that the greatest opportunity for recovery exists within a limited window of time after a stroke.

**Ischemic Infarct in Single- Versus Full-Whisker Array +3 Hours Groups**

Previous results demonstrated that late whisker stimulation increased the volume of infarct in +3 hours subjects compared with nonstimulated controls. Here, we compare infarct in the +3 hours full-whisker array group with +3 hours single-whisker infarct. The +3 hours full-whisker array infarct volume was found to be significantly larger than that sustained by single-whisker counterparts (mean\textsubscript{single} = 63.4±3.9 mm\textsuperscript{3}; mean\textsubscript{full} = 91.9±9.8 mm\textsuperscript{3}; t\textsubscript{[12]} = 2.69, P<0.05; Figure 4). Thus, when delivered too late, increased evoked cortical activity results in increased infarct volume.

**Discussion**

In the current study, we attempted to identify important aspects of protective whisker stimulation by altering components we thought might affect our results: pattern and distribution of stimulation and number of whiskers stimulated. Based on our previous work, we suspected that cortical activity was the critical factor in producing protection but were unsure whether an increase resulting from stimulating the full-whisker array would alter our results. Additionally, we considered the possibility that a patterned stimulus might be more salient to the rat cortex and also wondered whether condensing the stimulation (previously spread out over 120 minutes) into 10 minutes might alter our results.

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Davis et al Relevant Parameters for Protective Stimulation

**Figure 4.** +3 hours full-whisker array versus +3 hours single-whisker infarct volumes. The total infarct volume sustained by +3 hours single-whisker and +3 hours full-whisker array animals according to 2,3,5-triphenyltetrazolium chloride. Asterisk indicates significant difference in infarct volume between groups.

**Experimental Group**

**Ischemic Infarct in Single- Versus Full-Whisker Array +3 Hours Groups**

Previous results demonstrated that late whisker stimulation increased the volume of infarct in +3 hours subjects compared with nonstimulated controls. Here, we compare infarct in the +3 hours full-whisker array group with +3 hours single-whisker infarct. The +3 hours full-whisker array infarct volume was found to be significantly larger than that sustained by single-whisker counterparts (mean\textsubscript{single} = 63.4±3.9 mm\textsuperscript{3}; mean\textsubscript{full} = 91.9±9.8 mm\textsuperscript{3}; t\textsubscript{[12]} = 2.69, P<0.05; Figure 4). Thus, when delivered too late, increased evoked cortical activity results in increased infarct volume.

**Discussion**

In the current study, we attempted to identify important aspects of protective whisker stimulation by altering components we thought might affect our results: pattern and distribution of stimulation and number of whiskers stimulated. Based on our previous work, we suspected that cortical activity was the critical factor in producing protection but were unsure whether an increase resulting from stimulating the full-whisker array would alter our results. Additionally, we considered the possibility that a patterned stimulus might be more salient to the rat cortex and also wondered whether condensing the stimulation (previously spread out over 120 minutes) into 10 minutes might alter our results.

It appears that neither the pattern nor the distribution of stimulation is an important factor for protection but that the amount of cortical activation can augment the speed of recovery (or exacerbate injury when delivered late). Thus, early administration seems to be critical. This fits with current research, which suggests that the greatest opportunity for recovery exists within a limited window of time after a stroke.

Although still debated, the initial dip is generally associated with evoked neuronal activity and the overshoot with blood flow response; in any case, the recovery of both phases, and their underlying signal sources, have the same profile whether single- or full-whisker array stimulation is delivered. This similar progress of recovery of the initial dip and overshoot in both groups further supports this idea that activating the cortex early on is of more importance than the type of stimulation administered. Not all parameters of stimulation were explored, however, and it is possible that other, untested variables of whisker deflection might alter the outcome. Furthermore, it remains to be determined whether generating cortical activity in nonanesthetized animals could also be protective.

Previous research has demonstrated that direct electric stimulation of the brain, spinal cord, or peripheral nerves can temper impending stroke damage. It has been suggested that this stimulation may help maintain neurovascular coupling under ischemic conditions through collateral flow and that this is an important potential avenue for future stroke therapy. Targeting this coupling mechanism has also been suggested as a strategy more likely to succeed in translation to humans. Indeed, blood flow data from our previous research suggest that protected animals have collateral vessel-supported reperfusion. Additionally, in reference to the current results, it is reasonable that if stimulation-induced blood flow increases allow protection, patterned stimulation would not be more protective than random and increased stimulation could increase blood flow and accelerate recovery. Clearly long term re-establishment of blood flow is necessary for protection, but perhaps an acute reperfusion resulting from early stimulation-induced collateral flow maintains the cortex in a less compromised position during acute ischemia, allowing complete protection. Other possible mechanisms have also been proposed; some direct stimulation methods have been shown to induce various neuroprotective effects and agents. Whether initiation of neuroprotective agents or early, acute induction of collateral flow, or both is necessary for activity-induced complete protection from ischemia is yet unknown and requires more research.

Sensory-induced protection from ischemic stroke nonetheless appears to be a robust phenomenon unperturbed by alterations in pattern or distribution of stimulation, which can be accelerated with increased cortical activation. These results may simplify future investigations regarding the mechanism and although there is still much research to be done, this might also mean that translational application could be straightforward as long as sensory stimulation is delivered early on after ischemic onset.

**Summary**

Previous research in our laboratory demonstrated that patterned whisker stimulation given within 2 hours of pMCAO can fully protect from stroke damage. In the current article, we sought to determine whether altering various parameters of stimulation would alter recovery. Results demonstrate that altering the pattern and distribution of whisker stimulation does not perturb the protective effect but that increasing the number of whiskers stimulated in early treatment speeds...
recovery. Increasing the number of whiskers stimulated outside of the protective window (3 hours postMCAO) is not only no longer protective, but increases cortical damage compared with single-whisker counterparts.

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Disclosures
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