Displacement of Sensory Maps and Disorganization of Motor Cortex After Targeted Stroke in Mice

Thomas C. Harrison, PhD; Gergely Silasi, PhD; Jamie D. Boyd, PhD; Timothy H. Murphy, PhD

Background and Purpose—Recovery from stroke is hypothesized to involve the reorganization of surviving cortical areas. To study the functional organization of sensorimotor cortex at multiple time points before and after stroke, we performed longitudinal light-based motor mapping of transgenic mice expressing light-sensitive channelrhodopsin-2 in layer 5 cortical neurons.

Methods—Pulses of light stimulation were targeted to an array of cortical points, whereas evoked forelimb motor activity was recorded using noninvasive motion sensors. Intrinsic optical signal imaging produced maps of the forelimb somatosensory cortex. The resulting motor and sensory maps were repeatedly generated for weeks before and after small (0.2 mm³) photothrombotic infarcts were targeted to forelimb motor or sensory cortex.

Results—Infarcts targeted to forelimb sensory or motor areas caused decreased motor output in the infarct area and spatial displacement of sensory and motor maps. Strokes in sensory cortex caused the sensory map to move into motor cortex, which adopted a more diffuse structure. Stroke in motor cortex caused a compensatory increase in peri-infarct motor output, but did not affect the position or excitability of sensory maps.

Conclusions—After stroke in motor cortex, decreased motor output from the infarcted area was offset by peri-infarct excitability. Sensory stroke caused a new sensory map to form in motor cortex, which maintained its center position, despite becoming more diffuse. These data suggest that surviving regions of cortex are able to assume functions from stroke-damaged areas, although this may come at the cost of alterations in map structure. (Stroke. 2013;44:2300-2306.)

Key Words: brain mapping ■ cerebral cortex ■ mice ■ motor cortex ■ neuronal plasticity ■ somatosensory cortex

Recovery from stroke depends on the ability of surviving neural circuitry to reorganize and compensate for the loss of damaged regions. Cortical regions that are in close proximity to the stroke or are functionally related to the damaged region are well positioned for this type of vicarious function, particularly after small strokes. For example, destruction of the mouse forelimb sensory cortex by targeted stroke can cause a new sensory representation to emerge in the territory normally occupied by forelimb motor cortex. It remains unclear, however, whether the motor cortex can maintain its primary role in addition to shouldering the computational burden previously carried by the somatosensory cortex. The annexation of motor cortex by new sensory representations may require the underlying circuitry to abandon its original function, causing the motor map to be displaced. This type of maladaptive reorganization has been proposed as a mechanism for the secondary deficits that appear several weeks after stroke in some patients.

Cortical reorganization persists for months after stroke, but longitudinal experiments in animal models have been constrained by the limitations of intracortical electric stimulation. We made use of transgenic channelrhodopsin-2 mice that express a light-sensitive cation channel in layer 5 cortical output neurons to perform light-based mapping (LBM) of motor cortex. LBM has the advantages of being faster and less invasive than electrode-based mapping and can be repeatedly combined with intrinsic signal imaging of somatosensory representations in cranial window preparations. Here, we present the first longitudinal study of combined sensory and motor cortical reorganization after strokes targeted to mouse forelimb sensorimotor cortex.

Materials and Methods
For additional details, please see online-only Data Supplement.

Animals and Surgery
Animal protocols were approved by the University of British Columbia Animal Care Committee. Channelrhodopsin-2 transgenic mice were implanted with a cranial window over the right sensory-motor cortex and allowed to recover for 2 months before being used in mapping experiments. The majority of cranial windows remained viable for the full extent of the experiment (17 of 24 mice). Each group contained 4 male and 4 female mice (except motor stroke group: 5 males, 3 females). Age at mapping onset was consistent between groups (sensory 148.2±10.5 days,
motor 139.1±16.9 days, and sham 133.75±11.8 days; \(P=0.72;\) ANOVA).

**Intrinsic Optical Signal Sensory Mapping**

We conducted 20 to 40 imaging trials per experiment, each comprising 15 frames collected over 1.5 s preceding a tactile stimulus delivered to the contralateral forelimb by a piezoelectric device (1 s of 5 ms square pulses at 100 Hz) and 15 frames collected during and after the stimulus. Images were analyzed using an ImageJ plugin described previously\(^{14}\) to create an image of mean percentage change in 635 nm light reflectance thresholded at 33% of maximal response.

**Light-Based Motor Mapping**

LBM methodology has been described in detail.\(^{12,15}\) Briefly, we targeted a 473-nm laser beam to a grid of cortical sites in semirandom order. Evoked forelimb movement amplitudes were measured using laser range finders. This process was repeated 3 times to obtain a mean value for each pixel of the map.

**Photothrombotic Stroke**

To generate photothrombotic strokes, mice were injected with 1% Rose Bengal in phosphate-buffered saline (100 mg/kg IP).\(^{16}\) A circular region of cortex 1 mm in diameter was illuminated with the arc lamp of an epifluorescence microscope (10 mW green light, 10× objective, numerical aperture=0.3) for 13 minutes. Sham mice were injected with saline only and illumination was targeted to sensory forelimb (sFL).

**Histology**

Infarct volumes were calculated using ImageJ by measuring the area of the infarct in all coronal sections where it was visible and multiplying this value by the distance between sections.

**Statistical Analyses**

Data were analyzed using Graphpad Prism. The specific tests used are stated alongside all probability values reported.

**Results**

**Longitudinal LBM of Sensory and Motor Forelimb Representations**

Twenty-four Thy1-channelrhodopsin-2 transgenic mice\(^{10}\) were implanted with cranial windows that covered sensorimotor cortex of the right hemisphere (5 mm×5 mm, extending 1 mm across the midline and 2.5 mm anterior and posterior from bregma; Figure I in the online-only Data Supplement). Three baseline motor and sensory mapping sessions were performed...
for each animal (Figure 1A). Contralateral motor forelimb (mFL) maps were spatially stable, with a mean weekly shift in center of gravity of 0.42±0.22 mm (n=24 mice, all values±SEM unless otherwise stated). Contralateral sFL maps exhibited a similar weekly shift in center position during the baseline period (0.42±0.09 mm; n=14 mice).

One day after the third baseline mapping session, a phototothrombotic infarct was targeted to either sFL (sensory stroke group; Figure 1B) or a nonoverlapping portion of mFL (motor stroke group; Figure 1C). Infarct volume was comparable for the sensory- and motor-targeted groups (0.18±0.07 versus 0.23±0.06 mm³, respectively; P=0.54; t test), with sensory-targeted infarcts located more laterally than motor-targeted infarcts (2.71±0.27 versus 1.87±0.15 mm from midline; P=0.0194; t test). No differences were observed in infarct volume between females and males (0.20±0.04 versus 0.23±0.07 mm³; n=6 and 7, respectively; P=0.77; t test).

Spatial Properties of Sensorimotor Reorganization
As in previous studies, strokes targeted to sFL caused the reorganized sFL map to shift medially toward motor cortex (Figure 2A and 2C). Despite its occupation by the new sFL map, mFL was able to maintain its position after sensory stroke (Figure 2B). Similarly, strokes in mFL did not cause a subsequent shift of the neighboring sFL map (Figure 2B and 2C). Sham strokes caused no reorganization of sensorimotor cortex (Figure 2A–2C). Although spatial reorganization was largely confined to the stroke-damaged map, sFL displacement after sensory stroke was correlated with increased mFL displacement (Figure 2D). Displacements of sFL and mFL were not correlated with infarct volume or with the extent of overlap between sensory and motor maps, defined by the prestroke separation between their centers of gravity.

Changes in Sensorimotor Excitability After Stroke
To assess the responsiveness of the sensorimotor cortex to somatosensory stimuli, intrinsic optical signal values were measured in nonoverlapping regions of interest defined by the baseline positions of sFL and mFL. Vibrotactile stimulation of the contralateral forepaw caused an intrinsic optical signal response in sFL and to a lesser extent in mFL (Figure 3). These sensory responses were unaffected by sham- or motor-targeted strokes (Figure 3). Strokes targeted to sFL, however, caused a persistent deficit in sensory responses within somatosensory cortex (Figure 3, upper left). Responses to sensory stimulation were initially disrupted in mFL, but recovered after 6 to 8 weeks.

To examine the effect of targeted stroke on motor representations, each animal’s poststroke motor maps were normalized to their own baseline mean, aligned according to the position of the infarct and then averaged. Strokes in mFL caused a decrease in motor output from the infarct core (Figure 4), balanced by a substantial increase in peri-infarct motor output not seen after sensory-targeted or sham strokes (Figure 4). Motor output from the immediate vicinity of the stroke was significantly decreased for the first month after both sensory and motor strokes, but recovered by 6 to 8 weeks post stroke (Figure II in the online-only Data Supplement). Normalized map area and motor output after stroke were conserved overall after stroke (Figure III in the online-only Data Supplement). Normalized map area and motor output after stroke were conserved overall after stroke (Figure III in the online-only Data Supplement).

Figure 2. Map displacement after stroke. A, Displacement of sensory forelimb (sFL) center from its mean baseline position before and after sensory (blue), motor (orange), or sham (black) strokes. Asterisks signify P values (2-way ANOVA; F(2)=6.4; P=0.002; asterisks correspond to results of Bonferroni’s post test). B, Motor forelimb (mFL) displacement (2-way ANOVA; F(2)=9.572; P=0.0002). C, Mean weekly position of motor (left) and sensory (right) forelimb maps relative to their prestroke location. Stroke in motor cortex causes an anterior shift of the mFL map (orange path in left), whereas stroke in sensory cortex causes a posteromedial displacement of sFL (blue path in right). D, Correlation between shifts in sFL and mFL. Error bars in this and all subsequent figures are SEM.
in the online-only Data Supplement) and were not significantly correlated with infarct volume. No significant sex differences were observed for changes in map area or motor output after stroke.

**Effects of Stroke on the Integrity of Motor Representations**

Given the modest size of the infarcts created by targeted photothrombosis, it is perhaps unsurprising that these small strokes did not cause gross changes in motor output or map area. Interestingly, however, we observed that motor maps frequently exhibited an abnormally scattered or diffuse structure after stroke (Figure 1). This effect was particularly pronounced after stroke targeted to sensory cortex (Figure 5A).

Because such changes in map structure may not be accurately reflected in a map’s center of gravity (Figure 2) or overall motor output (Figure III in the online-only Data Supplement), we generated a spatial autocorrelation index (Figure 5B) for all motor maps by calculating the correlation between pairs of pixel values (movement amplitude) separated by a given distance. Motor maps were more diffuse after motor-targeted stroke and especially after sensory-targeted strokes, with a decrease in correlation between neighboring pixels (Figure 5C and 5D). Local correlation was negatively correlated with infarct volume for sensory strokes (Pearson $r=-0.89$; $P=0.04$; $n=6$ mice) and motor strokes ($r=-0.71$; $P=0.04$; $n=8$ mice).

Motor maps were generated by stimulating cortical sites in a random spatial order, which raises the possibility that decreased spatial correlation after stroke arose from fluctuations in motor output over the course of an experiment. This was not the case, however, because performing linear regression on plots of cumulative motor output over the course of a mapping session revealed linear rates of motor output before and after stroke (Figure IV in the online-only Data Supplement). The diffuse structure of motor maps after stroke may instead be a manifestation of the ongoing reorganization of the underlying cortical circuitry, with the emergence of a new sFL map forcing mFL to either devote its neurons to a hybrid sensory/motor role or to become a mosaic of intermingled motor and sensory neurons (Figure 6).

**Discussion**

We have exploited the development of a new method for light-based motor mapping12 to perform the first longitudinal study of sensorimotor reorganization after targeted stroke. Strokes targeted to a portion of forelimb motor cortex caused decreased motor output from the infarcted region that was offset by peri-infarct hyperexcitability, but did not affect the position or excitability of the sFL map. Sensory stroke displaced sFL maps toward the center of the mFL map, causing modest
secondary displacement of mFL that was strongly correlated with the extent of sFL shift but less than the map displacement seen after strokes within mFL itself. After sensory-targeted stroke in particular, motor map structure exhibited a diffuse structure that was not explained by fluctuating levels of motor output within an experiment. These data suggest that motor cortex is able to host new sensory representations without abandoning its cortical territory, albeit at the cost of manifest alterations to the motor cortical network. This pattern of reorganization may differ after larger strokes, particularly if the entire sensorimotor cortex was destroyed.

Remapping of cortical function is closely related to behavioral recovery. In particular, recovery tends to be best in patients or animal models where reorganization occurs primarily within the perilesional cortex of the stroke-affected hemisphere, typically after incomplete lesions of motor cortex. Despite the fact that it does not produce a large penumbra, the photothermal model is well suited to studying delayed reorganization in peri-infarct cortex. We observed that both motor and somatosensory maps initially displaced from their original location typically came to occupy the peri-infarct region (Figure 2). After strokes in motor cortex, peri-infarct cortex became hyperexcitable (ie, generated larger movements on stimulation than were observed during the prestroke baseline period), thereby preserving overall levels of motor output (Figure 4; Figures II and III in the online only Data Supplement). Similar disinhibition of motor cortex occurs after stroke in human patients. In contrast to the increased peri-infarct excitability seen after strokes in motor cortex, sham-operated mice exhibited a uniform decrease in motor excitability throughout the map area (Figure 4). This could be because of either changes in the viability of the cranial window over time or the effects of repeated anesthesia and stimulation of the periphery (during sensory mapping) or cortex (during motor mapping). The decreased excitability of sham mice makes the peri-infarct hyperexcitability seen after motor stroke even more striking. This is the first study of its kind involving longitudinal light-based motor mapping and as such it will need to be compared with future experiments using alternate surgical preparations or stimulation parameters to further address this question.

The diffuse structure of motor maps after stroke, evidenced by their decreased local spatial correlation (Figure 5), has not previously been reported. Maps may be altered by the incorporation of new regions of cortical output that were masked by inhibition before stroke. Map area remains constant after stroke (Figure III in the online only Data Supplement), but this could reflect the addition of new, more distant regions to the map offsetting the loss of motor output from the area
of the infarct (Figure 4; Figure II in the online-only Data Supplement). Curiously, the diffuse motor map structure was most pronounced after strokes targeted to sensory cortex. This could be because of an expanded region of motor cortex devoted to mixed sensory/motor function (Figure 6). After stroke, this region may contain more neurons performing a dual sensory/motor role or an intermingled mixture of single-role neurons devoted solely to motor or sensory function. Either of these scenarios could account for the observation of diffuse motor map structure after stroke. Future studies could combine LBM with imaging of microscopic cellular structure and function after stroke to glean additional detail.

Strokes targeted to motor cortex caused an overall decrease in motor map area of ≈50% in the first week post stroke (Figure III in the online-only Data Supplement), but variability within groups prevented this trend from reaching statistical significance. In the cortical region immediately surrounding the infarct, motor output was significantly diminished (Figure II in the online-only Data Supplement) in the first month after stroke and recovered to baseline levels by 2 months. Motor output was not completely and permanently abolished from the vicinity of the infarct (Figures 1 and 4), perhaps because the infarcts were relatively small. It is possible that these small infarct volumes fostered plasticity by sparing the majority of sensorimotor cortex; larger lesions may result in reorganization predominantly within the contralesional hemisphere. Individual microinfarcts, such as those created in this study (≈0.2 mm³), may go unnoticed in a human brain, which is 3 orders of magnitude more massive than that of a mouse. If scaled directly, these infarcts would still be only ≈0.7 cm³ in a human, comparable with the lesion produced by a transverse hemispherectomy in a mouse. Transient ischemic attacks are known to cause increased cortical excitability in the affected hemisphere, which agrees with our findings. We chose not to create larger infarcts because they would be associated with elevated mortality rates; increasing the infarct size also decreases the amount of surviving cortex that can be studied within the limited area of the cranial window. In the future, bilateral studies of reorganization could take advantage of the spared hemisphere to expand the mapped area. Performing motor mapping in the hours or days after stroke may also reveal greater reductions in motor output.

We have demonstrated the feasibility of longitudinal sensorimotor mapping and characterized the spontaneous cortical reorganization that occurs in the absence of any intervention. It will now be possible to test the efficacy of preventative, protective, or rehabilitative therapies in the context of motor recovery, while monitoring the organization of sensorimotor cortex. Ultimately, these optimized rehabilitation strategies could be translated to humans to enhance recovery from stroke and other forms of brain injury. Acknowledgments We thank Cindy Jiang, MSc, for her assistance with surgery and animal husbandry.

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SUPPLEMENTAL MATERIAL

Displacement of sensory maps and disorganization of motor cortex after targeted stroke in mice

Thomas C. Harrison BSc, Gergely Silasi PhD, Jamie D. Boyd PhD, Timothy H. Murphy PhD

Department of Psychiatry and Brain Research Centre,

University of British Columbia, Vancouver, BC
Supplemental Methods

Animals and surgery

Channelrhodopsin-2 transgenic mice \(^1\) (line 18, stock 007612, strain B6.Cg-Tg(Thy1-COP4/EYFP)18Gfng/J) from Jackson Labs established a breeding colony. Anaesthesia was induced with isoflurane (1.5 % in air) and body temperature was maintained at 37˚C using a feedback-regulated heating pad. A craniectomy of approximately 5 mm by 5 mm was made over the right sensory-motor cortex using a dental drill. The craniectomy was sealed with a cover slip and dental acrylic \(^2,3\). Mapping was conducted weekly, with motor maps collected one day after sensory mapping. In cases where the windows became unsuitable for intrinsic imaging, motor mapping was also terminated and no additional data were collected after that time point.

Intrinsic optical signal sensory mapping

Mice were anesthetized with isoflurane (1% in air) and their heads immobilized in a stereotax while maintaining body temperature at 37 ˚C. After capturing an image of the cortical surface under 525 nm green light, we switched to 635 nm red light and focussed ~200 µm beneath the cortical surface to obscure artefacts from surface vessels. Images were acquired through a video macroscope (4.3 mm field, 8.4 µm per pixel) using a Dalsa M-60 camera and XCAP software (EPIX). We completed 20-40 imaging trials per experiment, with each trial consisting of 15 frames collected over 1.5 s preceding a tactile stimulus delivered by a piezoelectric device (1 s of 5 ms square pulses at 100 Hz) and 15 frames collected during and after the stimulus. Trials of contralateral forelimb and hindlimb stimulation were alternated, with 10 s between trials. Images were analyzed using an ImageJ plugin described previously \(^3\) to create an image of percentage change in 635 nm light reflectance. We applied a threshold at 66
% of maximal response amplitude to produce colour-coded maps of forelimb and hindlimb sensory cortex that could be overlaid onto the image of the cortical surface captured under green light. For analysis of sensory response profiles before and after stroke, 1mm diameter ROIs were placed in non-overlapping positions defined by the baseline positions of somatosensory forelimb (sFL) and motor forelimb (mFL) maps to plot percent change of reflectance over time. IOS maps could not be obtained at all time points; this is reflected in the number of mice included for each measurement.

***Light-based motor mapping and map analysis***

We used a scanning stage (ASI MS-2000) controlled by custom Igor Pro software (Wavemetrics) to direct a fixed 473 nm laser beam (Crystalaser, focused to 100 µm diameter, 10 ms pulses, 1-5 mW total or 127-635 mW/mm²) to an array of cortical sites (typically 13 x 13, with 300 µm spacing between sites). This process was repeated 3 times to obtain a mean value for each pixel of the map. Stimulation was delivered in a semi-random order with identical stimulus intensity for all sites within a map, with the requirement that sites within 750 µm of each other could not be stimulated consecutively. At each site, 500 ms of baseline movement data were collected before a 10 ms pulse was delivered and then an additional 990 ms of post-stimulus data were recorded. Movements were measured using laser range finders with µm sensitivity targeted to the forelimb and hindlimb (Keyence LK-081). Bracelets made of surgical tubing with a 12 mm diameter round cover slip glued to their sides were placed over the contralateral paws to provide a large, flat target for the laser range finders and to suspend the limbs slightly above the ground so that they could move freely along the axes of measurement of the range finders. In
order to exclude artifacts (e.g. from breathing or electrical noise), responses were considered to be
genuine only if their amplitude exceeded three times the standard deviation of the 500 ms pre-
stimulus period within 100 ms after stimulus onset. A single injection of ketamine/diazepam
(100/10 mg/kg) was administered at the beginning of the experiment. To minimize the possibility
of anesthetic complications, ketamine/diazepam was not supplemented during mapping. If
necessary, isoflurane (0.2-0.5 % in air) was administered to prolong anesthesia until completion
of the map. In some cases when suitable anesthetic depth could not be maintained, mapping was
terminated after a minimum of one map repetition but before all three repetitions were
completed.

Light-based motor mapping has been performed repeatedly within animals in the past \textsuperscript{4,5},
but never in experiments lasting months before and after experimental manipulations such as
stroke. We made several slight modifications to the mapping procedure originally published \textsuperscript{4} to
optimize the method for longitudinal experiments. This included increasing intervals between
mapping stimuli to 3 s and substituting ketamine/xylazine anaesthesia for ketamine/diazepam to
avoid epileptogenesis \textsuperscript{5}. We also found that regrowth of bone at the edges of cranial windows
was most pronounced along the medial edge of the window. Extending the cranial window
across the midline (i.e. an asymmetric bilateral window) greatly reduced the problem of
regrowth. Invariant landmarks in the cranial window (e.g. features of the cement sealing the
window and major blood vessels) were used as reference points to track map positions over time
and relate motor and somatosensory maps. Spatial autocorrelations were calculated by binning all
map pixel pairs according to the distance between them (in 300 micron bins) and then determining
the correlation value for the pixel pairs in each bin. Correlation was then plotted against distance to yield a correlogram.

**Histology**

After being deeply anesthetized with sodium pentobarbital, mice were transcardially perfused with 10 mL of 0.1 M PBS and then 10 mL of 4 % paraformaldehyde in PBS. The brain was dissected, immersed in 4 % paraformaldehyde for 24 hours, and then transferred to 30 % sucrose in PBS for 24 hours. A vibratome (Leica) was used to cut 100 µm sections, with every third section mounted for epifluorescence imaging. Infarct volumes were calculated by identifying the section where the area of the infarct was largest, and multiplying this value by the anterior-posterior extent of the infarct.
Motor Forelimb (mFL)

Sensory Forelimb (sFL)

Bregma (approx.)
Figure SI: Approximate positions of motor and somatosensory forelimb maps overlaid onto an image of the cortical surface acquired through a cranial window. Note that because the bone overlying the midline was removed during cranial window preparation, bregma was not visible in any of the animals and its position here is estimated.
Figure sII: Motor output is initially depressed in the immediate vicinity of the infarct, but recovers two months after stroke. Each line represents the percentage change in motor output relative to the baseline time period from cortical areas plotted according to their distance from the infarct. After both sensory (top panel) and motor (middle panel) stroke, motor output is decreased at sites within 300 µm of the infarct (asterisks denote p values from Bonferonni post-test against the baseline mean). In both cases, motor output was restored by 6-8 weeks post-stroke. Sham stroke caused no statistically significant changes in motor output.
A  
Overall motor map area

- sensory stroke n=8
- motor stroke n=8
- sham stroke n=8

B  
Overall motor output
Figure sIII: Overall motor excitability is conserved after stroke. A Motor map area, defined by the number of cortical sites capable of generating movement, is not significantly altered by stroke (2-way ANOVA p = 0.90, see Methods for details of criteria for identifying movement). B There were no significant group differences in normalized motor output (mean movement amplitude from all stimulus sites, 2-way ANOVA p = 0.14). Note that the two final time points (post-stroke weeks six and eight) are binned by averaging.
Figure sIV: Plots of cumulative motor output evoked by individual laser stimuli in a single mapping session. Each dashed line represents an individual animal’s mean from time points before (black lines) and after (red lines) sensory-targeted stroke. Thick, solid lines represent the group mean. Linear relationships indicate a constant rate of motor output and the slope represents the average movement amplitude. Performing linear regression on plots of cumulative motor output over the course of a mapping session revealed linear rates of motor output before and after stroke (sensory stroke $r^2 = 0.98 \pm 0.01$ vs. $0.99 \pm 0.01$ respectively, $p = 0.38$; motor stroke $0.99 \pm 0.002$ vs. $0.99 \pm 0.001$, $p = 0.07$; sham $0.98 \pm 0.001$ vs. $0.99 \pm 0.002$, $p = 0.24$, paired t-tests). There were no significant changes in the rate of motor output (sensory stroke $= 0.05 \pm 0.01$ mm per stimulus pre-stroke vs. $0.04 \pm 0.01$ post-stroke, $p = 0.65$; motor stroke $0.02 \pm 0.004$ vs. $0.02 \pm 0.005$, $p = 0.68$; sham $0.04 \pm 0.01$ vs. $0.03 \pm 0.007$, $p = 0.31$, paired t-tests).
Supplemental References:


