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Enduring representational plasticity after somatosensory stimulation

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Somatosensory stimulation (SS), leading to increases in motor cortical excitability, influences motor performance in patients with brain lesions like stroke. The mechanisms by which SS modulates motor function are incompletely understood. Here, we used functional magnetic resonance imaging (fMRI, blood-oxygenation-level-dependent (BOLD), and perfusion imagings simultaneously acquired in a 3 T magnet) to assess the effects of SS on thumb-movement-related activation in three regions of interest (ROI) in the motor network: primary motor cortex (M1), primary somatosensory cortex (S1), and dorsal premotor cortex (PMd) in healthy volunteers. Scans were obtained in different sessions before and after 2-h electrical stimulation applied to the median nerve at the wrist (MNS), to the skin overlying the shoulder deltoid muscle (DMS), and in the absence of stimulation (NOSTIM) in a counterbalanced design. We found that baseline perfusion intensity was comparable within and across sessions. MNS but not DMS nor NOSTIM led to an increase in signal intensity and number of voxels activated by performance of median nerve-innervated thumb movements in M1, S1, and PMd for up to 60 min. Task-related fMRI activation changes were most prominent in M1 followed by S1 and to a lesser extent in PMd. MNS elicited a displacement of the center of gravity for the thumb movement representation towards the other finger representations within S1. These results indicate that MNS leads to an expansion of the thumb representation towards other finger representations within S1, a form of plasticity that may underlie the influence of SS on motor cortical function, possibly supporting beneficial effects on motor control.
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Keywords: Somatosensory; Motor cortex; Premotor; fMRI; Reorganization; Nerve stimulation

Introduction

Somatosensory input is required for control of skillful movements. For instance, propioceptive and tactile inputs are crucial for monitoring the position of a body part in space and for refinement of motor control (Pavlides et al., 1993; Gentilucci et al., 1997; Farrer et al., 2003; Rabin and Gordon, 2004; Xerri et al., 2004). Peripheral nerve stimulation, which activates group Ia large muscle afferents, group Ib afferents from Golgi organs, group II afferents from slow and rapidly adapting skin afferents, as well as cutaneous afferent fibers (Campbell, 1999; Kimura, 2001), results in enhanced corticomotoneuronal excitability targeting muscles in the stimulated body part (Hamdy et al., 1998; Ridding et al., 2000; Kaelin-Lang et al., 2002). Additionally, somatosensory stimulation may have a role in neurorehabilitation by influencing motor function in patients with brain lesions (Johansson et al., 1993; Hamdy et al., 1998; Powell et al., 1999; Wong et al., 1999; Conforto et al., 2002).

Somatosensory stimulation activates primary sensorimotor and secondary somatosensory cortices as well as the supplementary motor area (Ibanez et al., 1995; Backes et al., 2000; Kampe et al., 2000; Hashimoto et al., 2001; Golaszewski et al., 2002b). A period of somatosensory stimulation results in more prominent task-related activation outlasting the stimulation period in various cortical areas including pre- and postcentral and medial and superior frontal gyri, as studied with 1.5 T fMRI blood oxygenation level (BOLD) response (Golaszewski et al., 2002a, 2004). The effects of somatosensory stimulation on baseline blood flow, which could influence the BOLD response, are not known and could be studied using perfusion fMRI (for review, see Logothetis and Wandell, 2004). Data obtained from BOLD and perfusion fMRI could complement and provide more information than data originated in any of the two alone.

Here, we used a single shot perfusion labeling (SSPL) pulse (van Gelderen et al., in press) to examine simultaneously the effect of a 2-h period of peripheral nerve stimulation on movement-dependent changes in blood flow (tissue perfusion) and blood oxygenation level (BOLD) in a group of healthy volunteers using a

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3 T scanner. The study was designed to measure baseline blood flow and task-related activation patterns with fMRI perfusion and task-related activation patterns with BOLD fMRI. Our results show that somatosensory stimulation led to characteristic increases in activation in primary motor, somatosensory, and premotor cortices in the absence of changes in baseline blood flow and to a displacement of the center of gravity for the thumb representation towards the other finger representations located more superiorly within S1. Additionally, we found that signal intensity changes documented with perfusion fMRI were less variable than those obtained with BOLD fMRI.

Methods

Subjects

Nineteen healthy right handed volunteers participated in this study (mean ± SD age, 31.11 ± 7.76 years) that was approved by the Investigational Review Board of the National Institute of Neurological Disorders and Stroke, National Institutes of Health. Informed consent was obtained from all volunteers preceding the study.

Experimental design

The main study was conducted to evaluate the BOLD and perfusion signal changes associated with performance of voluntary thumb movements before and after three interventions pseudo-randomly ordered: 2-h period of (a) median nerve stimulation (MNS, n = 9), (b) stimulation of the skin overlying the shoulder deltoid muscle (DMS, n = 8), and (c) no stimulation (NOSTIM, n = 8), in different sessions on different days (for summary of the experimental paradigm, see Fig. 1). The NOSTIM group was used as a control for the MRI signal stability over the time course of 2 h. In a separate study, five of the subjects underwent an additional session with MNS to evaluate changes in baseline blood flow.

Stimulation and recording procedures

During the 2-h interventions, subjects remained seated, reading books or magazines. They were instructed to minimize their arm/hand movements, but they were allow to adjust their arm/hand position to be more comfortable. The paradigm for peripheral nerve stimulation was adapted from an earlier study (Kaelin-Lang et al., 2002). For MNS, we identified the optimal wrist position which, upon stimulation, elicited largest peripheral M-responses with the lowest stimulus intensity. Similarly, for DMS, we identified the optimal position on the skin overlying the deltoid muscle, which, upon stimulation, elicited the most prominent deltoid muscle response with the lowest stimulus intensity. For MNS and DMS, trains of electrical stimulation were delivered every second (Grass stimulator S 8800 with SIU5 stimulus isolation unit, Grass Instrument Division, Astro-Med Inc., West Warwick, RI USA) through silver–silver chloride electrodes (diameter 10 mm) positioned with the cathode proximal. Each train consisted of five continuous (1 ms pulse width) single pulses at 10 Hz over 500 ms with a 50% duty cycle. The stimulus intensity was adjusted to elicit small (50 mV) muscle action potentials in 50% of the stimulation trials, in the absence of any visible muscle twitches and movements from the fingers or arm. This stimulus intensity represents approximately 2–3 times the perceptual threshold. Stimulation applied at the median nerve evoked tickling and vibration sensation and mild paresthesiae in the thumb, index, and middle fingers (and occasionally in the ring finger), as well as in the median half of the palm. Stimulation applied at the shoulder induced similar sensations in the upper arm. Neither pain nor discomfort was reported throughout the stimulation.

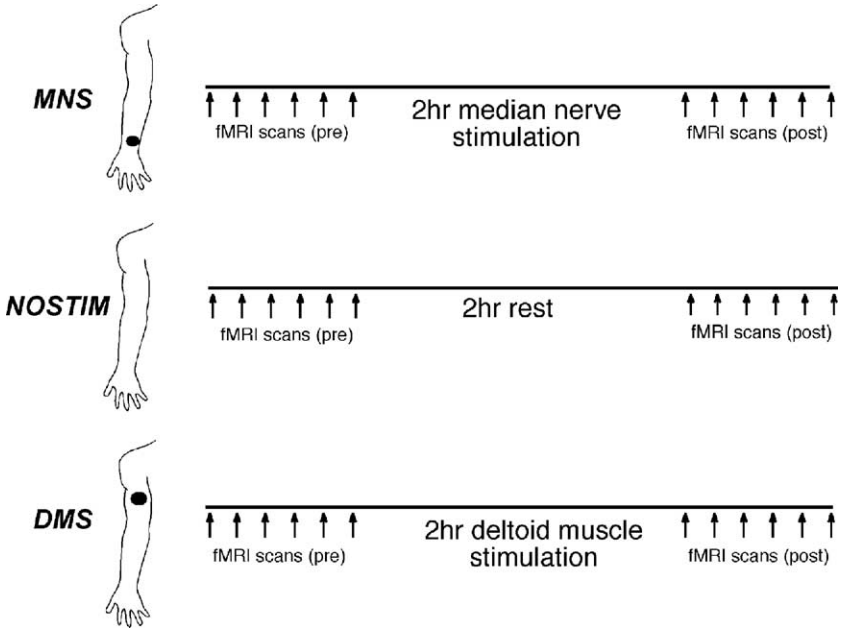

Fig. 1. Experimental procedure. Subjects participated in three different sessions in which they received MNS, NOSTIM, or DMS (see Methods). Each session started with baseline determination of fMRI activation patterns associated with thumb movements (6 runs) followed by 2-h interventions outside the scanner and finally post-intervention fMRI activation patterns (6 scans).

fMRI scanning

Subjects were studied with a 3 T whole body imaging scanner (GE medical System, Milwaukee, WI) with RF head transmit coil and a flexible quadrature surface RF detections coil (Nova Medical, Wakefield, MA) attached to the scalp overlying contralateral sensorimotor cortex. Subjects lay supine on the scanner bed with the custom-made molded cast fixed to the wrist joint and hand for the movement control during the scan. To reduce head motion during scanning, a bite bar made of a dental impression material was custom-made for each subject and fixed to a cradle of the head coil. The first set of 6 consecutive fMRI runs were collected to serve as the baseline, and then subjects left the scanner and underwent one of the three interventions for 2 h. Immediately following the intervention, subjects returned to the scanner and received the second set of 6 consecutive fMRI runs in blocks of 10 min each. Therefore, results from a total of 12 runs (six before and six after) were included for analysis for each subject in each of the three interventions. Before each set of fMRI acquisition, axial anatomical T2 weighted images (TR = 3800, TE = 107, slice thickness = 5 mm, matrix size = 256 × 192, field of view = 24 × 24 mm) were acquired to identify the location of the hand knob of the motor cortex (Yousry et al., 1997). The surface coil was wrapped up on subject's head with bandage gauze throughout the entire experiment to minimize position shifts. Anatomical images were obtained after each intervention to match the angle and slice location with preintervention determinations. Additionally, the TG, R1, and R2 of the second set of fMRI runs were adjusted to be identical to the first set of runs to ensure consistency in scanner's performance throughout the entire experiment.

Four slices of perfusion and BOLD fMRI images were acquired simultaneously in the axial plane in a 64 × 32 matrix size over a field of view of 24 × 24 cm^2, with 4 mm slice thickness and 1 mm spacing, with slice locations identical to the anatomical images. This generated a voxel size of 3.75 × 3.75 × 5 mm^3. The single shot perfusion imaging method sequence (i.e. SSPL) was used to collect high-sensitivity perfusion signal (Duyn et al., 2001) with addition of a BOLD acquisition (van Gelderen et al., 2001, 2005). The inversion times were 1250 ms and 250 ms respectively, the selective inversion slice thickness was 30 mm. A single shot EPI readout was used with a bandwidth of 250 kHz and 50% ramp sampling. The echo time was 18 ms for perfusion and 38 ms for the BOLD. In a separate experiment, a reference scan was added with two non-selective inversions to give a good estimate of the baseline perfusion levels (Duyn et al., 2001). As a result of adding reference scans in every other perfusion image repetition, the overall TR of this series of scan increased twofold. Bipolar crusher gradients with amplitude of 20 mT/m (2 ms duration and separation) were applied during data acquisition to selectively eliminate contributions from large blood vessels.

Motor task

Subjects performed voluntary thumb movements visually paced by a GO signal projected on a computer screen at 1 Hz. Stimulus presentation was controlled from a SuperLab (Cedrus, Phoenix, AZ) program. Each MRI run consisted of 5 right thumb movement periods (30 s each) alternating with rest. The right hand was placed in a molded cast that allowed thumb flexion–extension movements of up to 5 cm displacement measured at the distal phalanx. Subjects were instructed to perform flexion–extension thumb movements at the paced rate touching the physical boundaries of the cast for both movement directions in a consistent manner. The rest of the fingers were immobilized inside of the molded hand cast. Small, light-weighted three-dimensional accelerometers (Kirsler Instrument Corporation, Amherst, NY, USA) were mounted at the interphalangeal joint of the right thumb connected with shielded-cables to the LabView data acquisition board. Kinematics data collection and analysis were performed using an in-house program written in LabView (National Instrument, Austin, TX, USA; sampling rate, 1000 Hz) and IDL (RSI, Boulder, CO) (Kaelin-Lang and Cohen, 2000; van Gelderen et al., in press). Acceleration signals were recorded in both the vertical (extension and flexion) and horizontal (adduction and abduction) axes.

fMRI data analysis

Image reconstruction and processing was implemented using an in-house written IDL program (RSI, Boulder CO, (van Gelderen et al., 2001, 2005; Yongbi et al., 2002)). In short, for EPI image reconstruction, the ramp-sampled data were transformed using a direct matrix multiplication with the inverse of the encoding matrix containing the appropriate Fourier coefficients. A phase correction to compensate for the differences between odd and even echoes was calculated from a reference echo from the center of *k*-space after temporal low-pass filtering (Bruder et al., 1992). For the perfusion scans with reference, the reference signal was subtracted from the perfusion-weighted data. The time series image data were then analyzed by curve-fitting using multi-linear regression.

Spatial realignment of head position was performed to correct for head movements. The functional images from the first volume of every run (i.e. perfusion images) were aligned to that in the first run. Spatial registration was performed to obtain the best shift and rotation for each run as determined by the least sums of square of the difference, with cubic spline interpolation (Thevenaz et al., 2000). Only the brain regions that were covered in both volumes (pre- and post-interventions) were used for further analysis. Coregistration of the T2 weighted anatomical images to the same reference (the first functional run) was performed manually and involved only inplane translations, which were mostly due to differences in reconstruction of the anatomical and functional data. Three regions of interest (ROIs) including primary motor cortex (M1), primary somatosensory cortex (S1), and dorsal premotor cortex (PMd) were defined based on anatomical landmarks (Picard and Strick, 2001; Hanakawa et al., 2003): primary motor cortex (M1), between the anterior bank of the central sulcus and precentral gyrus; primary somatosensory cortex (S1), between the posterior bank of the central sulcus and postcentral gyrus; and dorsal premotor cortex (PMd), between the anterior bank of the precentral sulcus and precentral gyrus, considering regions posterior to the precentral sulcus as the human homologous to primate PMd proper (see Fig. 2, also see Picard and Strick, 2001; Hanakawa et al., 2003).

Functional maps were calculated using voxel-wise cross-correlation methods. A multiple-regression analysis modeled to the expected hemodynamic response curve function with a σ of 3.5 s and a delay of 5.5 s. Any volume that differed from the average by more than 2.7 times the standard deviation of the difference was excluded from the data analysis due to possible motion artifact. The regression resulted in activation *t* score maps and signal intensity (amplitude) maps. Only significant voxels that passed a Bonferroni corrected threshold ($P < 0.05$) were

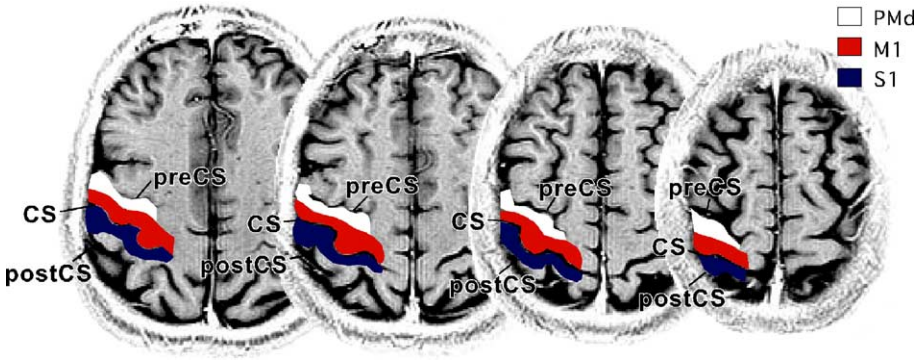

Fig. 2. ROIs were defined based on the sulci/gyri patterns of each individual in each of the four anatomical images (see Methods for details). PreCS: precentral sulcus; CS: central sulcus; postCS: postcentral sulcus.

considered as activated voxels for further analysis. Results from each ROI and run that contained less than 4 activated voxels were excluded (to avoid uncontrolled variability in the normalization of voxel counts, see below). Within each ROI, a mask was determined from the voxels that were activated at least once across 12 runs with either acquisition method. The signal intensity changes between task and rest periods were calculated within this mask. Same mask was applied across all 12 runs. Task-dependent signal intensity changes obtained with either method were normalized to the BOLD baseline value during the rest periods. The percentage of signal intensity changes relative to the BOLD baseline value and the numbers of activated voxels were calculated for each run.

Because of the intrinsic variability in signal intensity and number of activated voxels between and within subject and sessions (Cohen and DuBois, 1999; Waldvogel et al., 2000; Loubinoux et al., 2001; Saad et al., 2003), direct comparisons on raw data are difficult. Therefore, the percentage of signal intensity changes and the numbers of activated voxels in each run were expressed relative to the grand average of all runs before the intervention.

The center of gravity (i.e. center of mass) of fMRI activation was subsequently calculated as the vector sum of signal intensity changes in the superiorinferior (z axis), anteriorposterior (y axis), and mediolateral (x axis) coordinates. Changes in centers of gravity (COG) for each run were expressed relative to the grand average of centers of gravity in all runs preceding any intervention:

$$\sqrt{(x-X)^2+(y-Y)^2+(z-Z)^2}$$

where X is the mean COG location in the mediolateral axis (calculated from six runs preceding intervention), x is the COG location in the mediolateral axis in each run. Y and y as well as Z and z convey the same information on anteriorposterior and superiorinferior axes respectively.

In a separate experiment, the baseline perfusion intensity estimate was calculated in 5 subjects before and after MNS using pairwise subtractions of the non-slice selective inversion recovery images (perfusion scan) from the slice selective inversion recovery images (reference scan) during rest. Baseline perfusion intensity was estimated from the average difference of 30 perfusion and reference images during rest and normalized to the BOLD baseline value.

Additionally, we investigated the stability of the fMRI signals using the two acquisition methods (BOLD and perfusion) across 12 runs over 2 h. Coefficient of variation of signal intensity and COG were calculated from data collected in the NOSTIM session for each acquisition method. Coefficient of variation in signal intensity was measured in M1, the region with stronger signal, and coefficient of variation in COG was measured in S1, the region with detected changes in COG. Results from two methods were compared using two-tailed paired t tests.

Statistical analysis

The direction and magnitude of voluntary thumb movements were calculated from the first-peak acceleration vectors, averaged for each run, and compared using a two-way ANOVA with factors $\text{Time}_{(\text{pre- and post-intervention})}$ and $\text{Intervention}_{(\text{MNS, DNS, and NOSTIM})}$. A three-way ANOVA with factors $\text{Intervention}_{(\text{MNS, DNS, and NOSTIM})}$, $\text{Method}_{(\text{perfusion and BOLD})}$, and $\text{ROI}_{(\text{M1, S1, and PMd})}$ was used to examine differences in the number of activated voxels preceding intervention. The effects of intervention on voxel counts and signal intensity changes were calculated within each ROI using a three-way ANOVA with factors $\text{Intervention}_{(\text{MNS, DNS, and NOSTIM})}$, $\text{Time}_{(\text{pre- and post-interventions})}$, and $\text{Method}_{(\text{perfusion and BOLD})}$ and post hoc Scheffe's test. The duration of intervention effects and changes in normalized perfusion baseline estimates were examined using Student's t test corrected for multiple comparisons. The stability of the fMRI signal (12 runs over 2 h) was expressed as coefficients of variation and was compared across $\text{Method}_{(\text{perfusion and BOLD})}$ using two-tailed paired t tests. Within each ROI, COG location was evaluated first using a four-way ANOVA with factors $\text{Intervention}_{(\text{MNS, DNS, and NOSTIM})}$, $\text{Time}_{(\text{pre- and post-interventions})}$, $\text{Method}_{(\text{perfusion and BOLD})}$, and $\text{Axis}_{(\text{anteriorposterior } (Y), \text{ mediolateral } (X), \text{ and superiorinferior } (z) \text{ axes})}$ followed by separate three-way ANOVAs for each of the three axes. Data are expressed as mean ± SEM.

Results

Motor kinematics

ANOVA did not show significant effects of Time, Intervention, or Time × Intervention interaction on direction ($F_{(1,266)} = 0.0001$, $P = 0.998$; $F_{(2,266)} = 1.809$, $P = 0.166$; and $F_{(2,266)} = 0.028$, $P = 0.973$ respectively) or magnitude of the first peak acceleration ($F_{(1,266)} = 0.573$, $P = 0.449$; $F_{(2,266)} = 1.357$, $P = 0.259$; and

$F_{(2,266)}$ = 1.105, P = 0.333 respectively) of voluntary thumb movements during scanning sessions.

fMRI activation before interventions

The number of voxels activated was comparable preceding interventions across the three sessions using either technique. ANOVA did not show significant effects of Intervention ($F_{(2,728)}$ = 2.787, P = 0.063), Intervention × Method ($F_{(2,728)}$ = 0.818, P = 0.442), Intervention × ROI ($F_{(4,728)}$ = 1.682, P = 0.153), or Intervention × Method × ROI ($F_{(4,728)}$ = 0.460, P = 0.7648) on the number of activated voxels preceding application of any of the three interventions. Additionally, there was a significant effect of Method ($F_{(1,728)}$ = 13.457, P < 0.0005), ROI ($F_{(1,728)}$ = 59.916, P < 0.0001), and Method × ROI interaction ($F_{(2,728)}$ = 4.106, P < 0.05) indicating that the number of activated voxels preceding application of any intervention differed with the two methods across the three ROIs (Table 1).

fMRI activation after interventions

Primary motor cortex (M1)

Number of activated voxels. ANOVA showed a significant effect of Intervention ($F_{(2,538)}$ = 8.88, P < 0.0005), Time ($F_{(2,538)}$ = 4.76, P < 0.05), and Intervention × Time interaction ($F_{(2,538)}$ = 7.69, P < 0.001, Fig. 4A left panel) but not Method ($F_{(1,538)}$ = 0.358, P = 0.5498), Method × Intervention ($F_{(2,538)}$ = 0.946, P = 0.3891), or Method × Time ($F_{(1,538)}$ = 0.663, P = 0.4158) interaction on the number of activated voxels in M1. Post hoc testing demonstrated a significant increase in the number of activated voxels following MNS with both perfusion and BOLD acquisitions (Scheffe's test, P < 0.005 and P < 0.05 respectively; Figs. 3 and 4A, left panel) in the absence of changes with DMS or NOSTIM.

Signal intensity changes. ANOVA showed significant effects of all three main factors Intervention ($F_{(2,538)}$ = 14.481, P < 0.0001), Time ($F_{(1,538)}$ = 10.65, P < 0.05), and Method ($F_{(1,538)}$ = 5.508, P < 0.05) and Intervention × Time interaction ($F_{(1,538)}$ = 15.891, P < 0.0001) on signal intensity changes in M1. MNS led to a nearly 32% increase in signal intensity in this region with BOLD and perfusion (Scheffe's test, P values < 0.005 for both) in the absence of changes with DMS or NOSTIM (Fig. 4A, right panel). Changes in signal intensity with the perfusion method remained elevated for up to 60 min after the end of MNS (Fig. 5A, left panel).

Center of gravity. The four-way ANOVA did not show significant effects of Intervention, Time, Method, or Axis nor their interaction.

Primary somatosensory cortex

Number of activated voxels. There was a significant effect of Intervention ($F_{(2,470)}$ = 12.42, P < 0.0001), Time ($F_{(1,470)}$ = 4.62, P < 0.05), and Intervention × Time interaction ($F_{(2,470)}$ = 10.90; P < 0.001) on the number of activated voxels in S1. MNS led to the most prominent increase in the number of activated voxels detected with both perfusion and BOLD measurements (Scheffe's test, P < 0.05 and P < 0.01, respectively, Fig. 4B). DMS elicited a mild decrease and NOSTIM a mild nonsignificant increase in the number of activated voxels with BOLD measurement (Fig. 4).

Signal intensity changes. ANOVA showed significant effects of Intervention ($F_{(2,470)}$ = 5.76, P < 0.05), Time ($F_{(1,470)}$ = 10.11, P < 0.005), and Intervention × Time interaction ($F_{(2,470)}$ = 6.25, P < 0.05) on the magnitude of signal intensity changes in S1. Post hoc testing showed enhanced signal intensity changes with perfusion and BOLD after MNS (Scheffe's test, P < 0.001 and P < 0.05 respectively, Fig. 4B) that outlasted the stimulation period for at least 60 min (Fig. 5B).

Center of gravity. ANOVA showed a significant effect of Intervention × Time × Axis interaction ($F_{(4,1194)}$ = 2.991, P < 0.05) on the location of the COG of fMRI activation. A subsequent three-way ANOVA by axis showed that this significant interaction was due to changes in the superiorinferior (z) axis (Intervention × Time: $F_{(2,398)}$ = 7.663, P < 0.0005, Intervention × Method: $F_{(2,398)}$ = 11.139, P < 0.0001, and Intervention × Time × Method: $F_{(2,398)}$ = 11.139, P < 0.0001). The thumb COG_{S1} was displaced medially in the (z) axis with both BOLD and perfusion measurements (Scheffe's test, P < 0.001 and P < 0.05 respectively, Fig. 3) after MNS but not DMS or NOSTIM (Table 2, Figs. 4B, right panel, 5B) in the absence of changes in the other two axes.

Dorsal premotor cortex

Number of activated voxels. There was a significant effect of Intervention ($F_{(2,414)}$ = 7.117, P < 0.001) and Intervention × Time interaction ($F_{(2,414)}$ = 6.04, P < 0.005) on the number of voxels activated in PMd. MNS led to a significant increase in the number of activated voxels measured using perfusion (Scheffe's test, P < 0.05) and a similar trend using BOLD (P = 0.08) (Fig. 4C, left panel) in the absence of changes with DMS or NOSTIM.

Signal intensity changes. ANOVA showed significant effects of Intervention ($F_{(2,414)}$ = 6.71, P < 0.005) and Time × Intervention interaction ($F_{(2,414)}$ = 5.71, P < 0.005) on the magnitude of activation in PMd. MNS led to an increase in signal intensity with perfusion (Scheffe's test, P < 0.05) and a similar trend with BOLD (P = 0.07) (Fig. 4C, right panel) in the absence of changes with DMS or NOSTIM. Contrary to the results in M1 and S1, signal intensity changes in PMd were less stable across runs and among individuals (compare the SEM bar in Fig. 5C to Figs. 5A and B).

Table 1
Voxel counts within ROI of each group preceding interventions

Group	ROI	Number of activated voxels before interventions	
		Perfusion	BOLD
MNS	M1	18.021 ± 1.832	11.146 ± 1.256
	S1	11.217 ± 1.320	9.130 ± 0.734
	PMd	8.817 ± 1.345	5.209 ± 0.936
DMS	M1	19.056 ± 2.072	13.056 ± 2.035
	S1	12.093 ± 1.657	11.000 ± 1.688
	PMd	6.860 ± 1.345	5.321 ± 0.766
NOSTIM	M1	20.035 ± 2.388	13.784 ± 1.670
	S1	9.298 ± 0.976	10.149 ± 1.252
	PMd	5.290 ± 1.052	5.270 ± 0.994

Mean ± SEM.

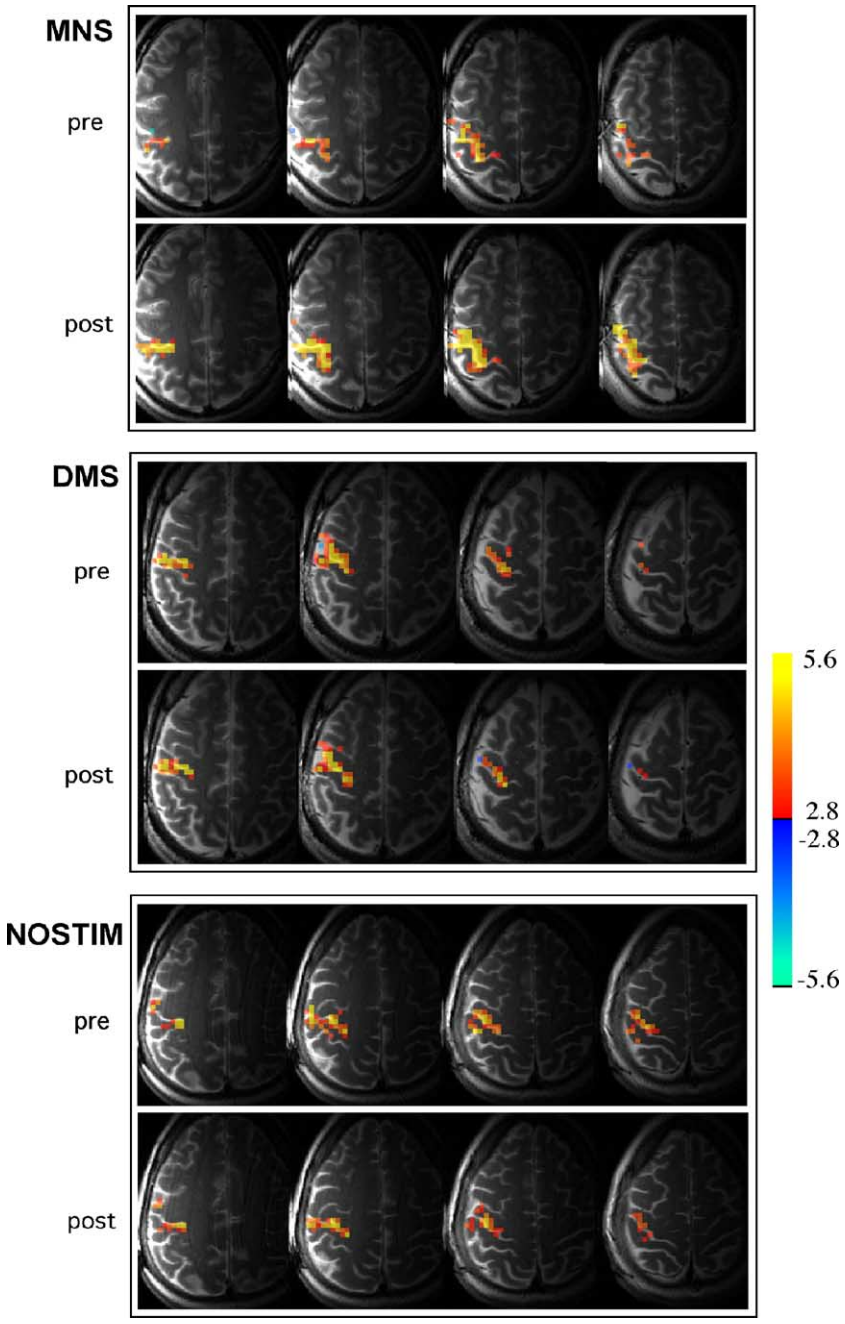

Fig. 3. Examples of perfusion *t* maps before and after each intervention. Note that MNS led to an increase in the number of activated voxels in the absence of overt differences with DMS and NOSTIM.

Center of gravity. The four-way ANOVA did not show significant effects of Intervention, Time, Method, or Axis nor their interaction.

Baseline perfusion during MNS2

Normalized perfusion baseline estimate at rest before and after MNS was comparable in the three ROIs (*t* test, $P = 0.44$ in M1, $P = 0.14$ in S1, and $P = 0.16$ in PMd, Table 3).

Comparison of BOLD and perfusion signal variability

Coefficient of variation of signal intensity was higher with BOLD than with perfusion (40% and 33% respectively, $P < 0.05$, Fig. 6, left panel) in the absence of differences in coefficient of variation of COG.

Discussion

The main result of this study was that median nerve stimulation elicited an enduring increase in task-related perfusion and BOLD responses in the thumb representation in the absence of changes in baseline blood flow. The most prominent increases occurred in the primary somatosensory and motor cortices followed by the premotor region. Within the somatosensory cortex, the thumb, innervated by the stimulated median nerve,

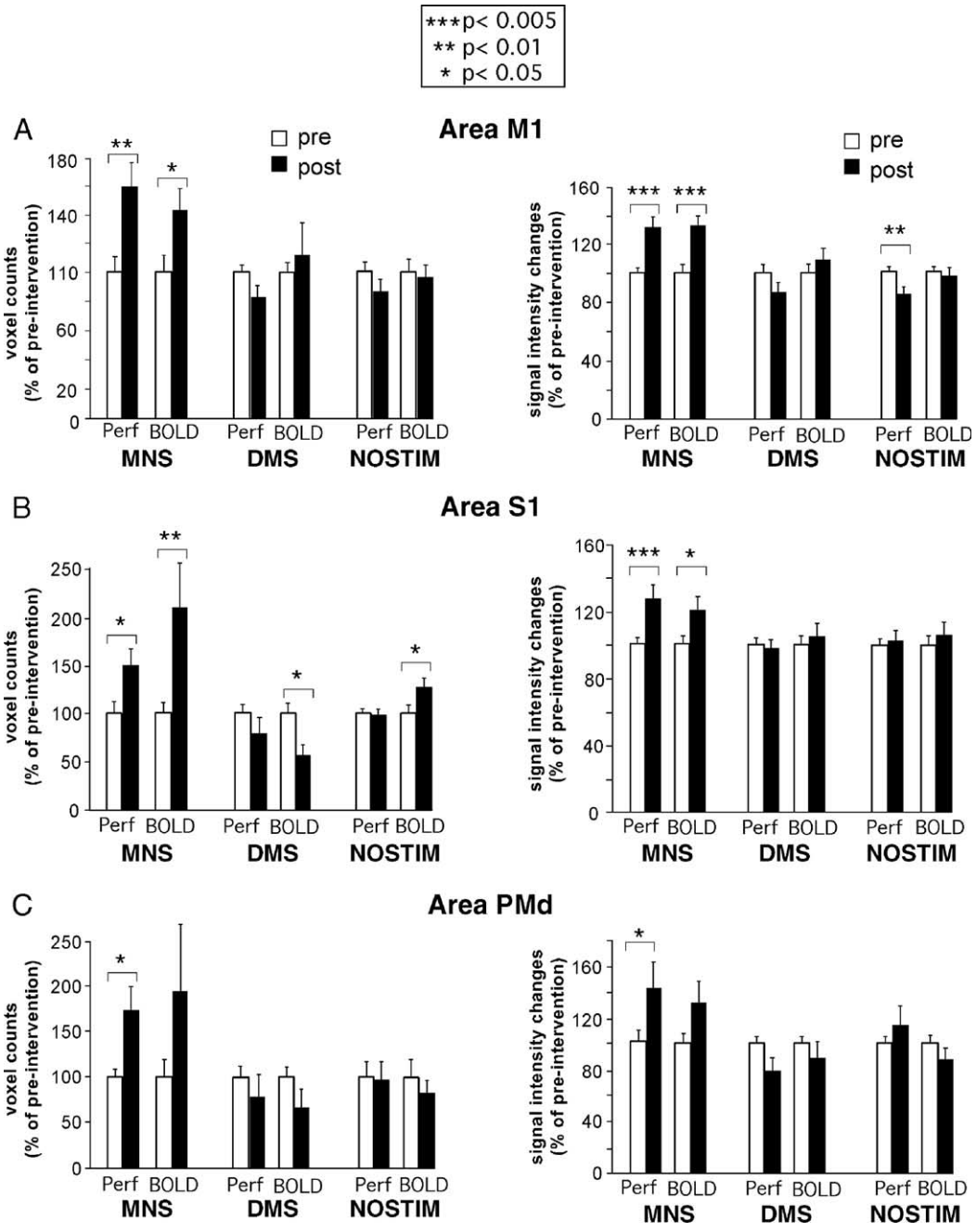

Fig. 4. Group data showing voxel count (left hand panels) and signal intensity changes (right hand panels) in each of the ROIs (M1, S1, and PMd). Note that MNS led to an increase in voxel count and signal intensity changes in M1 (top) and S1 (mid) with both BOLD and perfusion and in PMd only with perfusion. By contrast, DMS and NOSTIM showed either no changes or a decrease in both voxel counts and signal intensity. The number of voxels used as a mask in each intervention group was: MNS: 69.12 ± 4.39 in M1, 59.00 ± 3.224 in S1, 35.13 ± 5.76 in PMd. DMS: 59.86 ± 5.24 in M1, 49.71 ± 4.26 in S1, 26.29 ± 5.77 in PMd. NOSTIM: 52.33 ± 8.76 in M1, 46.47 ± 10.05 in S1, 31.33 ± 8.71 in PMd. Note that SEM of voxel counts was consistently higher than that of signal intensity.

was displaced up in the vertical axis towards other finger representations.

Influence of somatosensory input on motor cortical function

Somatosensory input is required for motor control (Salinas and Abbott, 1995; Gentilucci et al., 1997; Yao et al., 2002; Rabin and Gordon, 2004) and motor learning (Pavlides et al., 1993). Patients with pansensory neuropathy, in whom somatosensory input is severely disrupted, display characteristic motor abnormalities (Rothwell et al., 1982; Sanes et al., 1984; Sesto et al., 2003). Similarly, in healthy volunteers, interruption of tactile feedback results in poor control of skilled finger movements (Rabin and Gordon, 2004), a finding consistent with the reported reduction in corticospinal excitability targeting muscles located within an anesthetized body part (Rossi et al., 1998). These findings, evaluating the consequences of reduced sensory input, led to the proposal that somatosensory stimulation applied to one body part

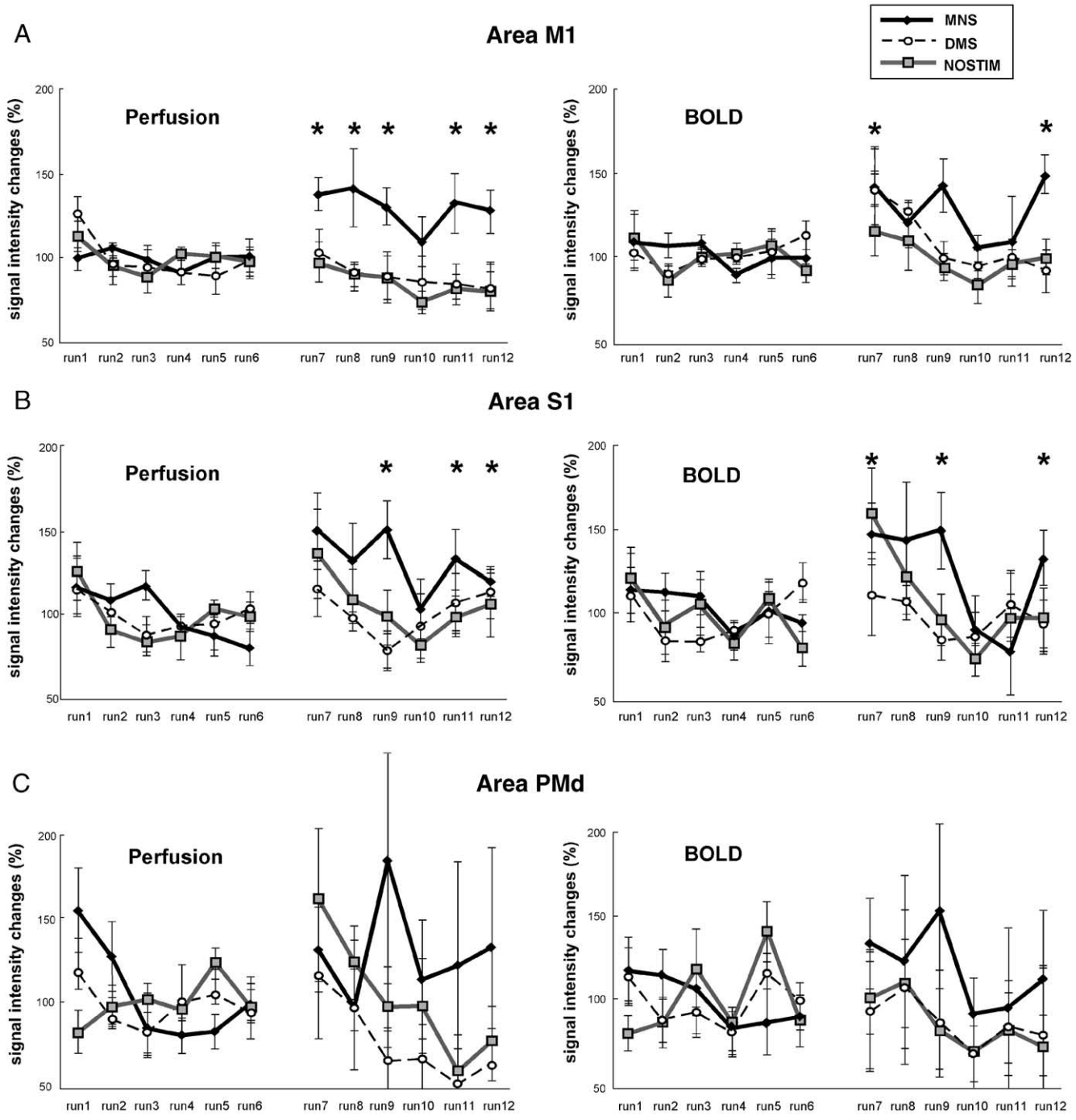

Fig. 5. Group data showing voxel count (left) and signal intensity changes (right) with perfusion and BOLD over 12 runs in each ROI. Note a lasting increase in signal intensity for up to 60 min following the end of stimulation that is more evident in M1 in nearly every run, to a lesser extent in S1, and not consistently evident in PMd. Note that, as opposed to the results from M1 or S1, the signal intensity in PMd was less stable across runs and among individuals (compare the SEM bars).

could have the opposite effect, enhancing motor cortical function within the stimulated body part representation.

Electrical stimulation of nerve trunks results in synchronized activation of muscle spindles and cutaneous afferents (Campbell, 1999; Kimura, 2001) that activate primary somatosensory and motor areas (Ibanez et al., 1995; Mauguiere et al., 1997; Backes et al., 2000; Kampe et al., 2000; Hashimoto et al., 2001; Golaszewski et al., 2002b). A period of somatosensory stimulation results in increases in motor cortical excitability (Ridding et al., 2000; Kaelin-Lang et al., 2002) and intracortical facilitation (Kobayashi et al., 2003) and a decrease in intracortical inhibition (Classen et al., 2000) that outlast the stimulation period. These changes in motor cortical excitability are influenced by GABAergic neurotransmission (Kaelin-Lang et al., 2002) and may involve LTP-like mechanisms (Godde et al., 1996; Stefan et al., 2000, 2002). A period of somatosensory stimulation also results in

Table 2
Changes in the COG following MNS intervention

Group	Anteriorposterior (y) axis shift				Mediolateral (x) axis shift				Inferiorsuperior (z) axis shift			
	Perfusion		BOLD		Perfusion		BOLD		Perfusion		BOLD	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
MNS	0.000 ± 0.046	0.172 ± 0.196	0.000 ± 0.049	−0.369 ± 0.392	0.000 ± 0.057	0.081 ± 0.205	0.000 ± 0.040	0.397 ± 0.0265	0.000 ± 0.014	0.33 ± 0.121**	0.000 ± 0.022	0.611 ± 0.011***
DMS	0.000 ± 0.05	0.402 ± 0.318*	0.000 ± 0.080	−0.135 ± 0.557	0.000 ± 0.030	0.000 ± 0.285	0.000 ± 0.268	1.264 ± 0.546*	0.000 ± 0.016	0.397 ± 0.167**	0.000 ± 0.020	−0.280 ± 0.201*
NOSTIM	0.000 ± 0.058	0.672 ± 0.0496	0.000 ± 0.039	0.341 ± 0.406*	0.000 ± 0.038	0.619 ± 0.335	0.000 ± 0.047	1.55 ± 4.17**	0.000 ± 0.039	−0.544 ± 0.154**	0.000 ± 0.031	0.271 ± 0.200

Summary for the shift in the center of gravity of activation. Mean ± SEM. Unit: mm. Statistics were based on one-tail Student's t test with unequal variance.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.005$.

Table 3
Perfusion baseline intensity before (pre) and after (post) MNS intervention

ROI	Normalized perfusion baseline estimate	
	Pre	Post
M1	0.090 ± 0.007	0.083 ± 0.007
S1	0.058 ± 0.004	0.065 ± 0.006
PMd	0.063 ± 0.004	0.071 ± 0.005

The normalized perfusion baseline estimate is calculated as perfusion baseline estimate after subtraction of perfusion scans from the reference scans divided to the BOLD baseline.

increased task-related BOLD activation in a distributed network of motor and sensory regions (Golaszewski et al., 2004). Documentation of these changes in motor cortical function triggered renewed interest in the possible role of somatosensory stimulation in neurorehabilitation. It has been proposed that somatosensory stimulation may directly benefit aspects of motor performance in the paretic hand or leg and in swallowing function of patients with chronic stroke (Hamdy et al., 1998; Conforto et al., 2002; Fraser et al., 2002; Struppler et al., 2003a,b; Uy et al., 2003; Sawaki et al., 2004; Wu et al., 2004). However, understanding of the mechanisms underlying the influence of somatosensory stimulation on human motor function is still limited.

Effects of somatosensory stimulation on fMRI activation

Preceding any intervention, the number of voxels activated was comparable across the three sessions using either technique, indicating consistent methodology. Median nerve stimulation, upper arm stimulation, and idle time elicited fundamentally different results. Overall, median nerve stimulation led to a site-specific increase and to representational reorganization in thumb-movement-related activation predominantly in primary somatosensory and motor and to some extent premotor cortices, in the absence of changes when stimuli were applied to the upper arm or with idle time.

In the somatosensory cortex, thumb-movement-related activation increased and the thumb center of gravity shifted up towards the other finger representations only after median nerve stimulation. Stimulation of a nerve trunk generates synchronized afferent volleys that reach the stimulated body part representation in the primary somatosensory cortex (Ibanez et al., 1995; Mauguiere et al., 1997; Backes et al., 2000; Hashimoto et al., 2001; Kimura, 2001). It is possible that repeated stimulation over 2 h resulted in strengthening connections within the cortical representation of glabrous aspect of the thumb and fingers 2 and 3 (innervated by the median nerve), a form of Hebbian plasticity (Hebb, 1949). The somatosensory cortex is organized with well-defined boundaries between finger representations, with the thumb located inferior and lateral and the other fingers superior and medial along the postcentral gyrus (Baumgartner et al., 1991; Beisteiner et al., 2001). The displacement of the thumb COG towards the other finger representations suggests that somatosensory stimulation primed the representation of median nerve-innervated fingers (thumb, index, and middle fingers). Our results suggest that performance of thumb movements during scanning recruited novel regions of the somatosensory cortex, possibly including the "primed" representations of resting fingers 2 and 3. The overall increased activation in S1 is consistent with a

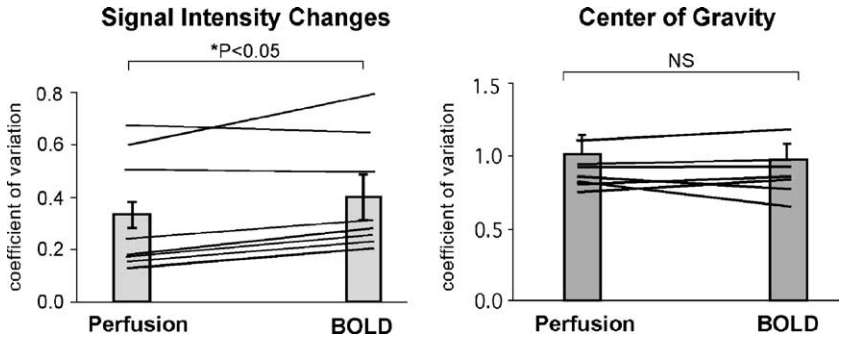

Fig. 6. Coefficient of variation of signal intensity and COG with perfusion and BOLD. Note the lower CV of signal intensity with perfusion than with BOLD. Solid lines showed individual data, whereas the bars display the group data.

previous report (Golaszewski et al., 2002b) and may reflect an enlargement in the cortical areas activated by thumb movements (Xerri et al., 1999).

In the primary motor cortex, thumb-movement-related fMRI activation increased with median nerve stimulation only, in the absence of changes in COG in any of the three axes. Increased voxel count and signal intensity in M1 could be explained by an increased excitability of voxels within the thumb motor representation, possibly subthreshold preceding median nerve stimulation (Saad et al., 2003; Huettel et al., 2004). This effect was site-specific because it was absent with proximal arm stimulation and with no stimulation and is consistent with previous TMS reports showing increased corticomotor excitability in the stimulated body part representation (Hamdy et al., 1998; Ridding et al., 2000; Kaelin-Lang et al., 2002). Reorganization within the motor cortex could be driven from direct input originated in S1 through LTP-like mechanisms, required for skill acquisition and motor control (Asanuma and Arissian, 1982; Sasaki and Gemba, 1987; Pavlides et al., 1993; Stepniewska et al., 1993; Kaneko et al., 1994a,b, Caria et al., 1997; Gentilucci et al., 1997; Wu and Kaas, 2003; Krubitzer et al., 2004; Rabin and Gordon, 2004). These representational increases in fMRI activation in the primary sensorimotor regions expand a recent study (Golaszewski et al., 2004) and could represent the neural substrates underlying reported beneficial effects of somatosensory stimulation on motor function. For example, somatosensory stimulation of a body part elicits improvements in motor performance in patients with chronic stroke (Conforto et al., 2002; Fraser et al., 2002; Struppler et al., 2003a; Wu et al., 2004). The lack of changes in COG_{M1} is not surprising given the mosaic-like organization of the M1 upper limb representation, characterized by lack of detailed boundaries between different finger representations (Donoghue et al., 1992; Wu et al., 2000).

In the dorsal premotor cortex, thumb-movement-related perfusion fMRI activation experienced a moderate increase with median nerve stimulation only, in the absence of changes in COG in any of the three axes. Performance of repetitive thumb movements requires close attention to movement kinematics, particularly movement direction and speed, and results in PMd activation (Morgen et al., 2004a,b). The left PMd, activated in our study, is specialized in planning and processing spatial patterns or trajectories of intended movements (Schubotz and von Cramon, 2003) required to perform this motor task. Interestingly, PMd receives inputs from somatosensory cortex as well as higher order parietal association areas (Strick and Kim, 1978; Zarzecki et al., 1978; Cavada and Goldman-Rakic, 1989; Wu and Kaas, 2003), possibly contributing to the participation of the internal representation of body scheme in programming the correct execution of direction-specific thumb movements (Schubotz and von Cramon, 2003). Possible explanations for the weaker activation in PMd than in M1 include the lower density of inputs directly originated in S1 and its weaker corticospinal output (Nudo and Masterton, 1990; Galea and Darian-Smith, 1994; Wu et al., 2000; Huffman and Krubitzer, 2001; Wu and Kaas, 2003). The participation of PMd in the control of executive motor functions may become more prominent after cortical lesions like stroke (Johansen-Berg et al., 2002; Miyai et al., 2002; Fridman et al., 2004).

BOLD and perfusion MRI signals

To monitor baseline blood flow, which may influence BOLD fMRI (Logothetis and Wandell, 2004), we simultaneously collected BOLD and perfusion data. It has been suggested that perfusion fMRI signal correlates well with neuronal spiking rate (Fox and Raichle, 1984; Mathiesen et al., 1998; Hoge et al., 1999; Hyder et al., 2000), is reproducible, and provides stable localization of activation sites (Kim and Tsekos, 1997; Luh et al., 2000). Results from our study showed comparable effects with both signals in primary somatosensory and motor cortices. These effects lasted for at least 60 min and did not rely on changes in baseline perfusion, consistent with previous PET studies (Fox and Raichle, 1984, 1986; Seitz and Roland, 1992; Ibanez et al., 1995). The duration of the effect is reminiscent of the duration of changes in corticomotor excitability in the previous TMS studies after somatosensory stimulation. Furthermore, comparing BOLD and perfusion showed a lower variability in signal intensity with the latter. It would be interesting to determine in future studies if subthreshold peripheral nerve stimulation elicits changes in activation patterns similar to those elicited by suprathreshold stimulation. An advantage of such approach would be to improve experimental approaches allowing double blind experimental designs.

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