

Whisker motor cortex ablation and whisker movement patterns

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Abstract

Previous studies, based on qualitative observations, reported that lesions of the whisker motor cortex produce no deficits in whisking behavior. We used high-resolution optoelectronic recording methods to compare the temporal organization and kinematics of whisker movements before and after unilateral lesions of whisker motor cortex in rats. We now report that while the lesion did not abolish whisking, it significantly disrupted whisking kinematics, coordination, and temporal organization. Lesioned animals showed significant increases in the velocity and amplitude of whisker protractions contralateral to the lesions, as well as a reduction in the synchrony of whisker movements on the two sides of the face. There was a marked shift in the distribution of whisking frequencies, with reduction of activity in the 5–7 Hz bandwidth and increased activity at <2 Hz. Disruptions of the normal whisking pattern were evident on *both sides* of the face, and the magnitude of these effects was proportional to the extent of the cortical ablation. We suggest that the observed deficits reflect an imbalance in cortical inputs to a brainstem central pattern generator.

Key words: whisking, vibrissae, sensorimotor, CPG, pattern generation, rat

Introduction

The whisker motor system of rodents has several features that make it a useful model for studies of motor control. The whiskers tend to move in unison (Carvell and Simons, 1990; Gao *et al.*, 2001), whisker movements are constrained, primarily, to a single plane (Bermejo *et al.*, 2002), the whisker load is constant, and the system is further simplified by the absence of a muscle proprioceptor feedback loop. However, while the central neuronal circuitry of the whisker system has been well characterized anatomically (e.g., Miyashita *et al.*, 1994; Jones and Diamond, 1995) we know little about the contribution of its component structures to the control of whisking. Because exploratory whisking persists after sensory denervation (Welker, 1964), cortical ablation (Semba and Komisaruk, 1984), or decerebration (Lovick, 1972), it has been assumed that rhythmic whisker movements reflect the output of a central pattern generator (CPG). In support of this hypothesis is a recent demonstration that bilateral whisker deafferentation in adult rats does not disrupt the generation, patterning, or coordination of whisker movements (Gao *et al.*, 2001). We have also recently identified brainstem regions as the substrate for a putative whisking CPG (Hattox *et al.*, 2002). We further demonstrated that brainstem serotonergic neurons are necessary and sufficient to produce rhythmic whisker movements, and are thus likely to be an important component of the whisking CPG

(Hattox *et al.*, 2003). As in other rhythmic motor acts, the CPG is thought to contribute to generation of the basic whisking rhythm, which is then modulated by interactions with sensory input from the whiskers and with descending influences from more rostral central structures.

A prime candidate for such a modulatory function is the whisker motor cortex (wMCx)—a band of cortex immediately rostral to Bregma and lateral to the midline. Microstimulation in this region elicits whisker movements (Donoghue and Wise, 1982; Weiss and Keller, 1994). This region is linked to the whisker somatosensory map in SI by reciprocal and topographically organized intracortical connections (Izraeli and Porter, 1995) and, via collicular and brainstem structures, to vibrissal premotor and motoneurons (Miyashita *et al.*, 1994; Hattox *et al.*, 2002).

Whisker movements can entrain rhythmic activity in wMCx neurons (Kleinfeld *et al.*, 1999) and activity in wMCx neurons has been recorded during periods of exploratory whisking (Carvell *et al.*, 1996). However, unit responses in wMCx do not correlate in any simple manner with whisker movements. Further, previous studies report that cortical lesions that include the wMCx produce no obvious disruptive effects on large-amplitude, rhythmic (6–9 Hz) exploratory whisking (Welker, 1964; Semba and Komisaruk, 1984), suggesting that rhythmic whisking is generated by subcortical structures. In these studies, ablation effects were assessed using

only *qualitative* observational techniques. We have developed procedures that facilitate *quantitative* analysis by monitoring whisker movement trajectories in real time with high spatiotemporal resolution. A recent lesion study of whisker *somatosensory* cortex using these procedures revealed disruptions in whisking kinematics that had not been observed in previous ablation studies (Harvey *et al.*, 2001b). In the present study we monitored whisker movement trajectories of individual whiskers prior to and following wMCx ablation. We now report that *unilateral* ablation of wMCx disrupts the kinematics, bilateral synchrony, and rhythmicity of whisking, and provide preliminary data on the time course of recovery from these effects.

Materials and methods

Subjects, surgical and histological procedures

Experimental procedures were conducted in accordance with NIH guidelines for the care and use of experimental animals and were approved by an institutional animal use and care committee. Under ketamine/xylazine anesthesia, five adult female Long–Evans rats were fitted with a dental cement head mount positioned stereotaxically so as not to invade the skull area rostral to Bregma (see Gao *et al.*, 2001). Following recovery and behavioral testing to obtain baseline data on whisking patterns, a unilateral craniotomy was performed, under ketamine/xylazine anesthesia, to remove the skull overlying the motor cortex and to retract the dura. The location of the vibrissa representation within this region was verified by using microstimulation to elicit whisker movements (see Weiss and Keller, 1994). Unilateral aspiration of the physiologically identified cortical tissue was then performed (right hemisphere, $n = 3$; left hemisphere, $n = 2$) with care being taken not to invade the subcortical white matter. Following completion of surgery, the cavity was filled with Gelfoam® and the skin sutured over the exposed region. Following recovery and subsequent behavioral testing, subjects were perfused with buffered 4% paraformaldehyde, the brains were sectioned at 60 μm and Nissl-stained, and the lesion sites were reconstructed by a researcher blind to the behavioral data.

Behavioral procedures and experimental design

For testing, subjects were head-fixed and body-restrained (see Bermejo *et al.*, 1998). In each subject the movement trajectories of a pair of corresponding whiskers on the two sides of the face (e.g., the right and left C-1 whiskers) were monitored, *with all whiskers present*, in 30 min daily test sessions during which the rats were whisking in air. To reduce stress, water was delivered directly into the mouth at random intervals during the session, but water delivery was independent of the occurrence of whisking; i.e., subjects were never reinforced for whisker movements. Each session involved 30 s trials whose termination was defined by the occurrence of 2 s periods during which the house light was turned off and data were saved to disk. A PC controlled data acquisition and water delivery. Three sessions of preoperative testing were carried out 4 weeks after the initial fitting of the head mount. A second set of three sessions was carried out 72 h after the cortical ablation, and a third set of two sessions 6 weeks postoperatively.

Monitoring and kinematic analysis of whisker movement trajectories

Methods for the high-resolution monitoring of individual whisker movements in head-fixed rats are described in detail elsewhere (Bermejo *et al.*, 1998; Gao *et al.*, 2001). Briefly, whisking was monitored optoelectronically in the rostro-caudal plane using a pair of laser-emitter/CCD detectors positioned on each side of the face perpendicular to the axis of movement. Movements of a whisker across the detector array interrupts the emitter beam and produces a voltage signal in a subset of the CCD elements, whose

location is linearly related to whisker position. A comparator circuit identifies the successive positions of voltages above a preset threshold and outputs the data to a PC for the computation and display of a “whiskogram” which plots changes in the position of the whisker over time (see, e.g., Fig. 2A). Individual whiskers selected for analysis had protraction amplitudes between 1° and 110° (the upper limit of the CCD). For each whisker software algorithms calculated protraction onset, velocity, and peak amplitude. The data were then transformed to degrees and downloaded to a spreadsheet program for statistical and graphic manipulations.

Analyses were based on data collected during three time points: (1) the last preoperative session; (2) 72 h following the lesions; and (3) 6 weeks following the lesions. From each of these sessions we analyzed data from the first two, middle two, and last two trials for each subject. Kinematic analyses (protraction amplitude and velocity) were performed with in-house software and with Microsoft Excel. Time series data (power spectra, cross correlations, and coherence) were analyzed in Matlab (The MathWorks, Novi, MI) and Neuroexplorer (Littleton, MA). Cross-correlograms were constructed by calculating the correlation coefficients between bilateral whisker movements. Coherence—correlation between the spectral content of two signals as a function of frequency—was calculated in Matlab with the following equation:

$$C_{xy} = \frac{P_{xy}}{\sqrt{P_{xx} \times P_{yy}}}$$

where P_{xx} is the spectral density of whisker trajectories on one side of the face, P_{yy} is the spectral density of whisker trajectories on the other side, and P_{xy} is the cross spectral density of both these signals. Coherence values were used to construct coherograms, which depict the coherence of the two whisker movements evaluated at frequencies from 0 to 50 Hz over time. Statistical analyses were performed in SPSS and Microsoft Excel.

Results

Figure 1 shows drawings of a series of sections through the lesions illustrating the extent of the ablations in cases with small, intermediate, and large lesions (rats P02, P04, and P05, respectively). In all cases lesions were restricted to cortical layers I through VI, and none involved the subcortical white matter.

Recovery was uneventful and none of the rats exhibited any abnormal symptoms or signs of discomfort. *Qualitative* observations revealed no apparent differences between the whisking behavior of normal and lesioned animals or between whisker movements on the two sides of the lesioned animals. However, comparison of the preoperative and postoperative movement records indicated obvious changes in the whisking patterns. Figure 2A presents whiskograms of movements of the right and left C-1 whiskers during a single trial, before, and 72 h and 6 weeks following unilateral ablation of wMCx in rat P05. These representative examples demonstrate that the lesions affected whisking kinematics on *both sides of the face*, and reduced the synchrony of whisking of the corresponding whiskers. These findings are quantified below.

Bilateral synchrony

During whisking in air (without contacts) whisker movements on both sides of the face are highly synchronous. This synchrony can be quantified by computing the coherence in whiskograms recorded

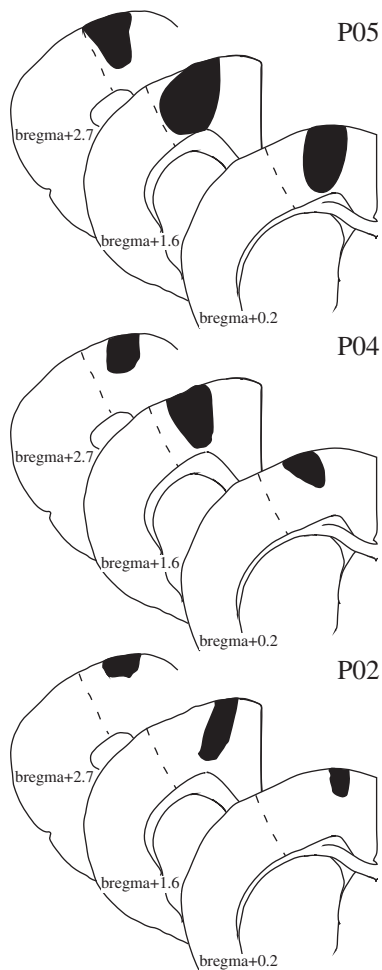


FIGURE 1. Drawings of coronal sections through the cortical hemisphere in three of the five animals, illustrating the extent of cortical damage in animals with small (P02), intermediate (P04), and large (P05) lesions. The lateral border of the histologically defined motor cortex is indicated by a broken line.

from corresponding whiskers (see Materials and methods). Figure 2B shows a coherogram (coherence plotted against whisking frequency over time) of bilateral whisker movements recorded during a long whisking epoch before and after cortical lesions in rat P05; in these analyses, a coherence of 1 represents perfect synchrony. In control recordings, there is a high coherence (near perfect synchrony) at whisking frequencies (≤ 20 Hz). By contrast, synchrony is severely attenuated 72 h after the cortical lesions (Fig. 2B). To quantify these changes we analyzed, for each animal, the coherence in bilateral whisker movements before, and 72 h and 6 weeks following the lesions. From each testing period we selected 100 whisking epochs, each lasting 3.5 s. A representative analysis is shown in Fig. 2C, which presents the mean \pm SD of coherence at frequencies ≤ 50 Hz, in animal P05. Seventy-two hours following the cortical lesion there was a significant ($p < 10^{-3}$; Mann–Whitney U-test) reduction in coherence at frequencies ≤ 20 Hz. Similar, statistically significant reductions in coherence at these frequencies occurred in all animals, 72 h following the lesions.

Six weeks following the lesion, coherence had returned to control levels.

To further illustrate lesion effects on whisking synchrony between ipsi- and contralateral whisker movements, Fig. 3 presents cross-correlograms for the three rats whose lesions are reconstructed in Fig. 1. These are based on data from complete testing sessions preoperatively, 72 h postoperatively, and 6 weeks following unilateral ablation of wMCx. Preoperatively, the cross-correlograms show main peaks centered about zero, with highly significant correlation coefficient values ($r = 0.45\text{--}0.70$; $p < 0.001$). There are smaller, symmetrical peaks at points corresponding to the dominant whisking frequency (5 Hz). Postoperatively, the correlation coefficients at both the 0 time lag and the side bands, though still apparent, were significantly ($p \leq 0.01$) reduced in four of the five rats (and in all of the rats shown in Fig. 3). This reduction was proportional to the lesion size (P05 > P04 > P02). Six weeks postoperatively there was a reversal of the reduction in these correlations, such that the correlations were indistinguishable ($p > 0.1$) from preoperative values.

These findings indicate that unilateral lesions of the wMCx result in significant, but reversible reductions in bilateral synchrony of whisking.

Protraction amplitude and velocity

In addition to reducing bilateral synchrony, cortical lesions affected the amplitude and velocity of individual whiskers (Fig. 2A). To quantify these changes, Figs. 4 and 5 present, for a single animal (P05), frequency distributions (left panels) and cumulative probability plots (right panels) of protraction amplitudes and velocities for the right and left C-1 whiskers. Preoperatively, individual protractions of these corresponding whiskers had similar amplitude and velocity distributions ($p > 0.02$; Kolmogorov–Smirnov test). Postoperatively, there were significant bilateral differences in both protraction velocities ($p < 10^{-3}$) and amplitudes ($p < 0.02$). These bilateral differences were due to significant ($p \leq 0.005$; Mann–Whitney U-test) *increases* in protraction amplitudes and velocities of whiskers *contralateral* to the cortical lesions, and significant ($p \leq 0.01$) *decreases* in these variables on the side *ipsilateral* to the lesions. Similar significant changes occurred in four of five animals, 72 h following the lesions. These results are reflected in the group data presented in Fig. 6 ($n = 5$ rats), which show that postoperatively, whisking amplitudes and velocities are significantly larger on the side contralateral to the lesion (amplitude, $p < 0.05$; velocity, $p < 0.01$). Such increases were seen in all but the animal with the smallest lesion (P02). Six weeks postoperatively, protraction amplitudes were still significantly larger for three of the animals ($p < 0.05$) while velocities remained significantly greater for four ($p < 0.002$).

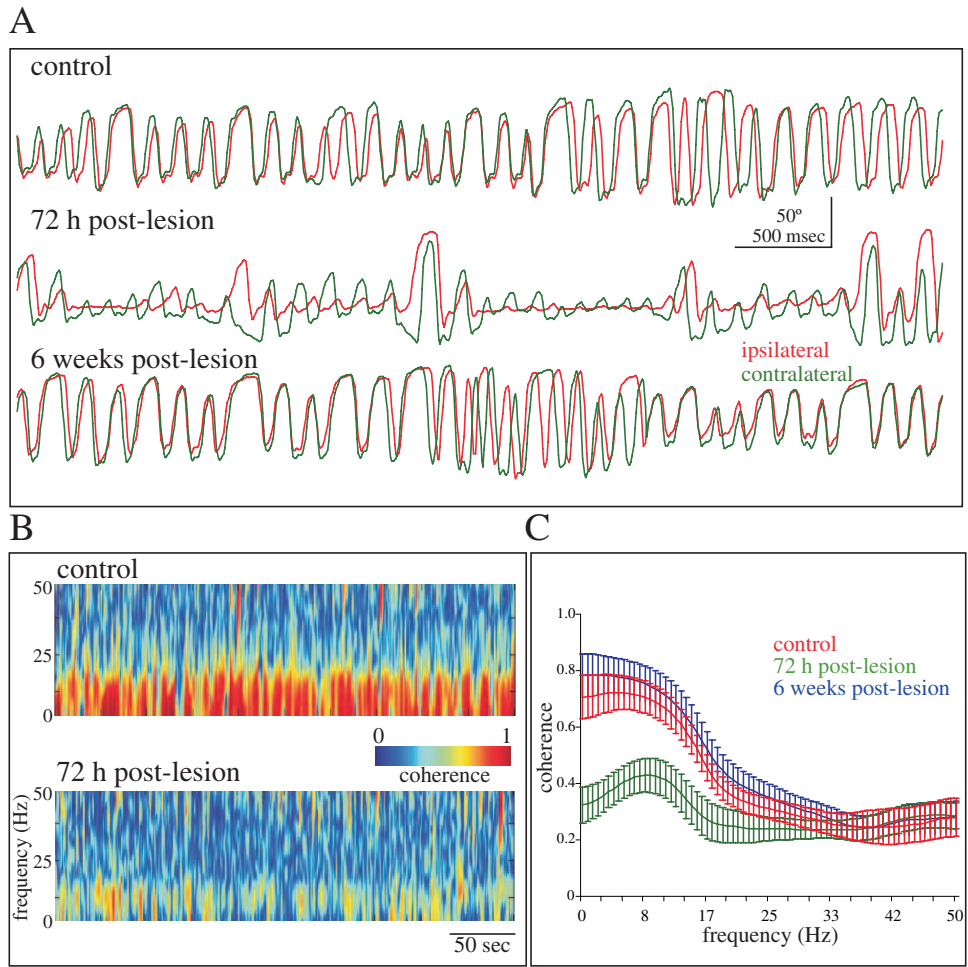


FIGURE 2. (A) Whiskograms illustrating movement trajectories generated by the right and left C-1 whiskers of animal P05 during single whisking epochs recorded preoperatively (control), and 72 h and 6 weeks following unilateral lesion of the right whisker motor cortex (wMCx). Protractions are plotted as upward deflections and retractions are plotted downwards. (B) Coherograms plotting the coherence in bilateral whisker movements, at 0–50 Hz, before (control) and 72 h following unilateral wMCx lesions. The means and standard deviations of these coherence values are plotted in (C), which also shows data recorded 6 weeks following the lesions. Note, in both (B) and (C), the significant reduction in coherence at frequencies ≤ 20 Hz, 72 h following the lesion, demonstrating that cortical lesions significantly disrupt bilateral whisking synchrony. This effect is reversed 6 weeks following the lesion (C).

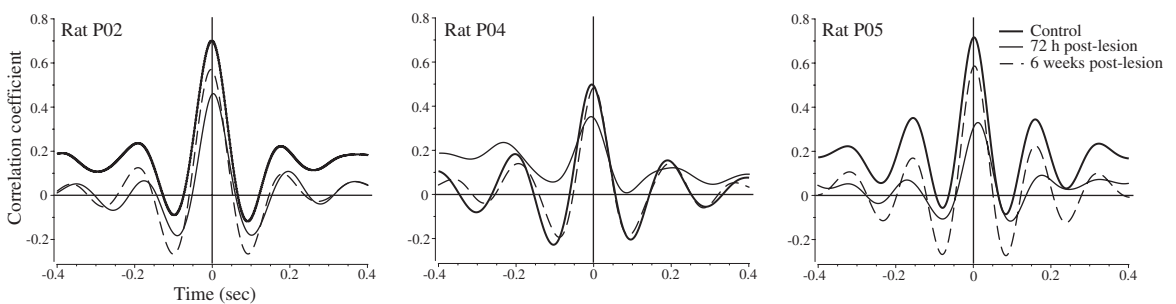


FIGURE 3. Unilateral whisker motor cortex (wMCx) lesions decrease the synchrony of bilateral whisker movements in the three animals whose lesions are reconstructed in Fig. 1. Shown are cross-correlograms of ipsi- and contralateral whisker movements recorded preoperatively (control), as well as 72 h and 6 weeks postoperatively. The peak correlation coefficients of whisker movements recorded 72 h following unilateral wMCx lesions were significantly decreased.

Whisking frequency

Cortical lesions also resulted also in significant, bilateral reductions in whisking frequency (Fig. 2A). To quantify this effect we computed power spectral density plots of whisker movements. Figure 7 presents a representative example of these plots, computed for rat P04 before, and 72 h and 6 weeks

following the lesions. Preoperatively, the whisking patterns of this animal, like the others, were characterized by a modal whisking rhythm with a peak between 4 and 7 Hz, and this rhythm was seen on both sides of the face. Postoperatively, there was a reduction in power at this bandwidth on *both sides* of the face, and increased activity at the low frequency end of the spectrum (≤ 2 Hz). This effect was

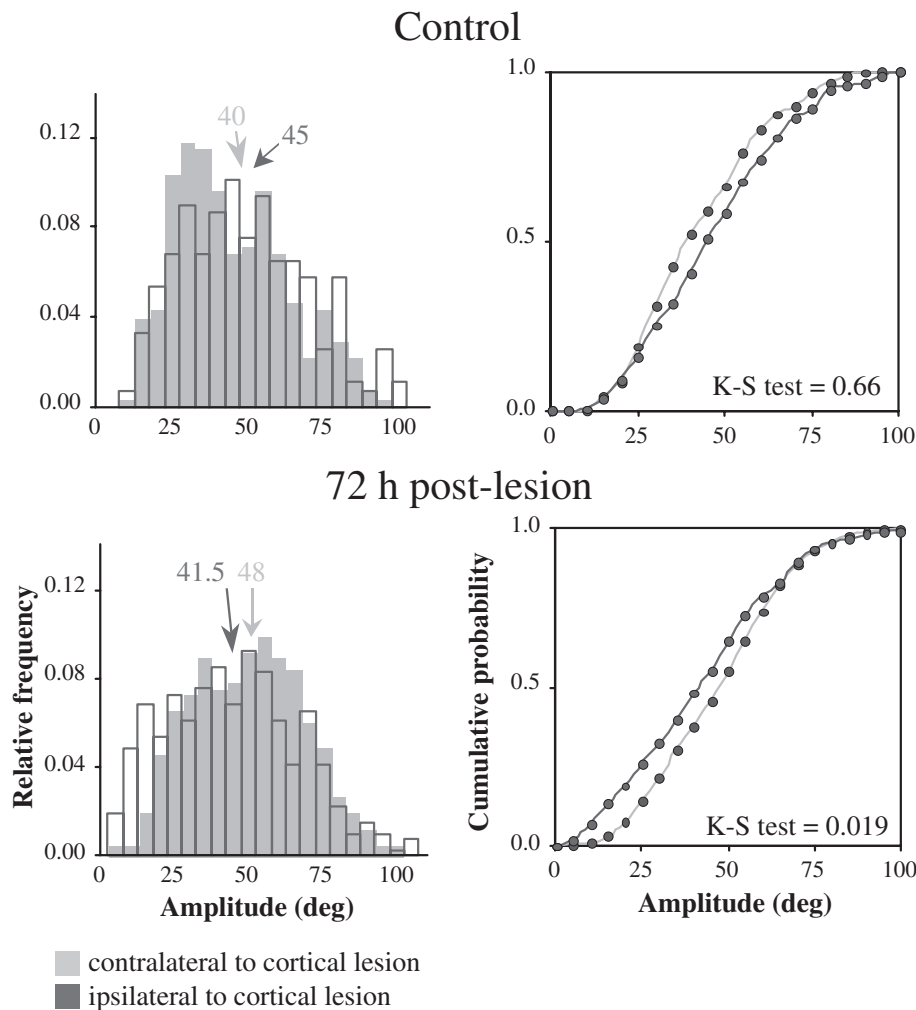


FIGURE 4. Frequency distributions (left column) of protraction amplitudes of corresponding whisker protractions recorded before (above) and 72 h after (below) a unilateral lesion of the right whisker motor cortex (wMCx) in rat P05. Arrows indicate the median values of each amplitude distribution. The right column shows cumulative probability distributions of protraction amplitudes. In control conditions, protraction amplitudes of corresponding whiskers are similarly distributed. wMCx lesion produces significant differences in protraction amplitudes, due to an increase in the amplitudes of contralateral protractions, and a decrease in the amplitudes of ipsilateral contractions. K-S test = Kolmorov–Smirnov test.

greatest *contralateral* to the lesion. Six weeks post-operatively these effects were completely recovered. Similar, significant ($p \leq 0.01$) reductions (22–35%) in the peak amplitudes of power spectral density plots were seen in four of the five rats.

Discussion

While most previous research on the rodent whisker system has focused on sensory processing (e.g., Jones and Diamond, 1995; Ahissar and Zacksenhouse, 2001) the challenge presented by its motor control mechanisms is complementary and equally formidable. The mystacial vibrissa of some rodents function as mobile sensors. They provide a continuous stream of information about environmental features encountered within the sensory penumbra created by the rhythmic, exploratory movements of the whisker array (Wineski, 1983; Carvell and Simons, 1990; Bermejo *et al.*, 2002). Contact with objects may elicit a shift in the whisking pattern, repositioning of the whisker pad, and modulation of whisker movement

parameters to provide more detailed information about object features. The effector system controlling the whiskers thus has three quite different functions: rhythm generation, control of pad position, and modulation of whisking parameters, and these functions must be integrated to maximize information flow within the animal's whisking space. Recent work from several laboratories has begun to focus on these motor control issues (Bermejo *et al.*, 2002; Kleinfeld *et al.*, 2002; Berg and Kleinfeld, 2003). The present study was designed to explore the contribution of the motor cortex to the control of whisking.

Although the whisker representation occupies a large region of the rodent cortical motor map (*c.* 30%), its role in motor control remains obscure. Previous reports, based on qualitative observations in freely moving animals, suggested that whisking remains intact after motor cortex ablation, but provided no quantitative data on ablation effects upon whisking kinematics or their temporal organization. Here we employed optoelectronic recording with

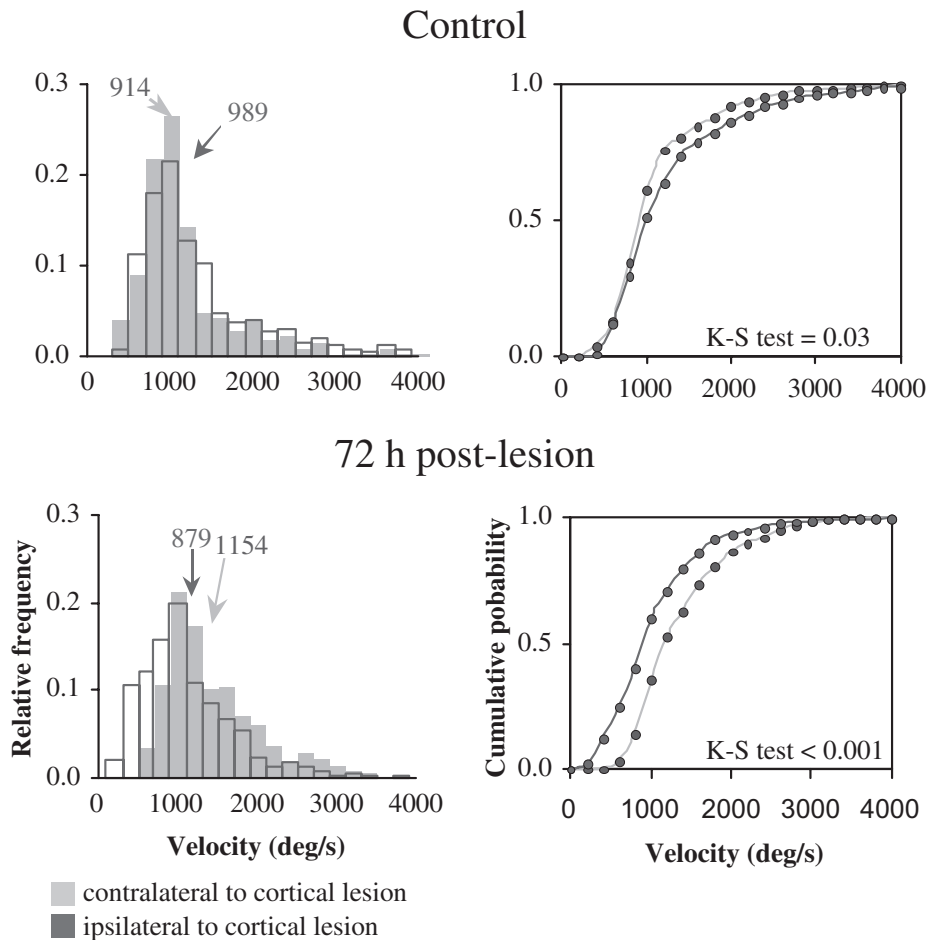


FIGURE 5. Frequency distributions (left column) of protraction velocities of corresponding whisker protractions recorded before (above) and 72 h after (below) a unilateral lesion of the right whisker motor cortex (wMCx) in rat P05. Arrows indicate the median values of each velocity distribution. The right column shows cumulative probability distributions of protraction velocities. In control conditions, protraction velocities of corresponding whiskers are similarly distributed. wMCx lesion produces significant differences in protraction velocities, due to an increase in the velocities of contralateral protractions, and a decrease in the velocities of ipsilateral contractions. K-S test = Kolmorov-Smirnov test.

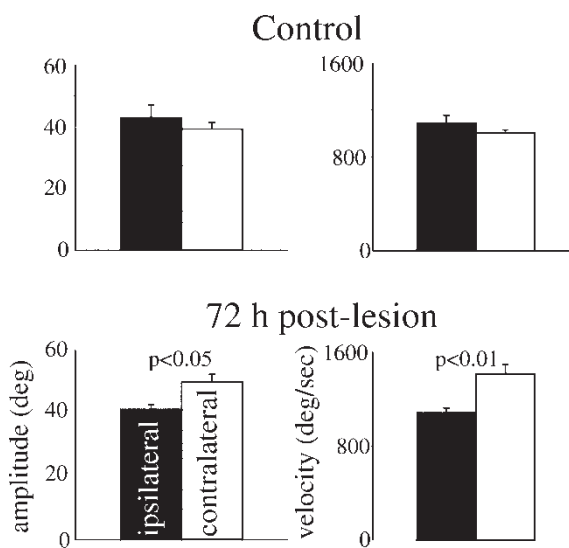


FIGURE 6. Group data, averaged from all five animals, showing the effects of a unilateral whisker motor cortex (wMCx) lesion on whisking kinematics. Comparisons of protraction amplitudes (left column) and velocities (right column) ipsilateral and contralateral to the lesion. wMCx lesions produce significant increases in both the amplitude and velocity of protractions on the side contralateral to the lesions.

high spatiotemporal resolution to monitor whisker movements under controlled conditions in head-fixed animals, before and after cortical ablation.

Our data were obtained in the absence of head or body movements, or of contact-generated vibrissal inputs (ex-afference), so that peripheral input to the whisker system originates from the whiskers' own rhythmic movements (re-afference). Under these simplified conditions, the sensorimotor circuitry mediating neural control of whisking is likely to involve, minimally, ascending trigeminal pathways, reciprocally connected sensory and motor cortices, brainstem pattern generating circuits, and facial motoneurons, each of which is present on both sides of the brain. Even in the absence of contact, whisker movements are known to provide a continuous flow of re-afference through the circuit to thalamocortical levels (Zucker and Weller, 1969; Brown and Waite, 1974). Since a major source of afferent input to motor cortex arises from somatosensory cortex (Farkas et al., 1999), the whisking patterns seen under the present conditions will reflect primarily the bilateral interactions of whisking re-afference with the properties of motor cortical output to the brainstem CPG.

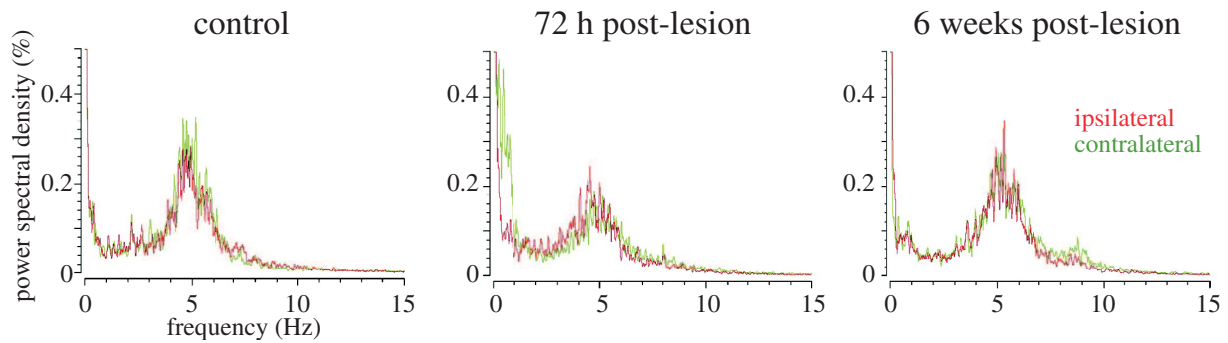


FIGURE 7. Power spectral density plots of whisking in animal P04 preoperatively (control), 72 h, and 6 weeks postoperatively. Data are normalized to the total power in the power spectral densities, and boxcar smoothed. Note the reduction, 72 h following the lesion, in the power at exploratory whisking frequencies (centered at 5 Hz), and the increase in power at frequencies ≤ 2 Hz. These effects are reversed 6 weeks following the lesions.

We now report that whereas *unilateral* ablation of wMCx did not abolish whisker movements on *either* side of the face, it disrupted both the spatial and the temporal organization of whisking behavior. In normal (head-fixed) animals whisking amplitudes are similar on the two sides, movements occur in phase, and a characteristic whisking rhythm is present. Lesioned animals exhibited a significant reduction in the degree of synchrony between whisker movements on the two sides of the face and significant increases in *both* the amplitude and the velocity of whisker protractions contralateral to the ablated side. The lesions resulted also in significant shifts in the normal distribution and power of whisking frequencies. The magnitude of these effects correlated with the extent of the ablation. Effects on whisking kinematics were primarily *contralateral* to the lesion but disruption of the normal whisking pattern was evident on both sides. Some degree of recovery was observed in all animals 6 weeks after the lesion.

The observation that unilateral wMCx ablation produces bilateral disruption, but that some effects were more marked contralateral to the lesion, is consistent with anatomical data. We recently reported that wMCx afferents terminate bilaterally in the brainstem, but that contralateral cortical inputs are more extensive (Hattox *et al.*, 2002). Differences between whisking amplitudes on the two sides of the face have also been reported after *unilateral* lesions of whisker somatosensory (“barrel”) cortex, although the direction of the difference could not be specified in that study (Harvey *et al.*, 2001b). Interestingly, *unilateral*, but not bilateral whisker deafferentation produces marked—though transient—effects on whisking patterns (Gao *et al.*, 2001). These observations suggest that the effects on whisking amplitude and velocity seen after unilateral cortical ablation may reflect an imbalance in cortical output to premotoneurons involved in the whisking CPG (see Hattox *et al.*, 2003). A clearer picture of the relation between sensory inputs to motor cortex and CPG activity might be obtained by combining motor cortex lesions with unilateral or bilateral whisker

deafferentation. Furthermore, the contribution of callosal connections to such interactions remains to be determined.

Carvell and Simons (1995) have shown that during tactile discrimination, whisker movement strategies are predictive of successful discrimination behaviors, suggesting precise (“voluntary”) control over whisking parameters. Reports from our laboratory demonstrating operant control of rodent whisking have shown that whisking has many of the characteristics of “voluntary” movements (Bermejo *et al.*, 1996; Gao *et al.*, 2003). Disruptions following motor cortex ablation, including changes in bilateral synchrony and whisking kinematics reported here, may significantly impair whisking functions dependent on cortical control. Studies of the effects of motor cortex lesions on operant control of whisker movements (Gao *et al.*, 2003) and on their contribution to discriminative behavior (Harvey *et al.*, 2001a) may clarify the role of this cortical region in the control of whisking.

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