Neural Activity in Human Primary Motor Cortex Areas 4a and 4p Is Modulated Differentially by Attention to Action


INTRODUCTION

Accurate performance of an action may require attention to many aspects thereof during its execution. This is most evident during the acquisition of a new motor skill. Many of our actions, however, have become automatic, e.g., walking or cycling, and we do not need to pay attention to them while they are performed. Also, in our everyday life we often perform two or more actions in parallel while focusing our attention on only one of them. The following question then arises: how do we manage to maintain a sufficient level of control for such less or unattended actions?

It is known that prefrontal, anterior cingulate, and parietal cortices are engaged during controlled motor performance and that their degree of activation decreases the more a task becomes automatic (Grafton et al. 1995; Passingham 1996). By contrast, orienting gaze (and thus attention) toward an action may lead to a general increase in neural activity in several motor relevant areas including the primary motor cortex, as suggested by a recent functional magnetic resonance imaging (fMRI) study (Baker et al. 1999). In our current study we used fMRI in normal volunteers to investigate the neural mechanisms associated with a stereotyped performance of a movement while gradually changing the amount of attention to this action to identify structures differentially engaged in the control of attended and nonattended action. Accordingly, we chose a dual visual and motor task in which subjects were asked to perform 1) a stereotyped right index finger movement that required no learning and 2) a visual distractor task. The latter was introduced to allow us to modulate subjects' levels of attention to motor task performance without interfering with movement type, amplitude, and frequency (Fig. 1). Kinematic recordings confirmed that mean frequency and mean amplitude of the forefinger movements did not differ between the three experimental conditions.

A preliminary account was published in abstract form (Binkofski et al. 1998).

METHODS

Subjects

Six healthy, right-handed volunteers, 25–35 yr of age (5 males and 1 female) participated in this study after providing informed consent. Handedness was assessed by the Oldfield inventory (Oldfield 1971). The study was approved by the local ethic committee of the Heinrich-Heine-University Düsseldorf.

Experimental procedure

Subjects were asked to move their right index finger back and forth in the form of a well-shaped “U” (Fig. 1A) at a constant amplitude and a frequency of 1.5 Hz (paced by a metronome to keep the movement constant throughout all experimental conditions), while they looked at a video display unit presented in the MR scans through a mirror. A red screen was presented in condition 1 with occasional short intermittent flashes of green light (100 ms) in conditions 2 and 3. Four to seven such flashes were presented in different time intervals in one scanning block (10 s). Prior to fMRI scanning subjects were trained to perform the four different tasks (3 experimental conditions plus baseline): 1) directed attention to the moving finger, while looking at the screen but not paying attention to it (condition 1); 2) directed attention to the screen and not counting the intermittent short flashes of green, while...
Brain activity was measured by fMRI using echo planar imaging (EPI) to exploit the blood oxygen level dependent (BOLD) effects. BOLD contrast image volumes were acquired at 1.5 T (Siemens VISION) with gradient-echo, echo-planar imaging (TR/TE = 5,000 ms/66 ms, α = 90°). Each volume comprised 30 contiguous 4-mm slices, with an in-plane resolution of 3 × 3 mm. Each subject underwent four consecutive imaging sessions comprising 320 such volumes. The first 10 volumes of each session were discarded to circumvent T1 saturation effects. For each subject separately, the EPI time-series images were realigned to the 20th image of each measurement, stereotactically normalized and smoothed with an isotropic Gaussian kernel of 8–10 mm FWHM resulting in an in-plane resolution of approximately 8 mm (Friston 1995; Friston et al. 1995, 1996). The entire imaging time series for each subject was used for a group analysis, representing 1,920 image volumes in total. Condition-specific effects were estimated using the “General Linear Model” and theory of Gaussian random fields as implemented in SPM97. A high-pass filter with a cutoff frequency of 0.19 cycles per min modeled and excluded low-frequency confounding effects in the time series. Adjusted voxel means for each condition and the adjusted error variance were generated. The differences between conditions were assessed by weighting the condition means with the appropriate contrast conditions. An additional conjunction analysis (Price and Friston 1997) was performed for all experimental conditions (conditions 1, 2, and 3) relative to the baseline. This analysis reveals the areas that behave congruently irrespective of the given level of attention. The imaging data were also compared with the subjective attention scores. Multiple subjects and the replication of conditions were taken into account by using linear contrasts to test hypothesis of regionally specific condition effects. The statistical parametric map SPM(2) for all comparisons was thresholded at a Z value of 3.09 (P = 0.001 uncorrected for multiple comparisons), and the resulting foci were characterized in terms of both spatial extent and peak height corrected for multiple comparisons at the 5% level (Friston 1995; Friston et al. 1995, 1996).

Comparison with the probabilistic maps

Cytoarchitectonic mapping of areas 4a and 4p was performed in 10 postmortem human brains obtained at autopsy from subjects with no history of neurological or psychiatric diseases. All brains were obtained through the body donor program of the Department of Anatomy, University of Duesseldorf, Germany. The brains were suspended at the basilar artery and fixed for approximately 5 mo in 4% formaldehyde or Bodian’s fixative. After fixation, T1 weighted MR scans (1.5 T Siemens Magnetron SP scanner, 3-D fast low angle shot [FLASH] sequence, flip angle 40°, TR 40 ms, TE 5 ms) were acquired for documentation of brain size and shape before histological processing. The brains were dehydrated in graded alcohols, embedded in paraffin, and sectioned coronally (20-μm whole brain sections). Images of the paraffin blockface were obtained after each 60th section with a charge-coupled device (CCD) camera. Each 60th section was mounted on a gelatin-coated slide and stained for cell bodies with a Nissl-like method (Merker 1983).

Rectangular regions of interest (ROIs) covering the right and left precentral gyrus were defined in each cell-stained section. In each ROI, the areal fraction of darkly stained cell bodies (gray level index; GL) was measured after adaptive thresholding (Schleicher and Zilles 1990) in square, adjoining fields (size 27 × 27 μm). The resulting data matrix covering the entire ROI is the GLI image (Schleicher and Zilles 1990). Equidistant density profiles (297 μm wide, oriented orthogonally to the cortical layers and extending from the border between layers I and II to the border between layer VI and the white matter, spacing between adjacent profiles 297 μm) were extracted from each GLI image and standardized to a cortical depth of 100% by resampling the data with linear interpolation. To quantify each profile’s shape, 10 numerical features based on the laminar neuronal...
densities (e.g., mean, skewness, kurtosis) were calculated for each profile and combined into one feature vector. A mean feature vector was calculated from a block of 10 adjacent profiles, and another mean vector from a neighboring block of 10 adjacent profiles. Differences between the mean feature vectors from two neighboring blocks of profiles were calculated as Mahalanobis distances $D^2$ (Mahalanobis et al. 1949). $D^2$ values were plotted as a function of the positions of the profile blocks relative to the cortex. The resulting distance function revealed maxima where the regions covered by profiles showed differences in their laminar patterns. Statistical significance was evaluated by a Hotelling’s $T^2$ test. The positions of significant maxima were then compared with the cytoarchitectonic pattern (for numerical data see Geyer et al. 1996; for further technical details see Geyer et al. 1999; Schleicher et al. 1999, 2000).

Each mounted and cell-stained histological section was digitized with a CCD camera. The histological volume of the brain was then reconstructed in three dimensions (3-D) from the images of the paraffin blockface, the digitized histological sections, and the MR volume of the same brain with linear and nonlinear transformations (Schormann et al. 1996). With an interactive voxel-painting program the extent of areas 4a and 4p was transferred from the histological parafine-embedded section to the corresponding sections of the reconstructed volume. Thus a microstructurally defined representation of cytoarchitectonic areas 4a and 4p was obtained in the 3-D reconstructed histological volume of each brain. Each histological volume (with the representations of areas 4a and 4p) was then spatially normalized to the reference brain of a computerized atlas (which is oriented in the 3-D space of the Talairach coordinate system) (see Roland et al. 1994) with an algorithm based on an extended principal axes theory and a fast automated multiresolution full-multigrid movement model (Schormann and Zilles 1998). The 10 normalized histological volumes were superimposed in the 3-D space of the reference brain. A population map was generated for each area that shows the degree of interindividually and interindividually structural variability by exemplifying, for each voxel, how many brains have a representation of this cytoarchitectonic region.

With the same warping algorithm the high-resolution Montreal Neurological Institute template and the SPM maps were aligned to the reference brain. The functional activation foci were then superimposed with the 50% isocontour (i.e., representation in $\pm$5 brains) of each area’s population map. The percentage of overlap between the volumes of the activation foci and the volumes of the 50% isocontour of areas 4a and 4p was calculated.

**Results**

**Morphological features of area 4a and 4p**

The primary motor cortex (Brodman’s area 4) is located in the precentral gyrus. The caudal border of area 4 (toward the primary somatosensory cortex) lies in the depth of the central sulcus close to its fundus. The nonprimary motor cortex (Brodman’s area 6) rostrally abuts on area 4. Dorsomedially on the cortical convexity (toward the midline), the border between area 4 and 6 lies on the exposed cortical surface on the vertex of the precentral gyrus. Further ventrolaterally (toward the Sylvian fissure), it recedes in a caudal direction and eventually disappears in the depth of the central sulcus. Areas 4a and 4p are two parallel bands within area 4 (rostral band: 4a; caudal band: 4p) running mediodorsally from the midline to the Sylvian fissure. Lower layer III pyramidal cells are small and loosely aggregated in area 4p, larger and more densely packed in area 4a, and even larger, more elongated, and sometimes arranged in several parallel rows like a palaxon in area 6. There are no differences in size, packing density, or arrangement of giant pyramidal cells between areas 4a and 4p (Geyer et al. 1996).

**Behavioral data**

The kinematic recordings did not show any significant differences between the three experimental conditions regarding the mean frequency (condition 1: $1.4 \pm 0.07$ Hz, mean $\pm$ SD; condition 2: $1.44 \pm 0.11$ Hz; condition 3: $1.38 \pm 0.49$ Hz) and mean amplitude (condition 1: $4.9 \pm 0.58$ cm; condition 2: $5.1 \pm 0.6$ cm; condition 3: $5.0 \pm 0.49$ cm) of the U-shaped finger movements. The analog assessment of the subjective levels of attention to movement, however, showed that significantly different values were reached in each condition (condition 1: $9.24 \pm 0.07$; condition 2: $5.95 \pm 1.28$; condition 3: $3.71 \pm 0.49$; Fig. 1B).

**Comparison between activation foci and the probabilistic maps**

The conjunction analysis (Price and Friston 1997) of all active conditions (conditions 1, 2, and 3; each contrasted with the baseline) revealed significant activation of the primary motor cortex (BA 4), the right cerebellum, and extrastriatal areas on both sides (Table 1A).

**Table 1. Significant activation areas**

<table>
<thead>
<tr>
<th>Activated Area</th>
<th>Stereotactic Coordinates</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Conjunction of active conditions versus control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area 4</td>
<td>$-48, -8, 56$</td>
<td>5.1</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>$12, -56, -16$</td>
<td>3.9</td>
</tr>
<tr>
<td>Extrastriatal r</td>
<td>$20, -96, 12$</td>
<td>5.3</td>
</tr>
<tr>
<td>Extrastriatal l</td>
<td>$-30, -92, 8$</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>B. Parametric changes in area 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a, not modulated</td>
<td>$-48, -8, 56$</td>
<td>5.1</td>
</tr>
<tr>
<td>4p, modulated</td>
<td>$-36, -20, 48$</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>C. Motor-directed attention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal r</td>
<td>$20, 60, 1$</td>
<td>3.2</td>
</tr>
<tr>
<td>vPMC r</td>
<td>$56, 16, 8$</td>
<td>3.3</td>
</tr>
<tr>
<td>Superior parietal r</td>
<td>$36, -48, 62$</td>
<td>3.8</td>
</tr>
<tr>
<td>Secondary sensory r</td>
<td>$56, -28, 24$</td>
<td>4.3</td>
</tr>
<tr>
<td>Intraparietal r</td>
<td>$28, -56, 52$</td>
<td>3.3</td>
</tr>
<tr>
<td>Temporo-occipital r</td>
<td>$44, -60, 16$</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>D. Visually directed attention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLPC r</td>
<td>$44, 40, 28$</td>
<td>3.3</td>
</tr>
<tr>
<td>vPMC l</td>
<td>$-56, 8, 40$</td>
<td>3.8</td>
</tr>
<tr>
<td>Posterior parietal r</td>
<td>$56, -52, 44$</td>
<td>3.5</td>
</tr>
<tr>
<td>Precuneus r</td>
<td>$4, -56, 48$</td>
<td>3.7</td>
</tr>
<tr>
<td>Fusiform gyrus r</td>
<td>$48, -86, -20$</td>
<td>3.4</td>
</tr>
<tr>
<td>Fusiform gyrus l</td>
<td>$-52, -56, -12$</td>
<td>3.6</td>
</tr>
<tr>
<td>Extrastriatal r</td>
<td>$32, -76, -16$</td>
<td>3.9</td>
</tr>
<tr>
<td>Extrastriatal l</td>
<td>$-16, -84, -12$</td>
<td>3.7</td>
</tr>
<tr>
<td>Primary visual l</td>
<td>$-8, -84, 8$</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Stereotactic coordinates in mm in Talairach space (Talairach and Tournoux 1988). A: conjunction analysis of all active conditions in contrast to the control condition (condition 1 + condition 2 + condition 3 > condition 4) showing the common activation areas related to right index finger movements. B: parametric evaluation of neural activity in Area 4 that was modulated (area 4p: posterior) and not modulated (area 4a: anterior) by attention to finger movement. C: motor-directed attention (condition 1 > condition 2 + condition 3). D: visually directed attention (condition 2 + condition 3 > condition 1). Area 4, Brodmann’s Area 4; modulated, modulated by attention to action; not modulated, not modulated by attention to action; vPMC, ventral premotor cortex; DLPC, dorsolateral prefrontal cortex.
Parametric comparison of the signals with attention scores revealed that the BOLD signal in the depth of the central sulcus co-varied with the subjective levels of attention to action (Table 1B; Fig. 2A). By contrast, the neural activity in a more lateral part of the central sulcus did not show such a co-variation (Table 1B; Fig. 2B). To assess whether these differential responses belonged to different subareas of primary motor cortex, the local maxima within these activation areas were co-registered with the probabilistic cytoarchitectonic population maps of areas 4a and 4p of the human primary motor cortex (Geyer et al. 1996). The focus modulated by attention overlapped by 92% with area 4p but did not overlap at all with area 4a (Fig. 2A). By contrast, the focus that was not modulated by attention overlapped by 74% with area 4a, and extended into area 6 (Fig. 2B), but did not overlap with area 4p. The real world distance between the centers of gravity of the two foci was 19 mm, and there was no overlap between two of them. The anatomical location of these two differentially modulated activation foci within area 4 and their relationship to the cytoarchitectonic probabilistic maps of areas 4a and 4p are shown in Fig. 2.

The categorical comparison between the experimental conditions with a high level of motor-directed attention (condition 1) and a high level of visual-directed attention (condition 3) yielded the following differences. Motor-directed attention relative to visually directed attention (condition 1 > condition 2 + condition 3) revealed increased neural activity basically in a right parietal-prefrontal circuit (prefrontal cortex, ventral...
premotor cortex, superior parietal, secondary somatosensory
area, intraparietal sulcus and temporoparietal cortex; Table 1C). By contrast, while visually directed attention relative to
motor-directed attention (i.e., condition 2 + condition 3 >
condition 1) revealed a bilateral circuit involving extrastriate
dorsolateral prefrontal cortex (right dorsolateral prefrontal
cortex, left ventral premotor cortex, right posterior parietal
cortex, right precuneus, bilateral fusiform gyrus, bilateral extra-
striatal cortex and left primary visual cortex; Table 1D).

**DISCUSSION**

Our data shed light on the basic mechanisms underlying
attention to action. The novel finding here was the observation
that neural activity within human primary motor cortex is
modulated differentially by attention. This novel finding par-
allels previous reports of neural activity in primary and sec-
ondary sensory cortices being modulated by attention in the
visual, auditory, and somatosensory domains (Corbetta et al.
1993; Desimone and Duncan 1995; Fink et al. 1996; Iriki
et al. 1996; Shulman et al. 1997; Steinmetz et al. 2000;
Woldorf et al. 1993) and extends current concepts of primary
motor cortex function: attentional modulation of human pri-
mary motor cortex activity strongly questions the classical and
simplestic view of the human primary motor cortex as a pure
somatotopically organized executive motor structure (Denny-
Brown and Botterell 1948; Foerster 1936; Leyton and Sher-
ington 1917; Penfield and Rasmussen 1950).

On the basis of recent cytoarchitectonic data showing a
subdivision of the primary motor cortex (Geyer et al. 1996), we
observed that these distinct subregions within primary motor
cortex show differential attentional modulation during motor
performance. These differentially modulated foci were 19 mm
apart from each other and could therefore be clearly separated
given the spatial resolution of 8–10 mm of our images even
when one also takes into account a spatial dispersion of the
BOLD-response of 3–5 mm (Malonek and Grinvald 1996).
There was an attention-modulated area within cytoarchitectoni-
cally defined area 4p in the depth of the central sulcus and
another area within the lateral part of the posterior bank of the
precentral gyrus that was not modulated by attention. The latter
area included cytoarchitectonically defined area 4a and ex-
tended into premotor area 6. Although our understanding of
anatomical and functional parcellation within human primary
motor cortex is only at its beginning, based on our data we
hypothesize that these separate regions within human primary
motor cortex may belong to different motor channels that allow
for parallel processing of motor information with different
attentional load in situations that necessitate simultaneously
attended and unattended action. Interestingly, differential ana-
tomical connections have also been demonstrated for these
areas: area 4p, which occupies the deep part of the posterior
bank of the precentral gyrus, is primarily connected with the
primary sensory cortex (Stepniewska et al. 1993). The modu-
lation of primary sensory cortex by a motor task (Hsiao et al.
1993; Iriki et al. 1996) could thus help to explain the atten-
tional modulation of area 4p in our current study. Area 4a,
which rostrally abuts on area 4p and lies more superficially
toward the free surface, is connected to the premotor cortex
(Stepniewska et al. 1993). These subareas of primary motor
cortex have different thalamic connections in the owl monkeys
(Stepniewska et al. 1994); however, whether such connections
also exist in the human brain remains to be investigated.

Geyer et al. (1996) have already provided some data sug-
gest a differential specialization of 4a and 4p, when show-
ing that a roughness discrimination task activated area 4p
relatively more than self-generated movements. Here we show
the differential mode of neural activity in areas 4a and 4p
according to the amount of attention directed toward the action.
A parsimonious explanation for the observed modulation in
area 4p in our study may then be that increased motor-directed
attention may also include increased attention to sensory feed-
back, which in turn could have led to increased neural activity
in area 4p. Likewise, it seems possible, although speculative at
present, that area 4a of primary motor cortex might be respon-
sible for maintaining the execution of a motor program, irre-
versible of the amount of attention paid to it.

The demonstration of attentional modulation of primary
motor cortex supports the cognitive role of human primary
motor cortex in line with electrophysiological evidence ob-
tained from animal experiments: nonhuman primate M1 neu-
rons are capable of “holding in memory” movement direction,
motor sequences, and the serial order of movements (Carpenter
et al. 1999; Pellizer et al. 1995). Neurons within area 4 were
also shown to be involved in mental rotation (Lurito et al.
1991). More recently, the existence of motor output indepen-
dent higher-order representations of task objectives and con-
straints in M1 were suggested on the basis of single joint
movement experiments in monkeys (Shen and Alexander
1997). Such monkey electrophysiological evidence is supple-
mented by magnetoencephalographical studies in humans,
which implicate M1 in motor imagery and movement obser-
vation (Hari et al. 1998; Schnitzler et al. 1997). Thus our
functional imaging results and previous data support the notion
that human primary motor cortex function goes beyond simple
motor output.

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