Frontal lobe contribution to voluntary movements in humans

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We assessed the contribution of human prefrontal cortex to movement related potentials (MRPs) generated prior to voluntary movements. MRPs were recorded during self-paced movements of the right thumb (experimental condition I), the left thumb (experimental condition II) and both thumbs (experimental condition III) from patients with focal lesions centered in dorsolateral frontal association cortex (PFCx, n = 11) and in age matched controls (n = 11). Controls generated a slowly rising readiness potential (RP) beginning at about 1000 ms prior to movement. A negative shift (NS') began at about 450 ms and a motor potential (MP) appeared at about 100 ms prior to movement. Both the NS' and MP were maximal over scalp sites contralateral to movements. Unilateral PFCx lesions preferentially reduced the RP and NS' components of the MRP. This indicates that PFCx is involved in a neural network beginning at least 1000 ms prior to movement. The differential PFCx effects on the early (RP, NS') and late components (MP) suggest that these MRPs index different movement-related circuits.

INTRODUCTION

Human movement-related potentials (MRPs) have been extensively studied in normals. Data have been reported on the scalp topographical distribution, and the effects of psychological and task-related variables. The observation that MRPs onset up to 1 s prior to movements suggest that these potentials are generated by neural circuits involved in motor preparation and initiation.

Intracranial recordings in humans have reported discrete MRP sources in pre- and postcentral gyrus with additional contributions from supplementary and premotor cortices. Data from animal, magnetic, regional cerebral blood flow, and human scalp topography studies indicate that motor, supplementary, premotor, thalamus, basal ganglia, and hippocampal structures may contribute to MRP generation. The role of each of these structures in human MRP generation is not completely defined.

Most investigators agree that the motor potential (MP) has its major neural source in the primary motor area. However, neural sources of earlier MRP components (readiness potential, RP; and late portion of the RP, termed as negative shift, NS') are a matter of controversy. Intracranial data in humans indicate that the sensorimotor cortex is a major contributor to both the RP and NS'.

Human lesion studies are few and the results inconclusive. Deecke et al. noted a reduction of the vertex maxima of the RP in patients with unilateral lesions of supplementary motor area (SMA). Impaired and normal MRPs have also been reported in patients with idiopathic Parkinson's disease. Focal brain lesions centered in posterior association Brodmann areas 39, 40 and 7 have been reported to reduce the NS' component of MRPs. Neuropsychological studies have documented the role of frontal cortex in control of complex goal directed movements. These findings coupled with anatomical data revealing extensive bidirectional prefrontal cortex connections to motor structures suggest that PFCx may contribute to MRP generation.

In monkeys, Johnson recorded the earliest onset of movement related slow negativity from areas 9, 10 and 46 of the prefrontal cortex about 2 s prior to movement at a time when no activity was seen in the motor cortex. In contrast, Gemba et al. failed to record the RP from various loci of the prefrontal cortex with chronically implanted surface and depth electrodes in monkeys. Thus, the data in non-human primates are inconclusive.

The present study was designed to assess the contribution of human frontal lobe to MRP generation by recording MRPs in patients with unilateral lesions in the dorsolateral prefrontal cortex.
MATERIALS AND METHODS

Subjects

Two groups of subjects were studied. Eleven neurologically normal subjects (8 male; mean age = 58.1 ± 11.2 years) constituted the normal control group. Subjects with history of substance abuse, psychiatric or serious medical disorders, dementia or multiple neurological events were excluded. All subjects gave informed consent and were paid for their participation.

Frontals

MRPs were initially recorded from 15 patients with lesions centered in prefrontal cortex. One patient was excluded due to excessive eye blinks. Three additional postsurgical subjects were excluded in order to decrease problems with interpretation of scalp topography data due to current shunting through their craniotomy sites. After this exclusion, the frontal group consisted of 11 patients (10 male; mean age = 63.1 ± 8.5 years) with lesions centered in dorsolateral Brodmann's areas 8 and 46 including variable portions of areas 6, 9, 10, 12, 11, 44 and 45 in individual subjects (5 right (R), 6 left (L); mean lesion volume = 39.4 cm³) (Fig. 1). Hypometabolism may have been present in structures anatomically connected to prefrontal cortex 15, 16, 44, 63. However, no metabolic data such as PET or SPECT scanning were available to address this issue. All lesions were due to single cerebrovascular events and all patients were studied at least 6 months post-lesion. All patients were functioning independently and had neither the classic frontal lobe syndrome seen in bilateral prefrontal disease 50 nor major psychological problems such as depression or anxiety disorder.

Lesion reconstruction

Patients were selected on the basis of CT scan evidence of focal unilateral damage in prefrontal cortex. Lesions evident on CT scan were transcribed onto corresponding CT templates. Software permitted reconstruction of the lateral perspective, determination of lesion volume and cytoarchitectonic areas affected, and construction of group-averaged lesions. Details are presented elsewhere 35.

Experimental design and recording

MRPs were recorded with Ag/AgCl electrodes placed at FP1, FPZ, FP2 (overlying superior frontal gyrus), F3, FZ, F4 (midfrontal gyrus near superior frontal cortex), C3, CZ, C4 (precentral gyrus) and, P3 and P4 (superior parietal lobule) 35. Three additional electrodes were placed over precentral areas: denoted as C3a, CZa and C4a. These were located 2 cm anterior to C3, CZ, and C4, respectively (between precentral and superior frontal gyrus). All electrodes were referenced to linked earlobes. A ground electrode was placed on the forehead. EMG responses were recorded from a pair of electrodes placed on the thenar muscle and the first metacarpal–phalangeal joint of the hand involved in the task. Electrode impedances were kept below 5 KΩ. EEG, EOG, and EMG were recorded using Grass P511 amplifiers. EEG and EOG were amplified (50 KΩ) and bandpass filtered from 0.01 to 100 Hz (time constant = 5 s). EMG activity was amplified (10 KΩ) and filtered from 10 to 100 Hz. Signals were digitized at a sampling rate of 128 Hz/channel by a PDP-1173 minicomputer. Digitized single trial epochs and coded button presses were stored on magnetic tape for off-line averaging and analysis. The stored data was averaged from epochs of raw EEG beginning 1400 ms prior to the trigger and continuing for 600 ms postmotion. Trials contaminated by eye

Fig. 1. Lesion extent in patients with focal unilateral damage centered in prefrontal structures (n = 11, 5 R, 6 L; mean lesion volume = 39.4 cm³). The lines on the lateral reconstruction indicate the location of the axial sections used in CT transcription. Lesions determined by CT scan from individual patients were transcribed onto 0° to canthomeatal line templates. A lateral view of the lesion extent was then projected from the axial sections by software reconstruction methods. The digitized lesion data from individual subjects was then averaged to generate the group lesion densities for both lateral and axial views. Unilateral right-sided lesions have been reflected onto the left hemisphere. The scale indicates the percentage of patients with damage in the corresponding area.
blinks, excessive EMG activity or amplifier blocking were rejected by computer algorithms prior to averaging. Sums of 100–150 artifact-free trials were obtained for each condition.

Procedure

Recording was conducted in a dimly lit, electrically and acoustically shielded room with the subject seated in a comfortable reclining armchair. Subjects were given a pushbutton (two push-buttons in the bimanual condition) mounted atop a cycle handle grip. The subject was instructed to loosely grasp the handle in the palm and briskly press and release the button with the thumb. Button excursion was about 8 mm. The button press was self-initiated and self-paced. The participants were required to fix their gaze at the tip of the button in all conditions and were further instructed to avoid eye blinking or lateral eye movements during the button press. Lateral eye movements and eye blinks were monitored by an EOG electrode placed below and slightly lateral to the inferior orbit of the eye. Trials contaminated by eye movements were excluded from averaging. The subjects were instructed to produce isolated thumb movements, suppress other motor activity and were also warned against synchronizing thumb movements with respiration. Subjects were trained in a practice session to press the button with an intermovement interval (IMI) of 2–7 s in order to decrease contributions from overlapping MRP epochs.

The experiment was divided into 3 counterbalanced conditions. Conditions 1 and 2 consisted of unilateral thumb presses with either the right or left thumb (RHP, LHP). During Condition 3 MRPs were recorded during simultaneous bimanual thumb presses (BMP). Each experimental condition was separated by a 5-min rest period. Subject performance was monitored on a closed circuit television monitor by the experimenter. The subject and the EEG were monitored for signs of drowsiness and recording was halted if drowsiness was noted. Subjects were given feedback on their performance when necessary through an intercom system. Testing was completed in about one and a half hours.

 Behavioral measures

IMI. The subjects were required to perform self-paced switch closures in a 2.7 s interpress interval. The IMI was compared between control and patient groups.

Perseveration and motor functions. In a computer-assisted manual tracking task, subjects were required to move a cursor around the circular track on the computer screen as quickly as possible. The scoring was done with regard to: (1) total time spent on the target; (2) total time spent off the target and (3) total distance on the track (in cm). All measurements were computer assisted. The Wisconsin Card Sorting Test (WCST) was administered to all subjects.

Data reduction and analysis

Four main MRPs were identified based on individual and group mean averages. A regression line was fitted to these MRP phases. The RP (or N1) was identified as the initial portion of the Donchin 46) prior to a movement onset. In this report, we will refer to this component as NS'.

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NS' of Knight et al. 40) and 400–500 ms (RP150 of Kutas and Donchin46). The NS' was computed as the potential difference between the N2a and N1. The MP was also calculated as the potential difference between the N2b and the sum of N1 and N2a components.

Isopotential group maps were constructed using normalized voltages from each subject. The electrode site values were first normalized to allow comparisons of the maps across groups and conditions with all scales ranging between 0 and 100 percent. An automated interpolation algorithm was employed which calculated the contribution of each electrode on each interelectrode point of the map. The contribution from each electrode inversely weighted as a function of the cube of the interelectrode distance.

Statistical analysis

Data were subjected to univariate and multivariate analysis of repeated measures (MANOVA)68 (subject x group x condition and electrode). Tukey test was used for post-hoc pairwise comparisons. Corrected t-tests were used to make specific electrode comparisons. Correlational analysis was carried out to evaluate the relationship between behavioral measures and MRPs.

RESULTS

Behavioral data

IMI. The mean IMI in controls (RHP, 3.07 ± 0.70; LHP, 3.42 ± 0.60; BMP, 3.34 ± 0.50 s) and frontals (RHP, 3.05 ± 0.53; LHP, 2.79 ± 0.64; BMP, 2.96 ± 0.48 s) did not differ between groups.

Manual tracking task and WCST. In the manual tracking task, controls and frontals performed comparably. No group difference could be determined with respect to: (1) time spent on the target; (2) time spent off the target; and (3) total distance covered. The PFCx group had significantly higher perseverative errors on the WCST relative to patients with lesions centered in posterior association cortex and normal controls (P < 0.01). The frontal group also achieved fewer sorting categories than controls (P < 0.001).

Electrophysiological data

Control group. Controls generated slowly developing negativity beginning at about 1000 ms prior to the switch closure (RP). The RP was symmetrical, widely distributed, and maximal at the frontocentral midline electrodes (CZ and CZA). The NS' began at about 450 ms prior to the switch closure. The NS' was maximal over frontocentral regions contralateral to right hand movement in controls (RHP, C3 vs C4, F1,10 = 4.2, P < 0.01).
Fig. 2. Overlapped group grand-averaged waveforms from control (solid) and frontal (dotted) subjects in a self-paced left (a) and right (b) hand button press. Note the contralateral enhancement of MRPs in controls in both the experimental conditions. Also note the decrement or absence of RP and NS' components in frontals. The MP, however, is observable over some leads. However, this effect was not significant in the LHP condition. The MP began at about 100 ms prior to the switch closure. The MP was maximal over contralateral sites for both left- and right-hand movements (RHP, C3 vs C4, \( F_{1,10} = 3.57, P < 0.02 \)). Larger responses were noted with the right-hand press condition in comparison to the left-hand press condition at central sites for the NS' (C3, \( F_{1,10} = 2.9, P < 0.05 \)) and MP (\( F_{1,10} = 4.2, P < \)).

Fig. 3. Overlapped group grand averages from control (solid) and right frontals (dotted) in a self-paced left (a) and right (b) hand button press. MRPs are reduced over most scalp leads in the frontals.
Fig. 4. Overlapped group grand averages from control (solid) and left frontals (dotted) in a self-paced left (a) and right hand (b) button press. MRP's are reduced over most scalp leads in the frontals.

Fig. 5. Overlapped group grand averages from control (solid), and (a) left frontals (dotted) and (b) right frontals in a self-paced bimanual switch closure. A comparable reduction is present in both the left and right frontals in this experimental condition.
During the bimanual condition MRPs were symmetrically distributed. The bimanual condition had a differential effect on MRP components. The MP tended to be enhanced during the BMP condition over some central and frontal leads (CZ, RHP vs BMP, $F_{1,10} = 2.68, P < 0.06$; CZ, LHP vs BMP, $F_{1,10} = 2.58, P < 0.07$). The mean amplitude of the RP and NS' were comparable to unimanual and bimanual conditions.

Frontal group. A clear RP beginning at about 1000 ms prior to the button press was observable in only two frontal patients. A small NS' arising at about 400–300 ms prior to the switch closure was seen in 4 of 11 patients. An MP was clearly observable in 8 of 11 patients (e.g., F3, F4, FZ, CZA). The MP started at about 100 ms before the button press and peaked at the trigger point on restricted frontal and central leads. Inspection of Fig. 3 shows a non-significant trend of contralateral enhancement of the MP (RHP, C3 vs C4, $F_{1,10} = 1.3$, n.s.) and NS' (RHP, C3 vs C4, $F_{1,10} = 1.43$, n.s.) during RHP and LHP conditions.

Control versus frontals. Due to the lack of an RP, premovement negativity in frontals did not onset until about 400 ms (PFCx, CZ, mean 410 ms; control, 1043, $P$
Fig. 7. Lesion extent in patients with focal unilateral damage centered in (a) areas 6, 8 (mean lesion volume 47.6 cm$^3$) and (b) areas 9, 46 (mean lesion volume 29.5 cm$^3$). Overlapped group grand averaged MRPs (c) from control (solid; n = 11), areas 6, 8 (dashed; n = 6) and areas 9, 46 (dotted; n = 5) groups. A greater reduction of MRPs is seen in the areas 6, 8 group.

< 0.01). In comparison to controls, MRP components in the frontal group were significantly reduced. A difference was found between the two groups for the RP (Over conditions, CZ, $F_{1,21} = 8.05$, $P < 0.01$); NS' ($F_{1,21} = 18.72$, $P < 0.001$); and MP ($F_{1,21} = 17.44$, $P < 0.001$). However, the MP component computed by the subtraction method was preserved over some leads in the patient group (for controls vs patients: FZ, $F_{1,21} = 3.1$, n.s.). These effects were found in the RHP, LHP and BMP conditions (see Figs. 2–4).

Frontals did not show contralateral enhancement in unimanual conditions. Controls showed a substantial amplitude increase of the NS' and MP components during the bimanual condition over some central and frontal leads. This bimanual effect was absent in the frontal group (for frontals: NS', BMP vs RHP, $F_{1,10} = 1.5$, n.s.; MP; $F_{1,10} = 1.4$, n.s.). The frontal group had absent or reduced RP and NS' components in comparison to controls, with relative preservation of the MP (F3, FZ, F4, C3a, C4a, Cza; subtraction method for the MP, Cza, $F_{1,10} = 1.9$, n.s.) in the bimanual condition (Fig. 5). Comparable effects were observed for right and left PFCx lesioned subjects (Fig. 5). MRPs were also equivalently reduced or abolished at scalp sites over both lesioned and non-lesioned hemisphere (Figs. 3–6). No evidence of focal MRP reduction over lesioned PFCx was observed in any condition. The P2 component appeared to be enhanced in the left frontals in comparison to controls and right frontals but the difference was not statistically significant.

Despite a considerable overlapping of lesions, the frontal group was further divided into 6 patients with lesions centered in areas 6 and 8, and 5 patients with lesions centered in areas 9 and 46 of the dorsolateral frontal cortex (Fig. 7). A significant difference was found between controls, areas 6, 8 and 9, 46 lesioned groups (MANOVA, group x condition x electrode, CZ, C3, F3, FZ) for the RP ($F_{4,15} = 3.8$, $P < 0.02$); NS' ($F_{4,15} = 3.9$, $P < 0.02$); and MP ($F_{4,15} = 6.1$, $P < 0.01$) components. Significant MRP differences were noted between control and the area 6, 8 lesioned groups for the RP ($F_{1,15} = 12.3$, $P < 0.01$); NS' ($F_{1,15} = 18.3$, $P < 0.01$); and MP ($F_{1,15} = 21.07$, $P < 0.01$) components. However, subtraction measures employed to obtain relatively pure MP component did not show a significant difference between the two groups over some precentral leads for the MP (FZ, $F_{1,15} = 1.6$, n.s.). Controls and area 9, 46 lesioned groups also differed significantly for the RP ($F_{1,14} = 8.6$, $P < 0.01$); NS' ($F_{1,14} = 8.8$, $P < 0.01$); and MP ($F_{1,14} = 8.5$, $P < 0.05$) components. Again, however, the MP component computed by the subtraction method was preserved over some precentral leads in the patient group (FZ, $F_{1,14} = 1.8$, n.s.). Thus, both patient groups had reduced RP and NS' components and partially preserved MPs relative to the controls. Comparisons at selected frontocentral sites between areas 6, 8 and 9, 46 lesioned groups indicated greater MRP reduction in areas 6 and 8 lesioned group. However, this effect was significant in only one experimental condition (RHP) (C3 and F3, RHP, RP ($t = 3.94$, $P < 0.01$); NS' ($t = 2.33$, $P < 0.05$); and MP ($t = 2.90$, $P < 0.01$).
DISCUSSION

Three premovement (RP, NS' and MP) and a post-motion (P2) component of the MRP were reliably recorded in normal controls. Unilateral focal lesions centered in dorsolateral prefrontal cortex reduced or abolished the RP and NS' premotion MRP components in all PFCx subjects indicating that PFCx provides premovement input into sensorimotor regions involved in MRP generation. The reduction of the RP and NS' was more pronounced than the late MP component in frontal lesioned subjects suggesting that the early and late components of the MRPs may index different neural circuits.

Animal studies and topographical, intracranial and magnetic recordings in humans point out that premovement-related potentials are generated in pre- and postcentral gyrus. Additional contributions may be provided from supplementary and premotor cortices. Multiple unit and slow potentials recordings in primates indicate that the N1 (RP) and N2 (MP) have a common source arising mainly from precentral gyrus.

In man, lesions in supplementary motor cortex significantly reduce the RP at the vertex electrode. The current results indicate that extensive regions of dorsolateral prefrontal cortex are also involved in MRP generation. Lesions centered both in areas 6, 8 and in areas 9, 46 had reduced MRPs relative to controls. A trend emerged for greater MRP reduction for lesions centered in areas 6 and 8 than in areas 9 and 46. This suggests that premotor (area 6) and frontal eye field (area 8) make larger contributions to MRP generation than areas 9 and 46 and is compatible with clinical and experimental data reporting clinically apparent motor deficits with premotor cortex lesions.

Unilateral lesions of both left and right frontal cortex resulted in bilateral MRP reduction indicating that each frontal lobe has bilateral input into sensorimotor regions. However, MRP abnormalities due to unilateral damage were not reversed by the remaining intact frontal lobe suggesting that MRPs may provide a sensitive index of motor dysfunction in unilateral frontal damage.

Bimanual press indexes bihemispheric activation as revealed by the symmetrical scalp distribution of MRPs in this experimental condition. Controls showed a substantial increase of the MP component during the bimanual condition in comparison to either of the unimanual conditions. In contrast, the frontal group showed no enhancement of this nor any other premovement components during the BMP further supporting the notion that unilateral frontal cortex has a bilateral influence on motor related structures.

The current data are consistent with neurobehavioral studies supporting the role of premotor and prefrontal cortex in movement preparation and execution. Behavioral data obtained from the frontal patients showed no impairment in the IMI or in manual tracking ability. These patients also showed no clinical evidence of apraxia, sequencing difficulties or elementary motor disturbances. Thus, simple and complex movement execution was unimpaired in patients with reduced RP and NS' components. However, these patients had significantly more perseverative errors on the WCST as compared to controls which may be due to inability in shifting attention. Similar impairments in WCST after unilateral prefrontal lesions have been reported by others.

Lesions of dorsolateral prefrontal cortex centered in area 46 correspond to the sulcus principalis region in monkeys which is critical for delayed response performance. Area 46 lesions result in abnormalities in attention capacity, goal-directed behavior, judgement, insight and temporal integration of external and internal inputs in humans. Neurophysiological attention deficits related to distractibility and disinhibition of sensory input are also reported in patients with prefrontal cortex lesions. Since attention and motivational factors are known to influence the Readiness potential, RP and NS' abnormalities in patients with PFCx lesions may be related to deficits in attention capacity in these patients.

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