RESEARCH ARTICLE

Reduced functional activation after fatiguing exercise is not confined to primary motor areas

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Abstract We have previously shown that following a period of unimanual fatiguing exercise, there is a reduction in primary sensorimotor cortex (SM1) activation with movement of either the fatigued or the non-fatigued hand by Benwell et al. (Exp Brain Res 167:160–164, 2005). In the present study we have investigated whether this reduction is confined to motor areas or is more widespread. Functional imaging was performed before and after a 10-minute fatiguing exercise of the left hand (30% of maximum handgrip strength) in seven normal subjects (4 M, mean age 25 years). The activating task was a handgrip against a low resistance (1 kg) in response to a visual cue (chequerboard reversal every 2 ± 0.5 s). We compared activation in SM1, supplementary motor area (SMA), cerebellum (CB) and primary visual cortex (V1) before and after the fatiguing exercise. After exercise, contralateral SM1 activation was reduced by 33% ($P < 0.05$) compared to baseline for the fatigued hand and by 49% for the non-fatigued hand ($P < 0.05$). A similar pattern was seen for the bilateral SMA and ipsilateral CB following exercise (45 vs. 50% for SMA; 30 vs. 35% for CB; fatigued versus non-fatigued). Activation was also reduced in V1 but to a lesser extent than in motor areas (19 vs. 24%; fatigued versus non-fatigued). These results show that although the reduced functional activation during the recovery period after fatiguing exercise is more marked in motor areas, it also extends to non-motor areas such as the visual cortex, suggesting that there are more widespread changes in cerebral haemodynamic responses after fatigue.

Keywords Functional imaging · Fatigue · Cerebral haemodynamics

Introduction

Previous studies employing transcranial magnetic stimulation (TMS) have shown that fatiguing exercise is accompanied by changes in the level of excitability and inhibition in the primary motor cortex (Taylor et al. 1996; Sacco et al. 1997, 2000), which are thought to represent central adaptive changes to peripheral fatigue and to changes in the dynamics of muscle contraction and afferent inputs (Benwell et al. 2006). In addition, following the completion of a fatiguing motor task there can be a sustained reduction in the amplitude of the motor evoked potential (MEP) recorded from the exercised muscle (Brasil-Neto et al. 1993; Sacco et al. 2000; Benwell et al. 2006) indicating that corticospinal excitability is reduced, although there is no deterioration in motor performance during this period (Lazarski et al. 2002; Humphry et al. 2004). Little is known about the adjustments in cerebral haemodynamics that accompany these changes in excitability and inhibition after fatiguing exercise.

We have previously shown that following a period of fatiguing exercise of the hand there is a reduction in the functional magnetic resonance imaging (fMRI) signal in the contralateral motor cortex when a motor task is performed, not only by the fatigued hand but also by the non-fatigued hand (Benwell et al. 2005). This

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reduction was found to be associated with an increased variance of the fMRI signal and it was suggested that this could explain the bilateral reduction in the measured signal. However, another explanation is that following fatiguing exercise there are changes in neurovascular coupling and cerebral haemodynamic responses that may affect the fMRI signal and it is possible that such changes may not be confined to motor areas.

To investigate this possibility, we have compared the functional activation in primary sensorimotor cortex (SM1), supplementary motor area (SMA) and cerebellum (CB), and in the primary visual cortex (V1), during a visually-cued hand grip task performed before and after a period of fatiguing hand exercise.

Methods

Subjects

With the approval of the Human Research Ethics Committee of the University of Western Australia and in conformity with the standards set by the Declaration of Helsinki, seven subjects (4 M, 23–36 years of age, six right and one left-hand dominant) gave written informed consent to participate in this study.

Handgrip device

The thumb was isolated from the other fingers of the hand by a plastic padded bar which lay across the palm of the hand (Fig. 1). Subjects pulled on a lever with their four fingers towards the bar (distance 30 mm). The load subjects pulled against was determined by a set of interchangeable springs (1–30 kg) attached to the opposite side of the lever. Fibre optic cables were located 5 mm into the start and the end of the movement range and were digitised by a PC outside of the scanner. These cables detected the onset of the movement, the duration and end of movement. From this we obtained behavioural measures of reaction time, squeeze time and release time, before and after the fatiguing exercise. There were two separate handgrip devices constructed, one for each hand.

Visual stimulus

Subjects viewed a screen through an adjustable angled mirror system attached to the head coil. The visual stimulus was a black and white half-field chequerboard that reversed unpredictably every 2 ± 0.5 s. Subjects were told to fixate on a small red circle in the centre of
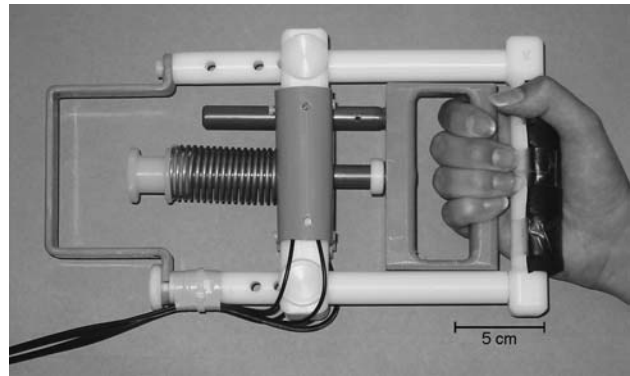

Fig. 1 Handgrip device. Subjects pulled on the lever against a resistance determined by an interchangeable spring. Fibre optic cables detected the start and end of movement and were digitised by a PC outside of the scanner

the screen at all times, to produce activation in the left or right V1 according to the half-field stimulated.

Motor task

Subjects alternated squeezing each hand, with the handgrip device, according to the hemi-field stimulated (left visual field chequerboard corresponded with a left hand squeeze and right visual field chequerboard with right hand squeeze, fixation point alone signalled for both hands to be at rest). Subjects were told to respond to the reversal of the chequerboard by squeezing the handgrip as quickly as they could against a low-resistance (1 kg spring load for both hands). Subjects were given time to practice the task before the study commenced.

Functional imaging

Subjects lay supine within the bore of a 1.5 T Siemens Magnetom Vision Plus scanner, with the head held in a bi-temporal clamp. Functional imaging was performed with a blood oxygen-level dependent (BOLD) gradient-recalled echo-planar sequence (90° flip angle, TR = 4 s, TE = 66 ms, 34 slices, 3 mm thick, 1 mm gap, 4×4 mm in-plane resolution, sagittal orientation, whole brain coverage). T1-weighted anatomical images were acquired with a MPRAGE sequence (1 mm³ iso-voxel resolution).

During functional imaging subjects performed alternating 24 s blocks of rest or the visually paced motor task of the left or right hand, each block comprising six whole brain acquisitions (data sets). A total of 15 blocks were acquired, interleaving rest, with right hand and left hand blocks in the order: rest, right, left, rest, left, right, etc. for a total of five blocks for each of the three conditions. This resulted in 30 data sets for each condition.

Two pre- and two post-exercise functional imaging runs were performed, with the above mentioned visually paced motor task. The first post-exercise run was performed immediately after the fatiguing exercise of the left hand (post-exercise 1), and the second run commenced 1 min after the end of the first post-exercise run (post-exercise 2). Subjects remained in the scanner during the fatiguing exercise.

Fatiguing exercise

For the fatiguing exercise, the spring resistance in the handgrip of the left hand was increased to ~30% of maximum handgrip force (measured using a hand-held dynamometer; average spring load ~8 kg). Subjects squeezed the handgrip for 3 s followed by 2 s rest (text cues signalled for subjects to squeeze and release). This cycle was repeated for ~10 min.

Force

The fatiguing exercise was repeated outside the scanner on a separate occasion for which maximum force measurements (hand-held dynamometer) were taken from the left and right hand before exercise, immediately after the fatiguing exercise and at 6 and 12 min post-exercise (in order to correspond with the timing of the two post-exercise imaging runs).

Data analysis and statistics

Image generation

For each acquisition block (comprising six data sets), the first two sets were omitted from the analysis to allow for the delay in the BOLD signal. Functional images were generated from the remaining 20 data sets in each condition comparing the rest and active phases, on a voxel-by-voxel basis, using Student's *t*-test with a significance level of $P < 0.001$ (*t*-score > 2.7; 38 *df*; Thickbroom et al. 1999). Images were filtered to remove any significantly activated voxels that were isolated (i.e. with no significantly activated neighbours).

Data analysis

Analysis was performed on four regions of interest (ROI) relevant to the visuomotor task (SM1, SMA, CB and V1). The ROIs were drawn manually on the T1-weighted anatomical image. For the SM1, the ROI encompassed voxels lying within and around the gyri directly anterior and posterior to the central sulcus in the hemisphere contralateral to the moving hand. The

ROI for the SMA included voxels lying bilaterally in the medial wall above the cingulate gyrus and between the anterior and posterior commisures. For the CB the ROI included all voxels activated in the ipsilateral lobe (incorporating the superior and inferior representations; Thickbroom et al. 2003). The V1 ROI incorporated activated voxels in the gyri immediately superior and inferior to the calcarine fissure in the occipital pole on the side contralateral to the stimulated hemi-field.

The total number of activated voxels was measured by incorporating data within the ROIs from all slices in which there was activation. The magnitude and percent signal change for each significantly activated voxel was also determined.

Statistical analysis

The number of voxels activated in each cortical region was compared at each of the four time points (two pre-exercise, two post-exercise) for both hands (left, right) using a two-way repeated measures ANOVA and post-hoc Student's *t*-tests incorporating Tukey's HSD correction for multiple comparisons (two-tailed, $P < 0.05$). The first two pre-exercise runs were used to test for reproducibility and the second pre-exercise run was used thereafter to compare to the post-exercise runs.

This analysis (two-way ANOVA; hand × time) was repeated for the force data (four time levels: pre-exercise, immediately post-exercise, post 1 and 2) and behavioural data (two time levels: pre-exercise, post-exercise). Force data is shown as a percentage of baseline. All data are presented as group mean ± standard error of the mean (SE).

Results

Force

The exercise was fatiguing as maximum voluntary handgrip force of the fatigued hand was reduced to 74 ± 5% of baseline immediately after exercise ($P < 0.05$, Fig. 2). Force in the fatigued hand had recovered by minute 6 post-exercise (95 ± 4%, $P > 0.05$, Fig. 2). The maximum voluntary force in the non-fatigued hand did not alter during the study ($P > 0.05$; Fig. 2).

Behavioural data

Pre-exercise reaction, squeeze and release times were comparable between the left and right hands ($P > 0.05$) and were 240 ± 6, 50 ± 4 and 60 ± 4 ms, respectively (pooled left and right hands). There was no significant
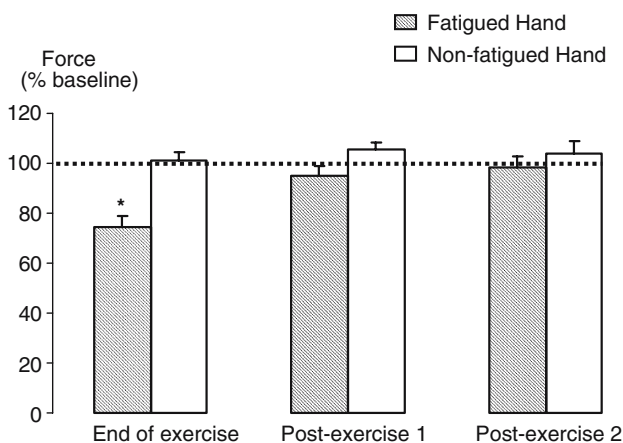
Fig. 2 Maximum voluntary force of the fatigued and non-fatigued hand. Results are mean force ± SE(% baseline). Maximum handgrip force was reduced immediately after unimanual fatiguing exercise of the left hand and had returned to baseline values by the end of the first post-exercise period. Force did not change in the right hand (*$P < 0.05$)

Table 1 Post-exercise performance measures of the motor task with movement of the fatigued and non-fatigued hand. All times are shown as mean ± SE (ms) during the first post-exercise run (as a percentage of pre-exercise)

| | Post-exercise (% pre-exercise) | |
	Fatigued hand	Non-fatigued hand
Reaction time	97 ± 4.1	98 ± 7
Squeeze time	113 ± 16	98 ± 5
Release time	100 ± 10	106 ± 7

change in these times from pre-exercise values, for either hand, after the unimanual fatiguing exercise of the left hand ($P > 0.05$, Table 1).

Functional imaging data

Primary sensorimotor cortex

There was no significant difference in activation (number of voxels) in SM1 during the two pre-exercise runs with movement of either hand (Left hand: 44 ± 8 vs. 45 ± 5, $P > 0.05$; Right hand: 34 ± 4 vs. 35 ± 6, $P > 0.05$). Movement of the non-dominant hand produced greater activation, on average, by ten voxels than the dominant hand ($P < 0.05$, Table 2).

With movement of the fatigued hand the number of significantly activated voxels was reduced in SM1 during the first post-exercise run (from 45 ± 5 to 30 ± 4, $P < 0.05$, corresponding to a reduction in volume of 0.72 cm^3, Figs. 3, 5). During the second post-exercise run activation was still reduced, although not significantly (32 ± 7 voxels, $P > 0.05$, Fig. 3).

Likewise, with movement of the non-fatigued hand activation of SM1 was reduced immediately after exercise (from 35 ± 6 to 18 ± 5 voxels, $P < 0.05$), and this reduction was sustained during the second post-exercise period (17 ± 4 voxels, $P < 0.05$, Fig. 4). The percentage decrease in activation during the first post-exercise period, compared to pre-exercise, was greater for the non-fatigued hand than the fatigued hand (49 vs. 33%, respectively; Table 2).

The magnitude and percentage signal change of the activated voxels in SM1 did not change significantly from pre-exercise values following fatiguing exercise (Table 3).

Supplementary motor area and cerebellum

Activation was significantly greater with movement of the non-dominant hand than the dominant hand in the SMA ($P < 0.05$) but not for the CB. The number of activated voxels during the first two pre-exercise runs was similar in the SMA and likewise for the CB (Figs. 3, 4).

With movement of the fatigued and non-fatigued hands the number of significantly activated voxels after exercise was reduced in the SMA (fatigued hand: from 40 ± 5 pre-exercise to 22 ± 8 post-exercise, non-fatigued hand: from 30 ± 4 pre-exercise to 15 ± 6 post-exercise, $P < 0.05$, Figs. 3–5). The SMA activation remained significantly reduced during the second post-exercise run ($P < 0.05$, Figs. 3, 4). Similar to SM1, there was a greater post-exercise reduction with movement of the non-fatigued hand than the fatigued hand (50 vs. 45%, respectively, Table 2).

On average, activation in the CB was approximately ten voxels less than the activation measured in the other motor areas. The number of voxels activated in the CB was reduced with movement of the fatigued hand, although not significantly, during the first post-exercise period, (from 30 ± 4 pre-exercise to 21 ± 5 post-exercise, $P = 0.066$, Figs. 3, 5) and was signifi-

Table 2 The number of activated voxels and percentage reduction in voxel number after fatiguing exercise. Results are mean number of voxels ± SE and percentage reduction in voxel number for the first post-exercise run (as a percentage of pre-exercise)

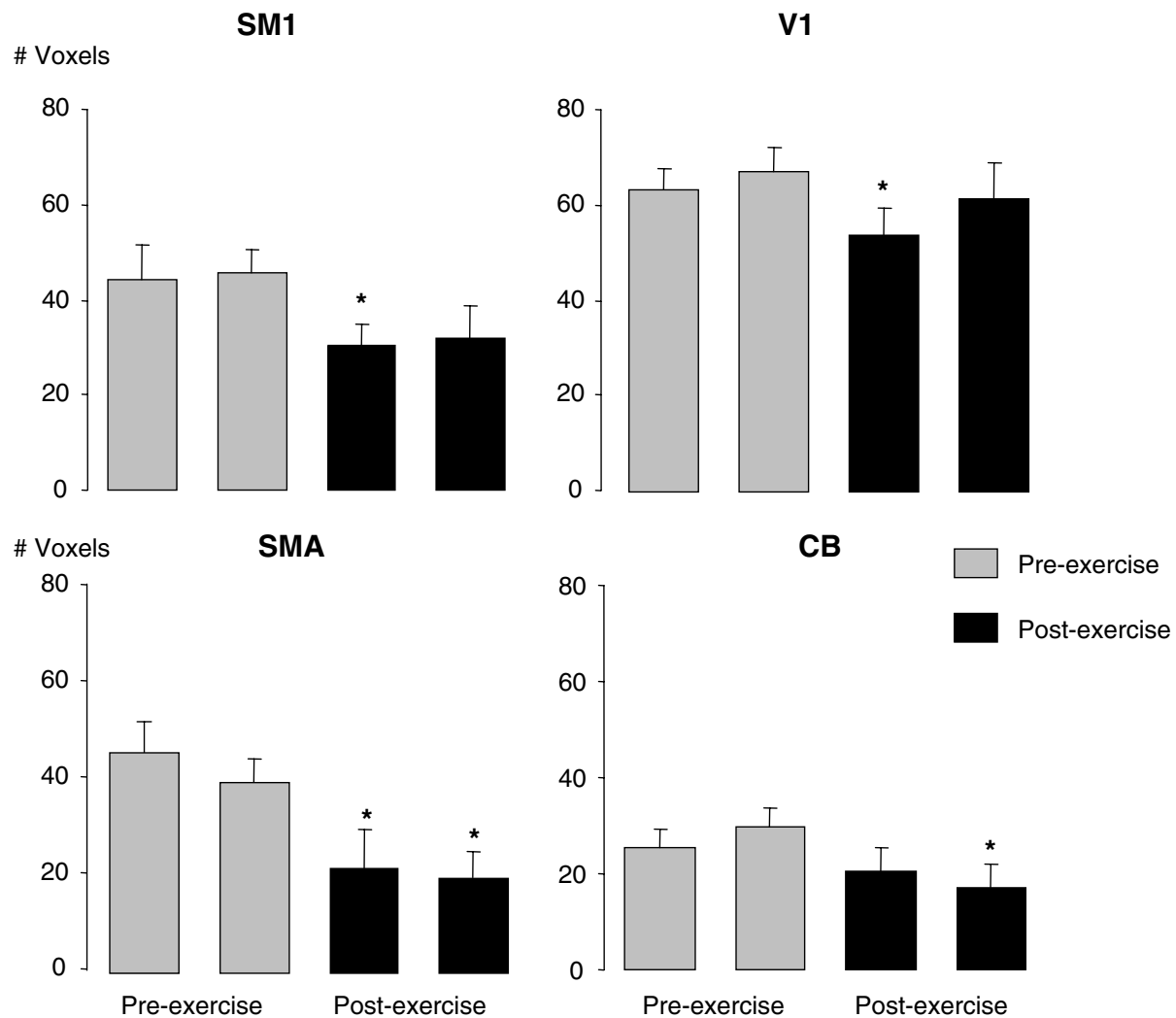| | Fatigued hand | | | Non-fatigued hand | | |
| | No. voxels | | Δ (%) | No. voxels | | Δ (%) |
	Pre 2	Post 1		Pre 2	Post 1	
SM1	45 ± 5.3	30 ± 4.3	33	35 ± 6.1	18 ± 4.5	49
SMA	40 ± 5.4	22 ± 8.3	45	30 ± 4.3	15 ± 6.5	50
CB	30 ± 4.1	21 ± 4.6	30	23 ± 3.1	15 ± 4.6	35
V1	72 ± 6.0	58 ± 6.5	19	68 ± 7.5	52 ± 8.9	24

Fig. 3 Number of activated voxels with movement of the fatigued hand showing a reduction in activation of SM1, SMA, CB and V1 after fatiguing exercise. Mean number of activated voxels during the first two pre-exercise periods (*grey*) and the two post-exercise periods (*black*). Group mean ± SE (*$P < 0.05$)

cantly reduced for the non-fatigued hand (23 ± 3 pre-exercise to 15 ± 5 post-exercise, $P < 0.05$, Fig. 4). The reduction was sustained for both hands during the second post-exercise period (Figs. 3, 4). Movement of the non-fatigued hand also produced a greater reduction in activation of the CB after fatigue than movement of the fatigued hand (35 vs. 30%, respectively, Table 2).

There was no change in the magnitude or percentage signal change of the activated voxels in the cerebellum or SMA after fatiguing exercise when compared to pre-exercise values (Table 3).

Primary visual cortex

The hemi-field reversing chequerboard resulted in equal activation in the left and right V1s (left 70 ± 4 vs. right 69 ± 5 voxels, $P > 0.05$, mean of two pre-exercise

runs) and considerably more activated voxels than in any of the other cortical areas measured (3.34 cm^3). The number of activated voxels was similar for both pre-exercise periods (left visual field: 68 ± 5 vs. 72 ± 6, right visual field: 70 ± 7 vs. 68 ± 8; $P > 0.05$).

During the first post-exercise period, visual stimulation of the V1 contralateral to the fatigued hand resulted in a reduced number of voxels compared to pre-exercise (from 72 ± 6 pre-exercise to 58 ± 7 post-exercise, $P < 0.05$, Figs. 3, 5). With stimulation of V1 contralateral to the non-fatigued hand a similar degree of reduction in activated voxels was also measured (from 68 ± 8 pre-exercise to 52 ± 9 post-exercise, $P < 0.05$, Fig. 4). However, the reduction was not sustained in either visual cortex and had returned to baseline values by the second post-exercise run (left V1: 66 ± 8, right V1: 67 ± 10; $P > 0.05$, Figs. 3, 4).
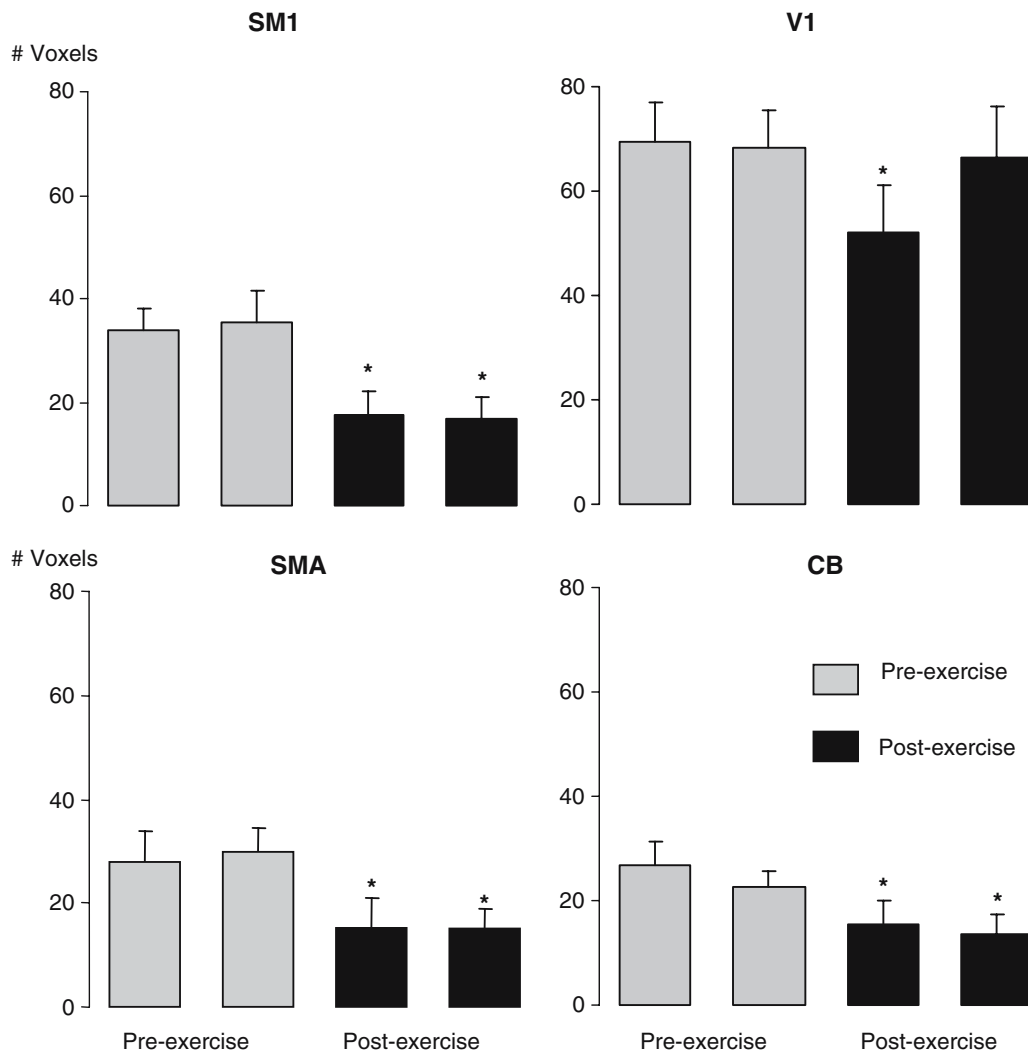
Fig. 4 Number of activated voxels with movement of the non-fatigued hand showing a reduction in activation of SM1, SMA, CB and V1 after fatiguing exercise. Mean number of activated voxels during the first two pre-exercise periods (*grey*) and the two post-exercise periods (*black*). Group mean ± SE (*$P < 0.05$)

Table 3 Measurements of the BOLD signal: magnitude and percentage signal change (mean ± SE) from activated voxels in the SM1, SMA, CB and V1 measured before (pre-exercise 2) and after (post-exercise 1) fatiguing exercise. Results are pooled for the fatigued and non-fatigued hands

	Pre-exercise		Post-exercise	
	Magnitude	Signal change (%)	Magnitude	Signal change (%)
SM1	26 ± 1.7	2.7 ± 0.1	27 ± 1.8	2.8 ± 0.2
SMA	24 ± 2.2	2.6 ± 0.4	24 ± 2.4	2.6 ± 0.4
CB	20 ± 1.2	2.0 ± 0.1	19 ± 1.0	1.9 ± 0.1
V1	35 ± 1.7	4.1 ± 0.2	34 ± 1.4	4.1 ± 0.3

Magnitude and percentage signal change of activated voxels did not alter significantly pre- and post-exercise for V1 (Table 3).

Discussion

In keeping with our previous finding of reduced SM1 activation after a fatiguing hand exercise, in this study we have shown that there is a reduction in the degree of activation in primary and secondary motor areas (SM1, SMA), as well as the cerebellum, and that there is also a bilateral reduction in activation in the primary visual cortex when a visually cued motor task is performed. However, these changes are not associated with any deterioration in motor performance. A number of factors may contribute to this pattern of signal reduction.

With TMS, we have previously described a post-fatiguing exercise shift in the balance of excitation and inhibition, with a long-lasting reduction in corticomotor excitability and a concurrent increase in short-interval cortical inhibition in the primary motor cortex (Benwell
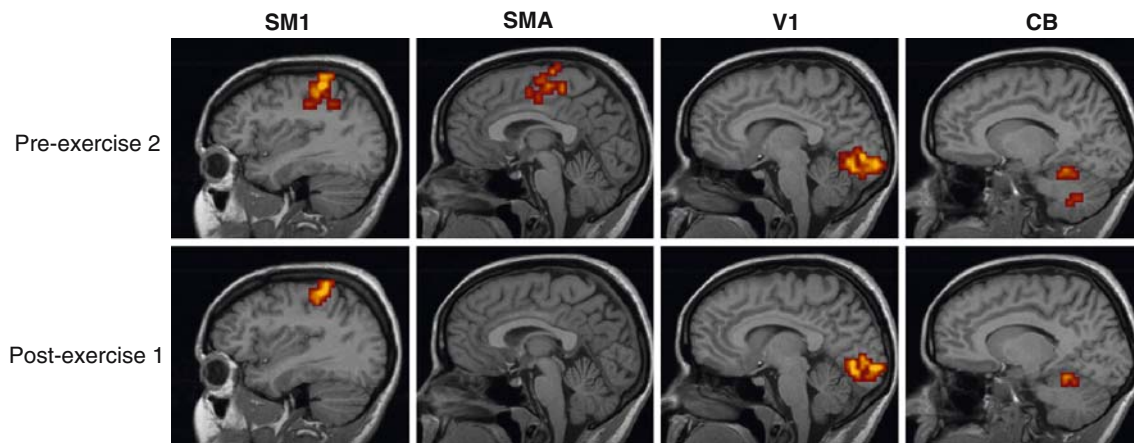
Fig. 5 Functional imaging: functional MR images of one subject with movement of the fatigued hand, showing a reduction in the number of activated voxels in SM1, SMA, CB and V1 after fatiguing hand exercise (one slice from each ROI shown)

et al. 2006). This could lead to a reduced fMRI signal as inhibitory networks are believed to have a lower metabolic demand than excitatory networks (Waldvogel et al. 2000). As well, the fMRI signal could be modulated by post-fatigue changes in sensory inputs that contribute to the signal from SM1. However, while these effects could be anticipated on the fatigued side, we also found signal reduction with movement of the non-fatigued hand. TMS studies have also shown a reduction in MEP amplitude in the homologous muscle after a unimanual fatiguing exercise, although the degree of the depression depends on the intensity and duration of exercise (Bonato et al. 1996; Humphry et al. 2004). As well, functional imaging studies have shown bilateral changes in activation during a fatiguing exercise (Liu et al. 2002, 2003). In fact, we found a greater percentage reduction in activation with movement of the non-fatigued hand than for the fatigued hand. The lower baseline activation for the dominant (non-fatigued) hand, which is in keeping with previously reported differences with movement of the dominant and non-dominant hands (Jancke et al. 1998), could have resulted in a larger percentage reduction in activation (compared to baseline) after fatigue. As well, inter-side differences in sensory afferent activity post-exercise could have differentially affected the fMRI signal.

These findings for SM1 are consistent with our previous findings with fatigue of the thumb flexors of the dominant hand (Benwell et al. 2005). In the present study we have added further controls for task performance (rate, squeeze and release time), which were unaltered by fatigue. Humphry et al. (2004) also showed no deterioration in movement or reaction time in the left or right biceps brachii after unilateral exhaustive biceps exercise. The observed reduction in

activation cannot therefore be accounted for on the basis of a change in task performance.

We have now been able to expand on our original findings to demonstrate that the bilateral pattern of signal reduction in SM1 also extends to other parts of the motor network. Motor performance involves a complex and inter-related network of cortical and sub-cortical regions, and it is perhaps not surprising that there should be a change in activity throughout this network after a fatiguing exercise. The cerebellum is involved in sensori-motor integration and, like the SM1, the smaller reduction in activation of the CB for the fatigued hand may be explained on the basis of additional sensory processing. For the SMA, a reduction in the level of attention after fatiguing exercise or increased automation of the task (Wu et al. 2004) could conceivably affect movement preparation and SMA activation. However, we were able to show that a simple measure of attention and automation, reaction time, was unaltered by fatigue. Overall, these results are consistent with a generalised reduction in activation of the motor network after a fatiguing exercise, which is similar to the generalised increase in activation of primary and secondary motor areas reported during intermittent sub-maximal contractions (Liu et al. 2003). We have shown however, that the reduction in activation after fatiguing exercise is not confined to the motor network, but also extends to the visual cortex.

We used a half-field chequerboard reversal to cue, unpredictably, the motor task for each hand. In this way, we could record motor reaction time and derive a measure of attention to the task after fatiguing exercise, as well as measure the activation in V1 from the visual stimulus. We found that activation in V1 was reduced after fatiguing exercise, but to a lesser extent than in the motor network. It is possible that some of this reduction

is because the visual stimulus was a trigger for a motor task, and thus would recruit visuo-motor integration networks. However, the finding of reduced activation in a primary sensory area not directly involved in the fatiguing motor task, suggests that other factors may be contributing to the post-exercise signal reduction, such as a change in regional and global cerebral haemodynamics and in the relationship between the BOLD signal and neural activity during the recovery period.

The BOLD signal contrast depends on more oxygen being delivered to an area of neural activity than is required to satisfy the metabolic demand. Thus the BOLD signal is affected by changes in blood flow and oxygen consumption, and blood volume, which have an impact on the relative level of blood oxygenation (Bandettini et al. 1997). At rest, the oxidation of glucose provides the main energy source for the brain. During activity, such as cycling, glycogen uptake increases more than the uptake of oxygen to supply the increasing metabolic demand (Dalsgaard et al. 2004). However, as the intensity of exercise continues to increase, to the point of exhaustion, there is a depletion in glycogen stores and lactate is substituted as the primary energy source (Ide et al. 2000; Dalsgaard et al. 2004). During recovery from exhaustive cycling exercise, there is an increase in glycogen and lactate uptake presumably to replenish depleted stores (Ide et al. 2000). However, more important to our measure of the BOLD signal, Ide et al. (2000) showed that oxygen uptake remained elevated for up to 30-minutes after exercise. Therefore, greater oxygen consumption after exercise could result in less oxyhaemoglobin in the venous system, and thus a smaller BOLD signal than measured pre-exercise. If similar processes occur during and after sub-maximal exercise and if we take the magnitude of the reduction in V1 as an indirect estimate of this generalized effect, then we are still left with a further reduction in the fMRI signal in motor areas that is presumably related to the changes in excitability and inhibition in the motor system after fatiguing exercise.

To conclude, we have shown that following a period of fatiguing unimanual exercise there are widespread changes in cerebral activation with performance of a motor task that are not confined to motor areas but also extend to non-motor areas such as the visual cortex. These findings suggest that in addition to the changes that occur in the motor network, there are more widespread changes in cerebral haemodynamic responses during the recovery period after fatiguing exercise.

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