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Brain Research 1057 (2005) 10 – 16
BRAIN RESEARCH
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Research Report

Reductions in interhemispheric motor cortex functional connectivity after muscle fatigue

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Accepted 25 June 2005
Available online 6 September 2005

Abstract

Muscle fatigue has been known to differentially affect the activation level of the primary motor cortices (MIs) of the brain's two hemispheres. Whether this fatigue-related decoupling influence on the motor cortical signals extends beyond the motor action to the after-fatigue-task resting state is unknown. This question can be addressed by analyzing functional connectivity (FC) of low-frequency oscillations of resting-state functional MRI (fMRI) signals of the MIs. Low-frequency oscillations (<0.08 Hz) have been detected in many fMRI studies and appear to be synchronized between functionally related areas. These patterns of FC have been shown to differ between normal and various pathological states. The purpose of this study was to examine muscle fatigue-induced resting-state interhemispheric motor cortex FC changes in healthy subjects. We hypothesized that muscle fatigue would create a temporary "disrupted state" in the brain, and would decrease resting state interhemispheric motor cortical FC. Ten healthy subjects performed repetitive unilateral handgrip contractions that induced significant muscle fatigue, with resting state fMRI data collected before and after the task. After excluding two subjects due to gross head motion, interhemispheric motor cortex FC was assessed by cross-correlating the MI fMRI signal time courses. We found that the number of significant interhemispheric correlations in the MI fMRI signals decreased significantly after the performance of the fatigue task. These results suggest that resting state interhemispheric motor cortex FC may be used as an index of recovery from fatigue.

Theme: Motor systems and sensorimotor integration
Topic: Cortex

Keywords: Muscle fatigue; Functional connectivity; Motor network

1. Introduction

When fatigue occurs due to prolonged voluntary muscle activities, the brain experiences a "disrupted" process not only in processing a large amount of sensory (fatigue) information, but also in forming continuously new descending commands to drive the fatiguing muscle to maintain desired muscle output. This assumption is supported by recent studies that reported substantial signal changes in a number of primary, secondary, and association cortical areas [19,21]. One observation made in these studies was that although muscle fatigue occurred only on one limb, both sides of the motor cortex (MI) exhibited signal alterations. For example, when human subjects sustained a maximal voluntary contraction for about 2 min, muscle output declined almost linearly but motor cortical fields on the left and right hemispheres showed an early increase-then-decrease pattern in the activation level [19]. During muscle fatigue induced by repetitive submaximal muscle contractions, the MI on both sides

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doi:10.1016/j.brainres.2005.06.078

exhibited a progressive increase of the activation level to maintain a given level of muscle force during most of the course of the task. However, the level of activation of the contralateral MI began to decrease while the ipsilateral MI activity continued to rise near the end of the task [21], indicating a fatigue-related disassociation of MI signals of the two hemispheres. Although these data demonstrate motor cortical signal adaptations during fatigue, it is unknown whether the effect of muscle fatigue on cortical activities lasts beyond the motor performance (i.e., during after-fatigue resting state). Given the observation of MI signal disassociation between the two hemispheres at the stage of severe fatigue, it is possible that the interhemispheric signal disassociation continues after the cessation of the fatigue task because recovery from fatigue does not occur immediately after the motor performance (review: [5]). This issue can be addressed by examining resting state low-frequency fMRI signal coupling between the two sides of the MIs before and after the performance of fatigue motor tasks.

Recent studies in functional MRI (fMRI) have shown slowly varying fluctuations that are temporally correlated between functionally related brain regions. These low-frequency oscillations (<0.1 Hz) seem to be a general property of symmetric cortices and have been shown to exist in the motor, auditory, visual, and sensorimotor systems, among others [2,4,11,22,25,26]. Thus, these fluctuations agree with the concept of functional connectivity (FC): a descriptive measure of spatio-temporal correlations between spatially distinct regions of cerebral cortex [7]. Several recent studies have shown decreased low-frequency correlations for patients in pathological states such as multiple sclerosis [23] or cocaine use [16]. Accordingly, low-frequency FC may be an important indicator of regular neuronal activity within the brain. The purpose of this study was to determine whether muscle fatigue would affect regular neuronal activities of the left and right MIs by evaluating the correlation of low-frequency (<0.08 Hz) fMRI signal fluctuations between the symmetrical MIs before and immediately after muscle fatigue. It was hypothesized that fatigue involving voluntary muscle activities creates a temporary "disrupted state" in the motor cortical regions, which is indicated by an altered interhemispheric correlation of the MI low-frequency physiological signals from normal state.

2. Methods

2.1. Subjects

Ten healthy right-handed male subjects (age = 32.3 ± 9.0 years) participated in the study. All experimental procedures were approved by the Institutional Review Board at Emory University. All subjects gave informed consent prior to their participation.

2.2. Fatigue motor task

Subjects performed repetitive right handgrips at 50% maximal voluntary contraction (MVC) level by gripping a bottle-like device [18,20]. Handgrip force was measured online by a pressure transducer connected to the device through a nylon tube filled with distilled water. The target level (50% MVC) was calculated based on the maximal grip force measured at the beginning of the experiment. Subjects performed the contractions by following visual cues (generated by a waveform generator [Wavetek Datron, San Diego, CA]) projected onto the screen above the subjects' eyes in the magnet. Each visual cue was a rectangular pulse that matched the profile (target amplitude for 50% MVC and desired duration of 3.5 s) of the desired handgrip contraction. The duration of each contraction was 3.5 s, followed by a 6.5-s inter-trial interval (ITI). The fatigue task lasted 20 min, with a total of 120 contractions performed by each subject. Immediately after the completion of the 120 contractions, the MVC handgrip force was measured again to determine the level of muscle fatigue. The 50% MVC level was chosen to fatigue the muscles within the 20-min time frame with the given length of contraction (3.5 s) and ITI (6.5 s).

2.3. Image acquisition

The fMRI experiments were performed on a 3 T Siemens Trio scanner (Siemens, Germany). Subjects were scanned using an EPI sequence to acquire resting state data before and after the fatigue task, described above. Resting state data were acquired using 10 oblique slices (parallel to a line connecting the anterior and posterior commissures), with an in-plane resolution of 3.44 mm × 3.44 mm, and slice thickness of 5 mm. Pulse sequence parameters were: repetition time (TR) = 750 ms, echo time (TE) = 35 ms, flip angle (FA) = 50°, and field of view (FOV) = 22 cm. The resting state data were acquired while the subjects were inactive (lying still with the visual fixation on the cross projected onto the screen above the eyes). The total scan time was 200 s before or after the fatigue protocol, with 280 images acquired. Based on prior experience [25,27], this gives adequate frequency sampling, while avoiding long scan times that lead to subject habituation/disaffect and possible head motion.

2.4. Connectivity analysis

Two subjects were excluded due to gross head motion. The remaining eight subjects' resting state fMRI data were first low-pass filtered (<0.08 Hz) to avoid unwanted artifacts (e.g., effects of the primary harmonics of the respiration and cardiac cycles), while preserving those frequencies contributing to FC [4,22]. Given our sampling

rate, the low-pass filter eliminates frequencies between 0.08 and 1.25 Hz, which in practice contains the primary harmonics of the respiratory and cardiac cycles [27]. Second, in each subject, the MIs in the two hemispheres were anatomically delineated by locating the precentral gyrus [30] and selecting the gray matter voxels in each cortex. This step was done in three slices for each subject that contained both ipsilateral and contralateral MIs for interhemispheric MI FC analysis. Third, the fMRI signal time course of each voxel in each MI (left and right side) was extracted and cross-correlated with the time courses of all other MI voxels (both left and right side) of the same slice. (The time course of a voxel represents signal changes of the voxel as a function of time. The duration of the time course was 200 s, corresponding to the total scan time.) Fourth, the number of significant positive correlations (using a $P < 0.05$ threshold) was then calculated and normalized to the total number of voxel pairs (from which pairwise correlations can be calculated), for both interhemispheric and ipsilateral correlations. This normalized connectivity measure was calculated for the three selected slices for all the subjects, and examined before and after the unilateral fatigue task to detect significant FC changes. Finally, the mean interhemispheric correlation maps were visually examined to determine fatigue-related changes in the resting-state correlation patterns. The maps were generated by averaging the interhemispheric correlation values on a voxel-by-voxel basis.

2.5. Statistical analysis

Pearson correlation analysis was used to determine the level of association in the fMRI signal fluctuations between signal time courses of voxels in each slice. The values of normalized connectivity of the eight subjects before and after the fatigue task were compared using a paired t test. In addition, the MVC handgrip force recorded immediately after the fatigue task was compared with that measured before the task using the paired t test to determine whether the MVC force declined after performing the fatigue task. A significant reduction in the MVC force is an indication of muscle fatigue because muscle fatigue is defined as an exercise-induced reduction in the maximal force capacity of the muscle [8].

3. Results

3.1. Fatigue-related handgrip force changes

The MVC handgrip force recorded immediately after the 20-min intermittent exercise protocol was significantly lower than that measured at the beginning (a 29% [±11%]

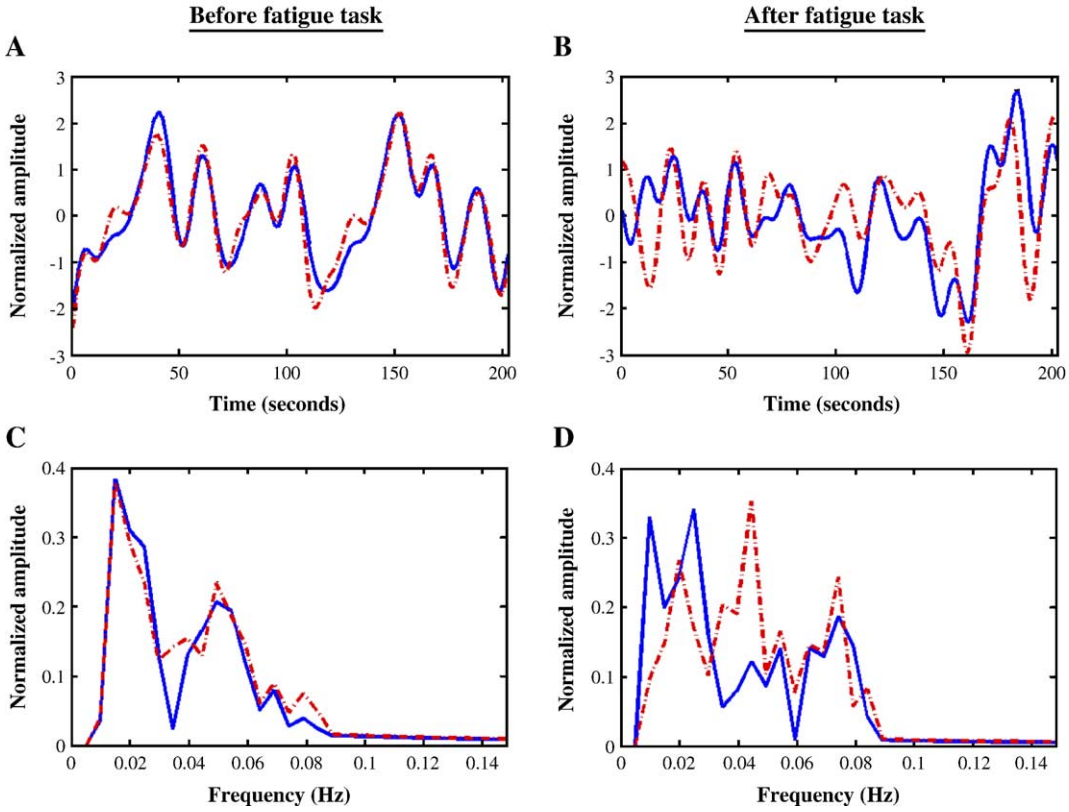

Fig. 1. Average time courses (A,B) and their corresponding power spectra (C,D, respectively) for the left (blue, solid) and right (red, dashed) motor cortices for a typical subject, before (A,C) and after (B,D) fatigue. The time courses and their corresponding frequency content are more dissimilar after the fatigue task, with the left and right motor cortices' time courses having a correlation of 0.95 before and 0.64 after the fatigue task.

Table 1
Correlation values between the left and right motor cortices' average time courses for each subject, averaged over all slices, before and after the fatigue task

Subject	Before fatigue	After fatigue	Difference
1	0.84	0.81	0.03
2	0.91	0.62	0.29
3	0.85	0.75	0.10
4	0.73	0.69	0.04
5	0.84	0.82	0.02
6	0.83	0.78	0.05
7	0.58	0.23	0.35
8	0.93	0.72	0.21

reduction, $P < 0.002$, for six of eight subjects, data for two subjects not available due to technical difficulties), indicating that significant muscle fatigue had occurred.

3.2. Resting state functional connectivity

Fig. 1 shows the average low-frequency signal time courses of the voxels located in the left (blue) and right (red) MI, before (A) and after (B) fatigue, for one subject (normalized to have zero mean and unit variance). Plots C and D illustrate the corresponding power of frequencies of the low-frequency resting state fMRI signals. The correlation of the time courses before fatigue was 0.95, whereas after fatigue it was 0.64.

Table 1 shows the average correlation between the left and right motor average time courses for all subjects. It can be seen that the correlation is reduced after the fatigue task, with a paired t test showing a significant difference ($P < 0.021$).

The normalized amount of interhemispheric correlation is shown in Fig. 2 for all subjects before (blue) and after (red) fatigue. The interhemispheric correlation decreased in seven of the eight subjects after the unilateral fatigue task. Table 2 displays the normalized correlation values for all subjects, for both interhemispheric and ipsilateral correlations. The difference in the normalized amount of correlation between the MIs of the two hemispheres before and after the fatigue task was statistically significant ($P < 0.004$). However, the ipsilateral correlations (left MI voxels with all other voxels on the left side of the slice, or right motor cortex voxels with all other voxels on the right side of the slice) did not change significantly ($P > 0.05$).

The changes in the interhemispheric connectivity can be seen in the individual mean interhemispheric correlation maps. Fig. 3A illustrates the mean interhemispheric correlation maps for subjects with significant patterns. Subjects 1, 4, and 5 did not have significant mean interhemispheric patterns either before or after fatigue, as reflected by their reduced normalized interhemispheric correlation values in Table 2. It can be seen that the displayed mean interhemispheric correlation in both cortices decreases after the fatigue task. There was a 72% reduction in the number of significant mean correlations ($P < 0.05$) from before fatigue across all subjects. This is shown in Fig. 3B, which is the histogram of the mean correlation values over all subjects before (red) and after (blue) fatigue.

4. Discussion

We have found that the interhemispheric low-frequency signal correlation in the primary motor cortices decreases

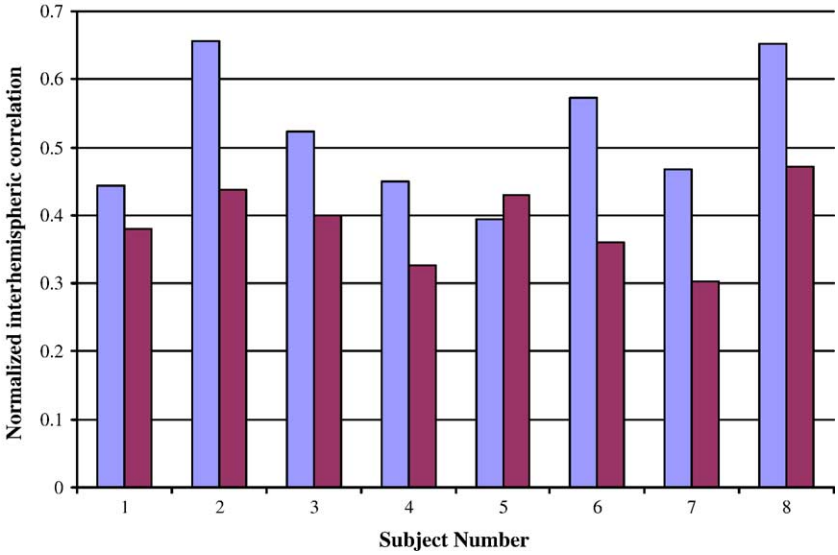

Fig. 2. Normalized amount of significant ($P < 0.05$) interhemispheric low-frequency fMRI signal correlation. The correlation in seven of eight subjects became lower after (red) compared with before (blue) the unilateral fatigue task.

Table 2
Normalized correlation values for both interhemispheric correlations between right and left cortices, and ipsilateral correlations for the right and left cortices separately

Subject	Interhemispheric		Right cortex		Left cortex	
	Before fatigue	After fatigue	Before fatigue	After fatigue	Before fatigue	After fatigue
1	0.44	0.38	0.43	0.34	0.45	0.38
2	0.66	0.44	0.63	0.45	0.70	0.68
3	0.52	0.40	0.46	0.47	0.54	0.37
4	0.45	0.33	0.43	0.40	0.38	0.37
5	0.39	0.43	0.39	0.41	0.42	0.40
6	0.57	0.36	0.53	0.26	0.52	0.40
7	0.47	0.30	0.45	0.46	0.46	0.50
8	0.65	0.47	0.70	0.50	0.60	0.55
Mean (SD)	0.52 (±0.10)	0.39 (±0.06)	0.50 (±0.11)	0.41 (±0.08)	0.51 (±0.11)	0.46 (±0.11)
Paired t test	$P < 0.004$		$P > 0.05$		$P > 0.05$	

after unilateral fatigue of finger flexor muscles. This study is the first to report fatigue-related changes in resting state FC of the two MIs. The results suggest that muscle fatigue not only affects cortical signals related to the descending command and processing of feedback (fatigue) information [19,21] during the fatigue task, but also influences the degree of correlation of the resting state signals of the motor areas of the two hemispheres. It seems that fatigue creates a temporary "disrupted state" in the MI that is indicated by reduced FC across the two sides of the brain. Reductions in the interhemispheric FC have been reported in patients with Alzheimer's disease [17] and multiple sclerosis [23] and also in cocaine addicts [16].

It is not clear exactly what factors contributed to the fatigue-related declines in resting state FC between the MIs. A reasonable surmise is that the MI contralateral to the performing limb was fatigued more than the ipsilateral MI during the task performance [21] and the effect of fatigue on the motor network lasted beyond the duration of the motor task. Studies using magnetic stimulation of human MI have reported that after unilateral fatigue of limb muscles, the contralateral MI excitability decreased significantly and the depression of the excitability lasted many minutes after the cessation of the fatigue task [3,24,28]. If the neurons on one side of

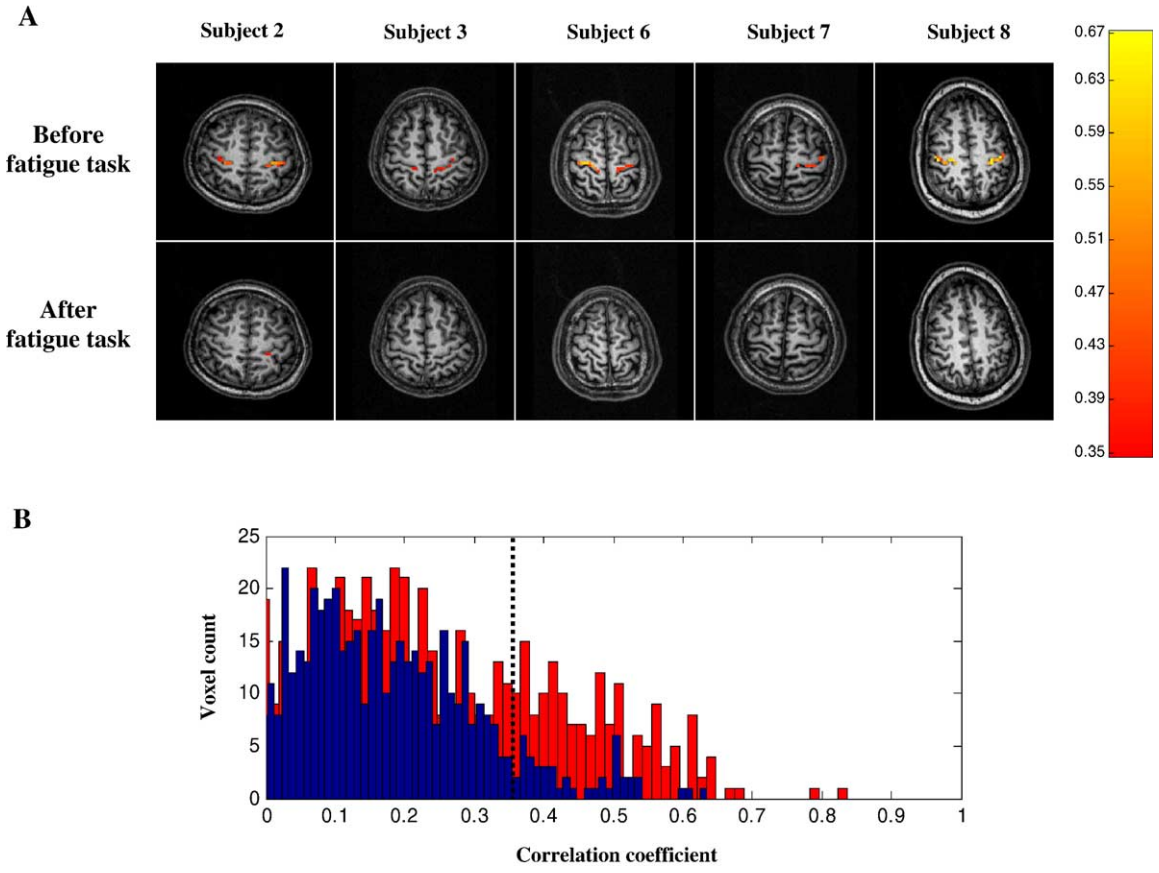

Fig. 3. (A) Comparison of mean interhemispheric correlation for each voxel in the motor cortex in five of the eight subjects before (top) and after (bottom) the fatigue task. The color bar indicates the corresponding mean correlation coefficient, with a lower threshold of $P < 0.05$, positive correlation. In four of the five subjects, no significant mean interhemispheric motor cortex correlation was found after the fatigue task. For the subject who showed significant after-fatigue interhemispheric cortex mean correlation (left column), the number of significant voxels was reduced significantly. (B) Histogram of the mean interhemispheric correlation values over all subjects. The dashed line corresponds to the significance threshold of $P < 0.05$. The number of significant correlations decreases after the fatigue task.

the MI are less excitable than the ones on the other side, the activation patterns (e.g., timing and amplitude) of the neurons can be affected. The unilateral activation pattern changes may influence the level of signal correlation with the neurons on the other side.

Two mechanisms might contribute to the fatigue-related changes in the activity or excitability of the MI. One is fatigue-related inhibitory input to the MI neurons. One source of such inhibitory input might be from group III and IV afferents that carry pain and other sensory information to the central nervous system. Increased inhibition from group III and IV afferents to alpha motor neurons in the spinal cord during muscle fatigue has been reported previously [9,10,12]. It is likely that the inhibitory input to the motoneuron pool in the spinal cord also projects to the output neurons in the motor cortex through ascending pathways and changes output signals of these cells. The inhibition effect on spinal cord motoneurons could last for minutes after the completion of the fatigue motor task [1].

Another mechanism that might alter MI neuron output is motoneuron intrinsic adaptation as a result of sustained stimulation. Motoneurons of cat subjected to constant intracellular or extracellular current injection exhibited significant reductions in the discharge rate of these neurons [14,29]. Since the output neurons during the unilateral fatigue task sustain lengthy activation, they may undergo intrinsic property changes that primarily alter the ipsilateral signal output. These changes in the ipsilateral side could then affect the relationship with the activities of the contralateral neurons.

Other dynamic changes besides unilateral fatigue may affect the interhemispheric connectivity before and after the muscle contraction task. Specifically, effects such as habituation and learning may alter functional connectivity in the motor network [6]. Investigations using both unilateral and bilateral tasks, along with measures of motor learning [15], may help further elucidate the interplay between these different dynamic mechanisms.

The present results may be extended in several ways. While a previous study has shown evidence relating functional connectivity to BOLD-related neuronal activity [25], the brain physiology linking neuronal activity to BOLD-related effects may be altered during fatigue. Thus, future work will include measures of CBF/CBV, in order to look at possible fatigue-induced physiological changes that could affect the resting-state BOLD signal by increasing/decreasing the signal relative to noise and thus increase/decrease the correlation significance. Additionally, concurrent recordings of both signal and noise sources will be undertaken: EMG recordings of the muscle activity will be used in order to further explore the functional consequences of muscle fatigue [19] and the cardiac and respiration waveforms of the subjects will be collected in order to remove their effects in post-processing [13].

Acknowledgments

The authors would like to thank Robert Smith for assistance in data acquisition. This study was partially supported by NIH (NS37400, EB002009) and Department of Defense (DAMD17-01-1-0665) grants and by the Risman R&D Fund at The Cleveland Clinic Foundation.

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