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Bereitschaft (readiness potential) and supplemental motor area interaction in movement generation: Spinal cord injury and normal subjects

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Abstract—The readiness potential (BP) consists of movement-related cortical potentials (MRCPs) peaking in the motor potential (MP). Our objective was to better understand the role of the BP and MP in the production of voluntary movements and to help define the relative roles of the supplementary motor area (SMA) and the BP in the generation of self-paced and passive finger movements. The ultimate goal was to relate the BP (or the SMA) to external devices via conversion of potentials to a language "understood" by the receiving devices.

Key words: brain-computer interface, readiness potential, supplementary motor area.

INTRODUCTION

A network that includes the supplementary motor area (SMA), primary motor area (M1), and primary and secondary sensory areas (S1 and S2, respectively) generates the BP (readiness potential) [1–3]. The peak of the sequence of movement-related cortical potentials (MRCPs) [4], i.e., the motor potential (MP), is recorded in the contralateral M1 and thought to be the final event triggering the neuronal discharge into the pyramidal tract, descending to activate the spinal cord [5]. The BP includes implications of SMA activity for understanding spinal cord injury (SCI) and rehabilitation. How is SMA activity involved? In passive movements, the SMA is not activated but the M1 is activated. The implication of SMA involvement in movement execution is that it is active in volitional movement only. The SMA may cooperate with the M1 in movement execution. Its activation precedes that of the M1 and does not depend upon the latter. If the assumption that the SMA plays a role in triggering volitional movements is true, then signals taken from

Abbreviations: AVM = arteriovenous malformation, BEM = boundary element method, BP = readiness potential, DC = direct current, DSA = dipole source analysis, DSL = dipole source localization, EMG = electromyogram, fMRI = functional magnetic resonance imaging, Hr-EEG = high-resolution electroencephalography, M1 = primary motor area, MP = motor potential, MRCPs = movement-related cortical potentials, MRI = magnetic resonance imaging, SCI = spinal cord injury, SMA = supplementary motor area.

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the SMA, possibly in combination with those from the M1, could be used to activate external prosthetic devices as a rehabilitation measure.We have previously reported that MPs in SCI patients were mapped to a more posterior location than in normal subjects [6,7]. This was reversed in some patients who recovered. Patients with paraplegia rarely recovered function unless they had this posterior reorganization. We have shown that in SCI, the activation of the M1 moves posterior in both passive and active movements. In addition, the activation of the SMA has a more posterior location in the SCI patients with active movement. This posterior location could be of prognostic significance as we follow the patients who receive the standard of care in our rehabilitation department. We have observed movement of this posterior location to a more anterior location as recovery ensued. More recently, we saw the M1 move forward in one SCI patient as he gained recovery and then observed it move back just before he suffered a setback in complications from a spinal arteriovenous malformation (AVM).

We will present new data that emphasize the relevance of the MRCPs to rehabilitation research. The BP generates activation of voluntary motor activity and is especially connected to the SMA. **Figures 1** and **2** show normalized coordinates on *x*-*y* grids demonstrating the SMA, active "MP-M1" potentials, and passive movement dipoles.

METHODS

Patients and Controls

Sixteen SCI subjects and ten normal controls were examined with the use of the methods of high-resolution electroencephalogram (Hr-EEG) and CURRY Dipole Source Localization (DSL) Program. The subjects included 11 paraplegics and 5 tetraplegics. The average age of the SCI patients at examination was 47.29 years (paraplegics = 46.04, tetraplegics = 50.03). The average age of the controls was 36.67 years. This is a cross-sectional study with two independent samples (groups). The age difference is statistically significant in the two groups. The average time from SCI to the dated of examination was 8.67 years (paraplegics = 9.82, tetraplegics = 6.12, range = 1 month to 28 years). Each subject performed self-paced movements of the middle finger (flexion-extension every 5 s to 10 s) and had the same finger moved in a similar manner by an operator (passive

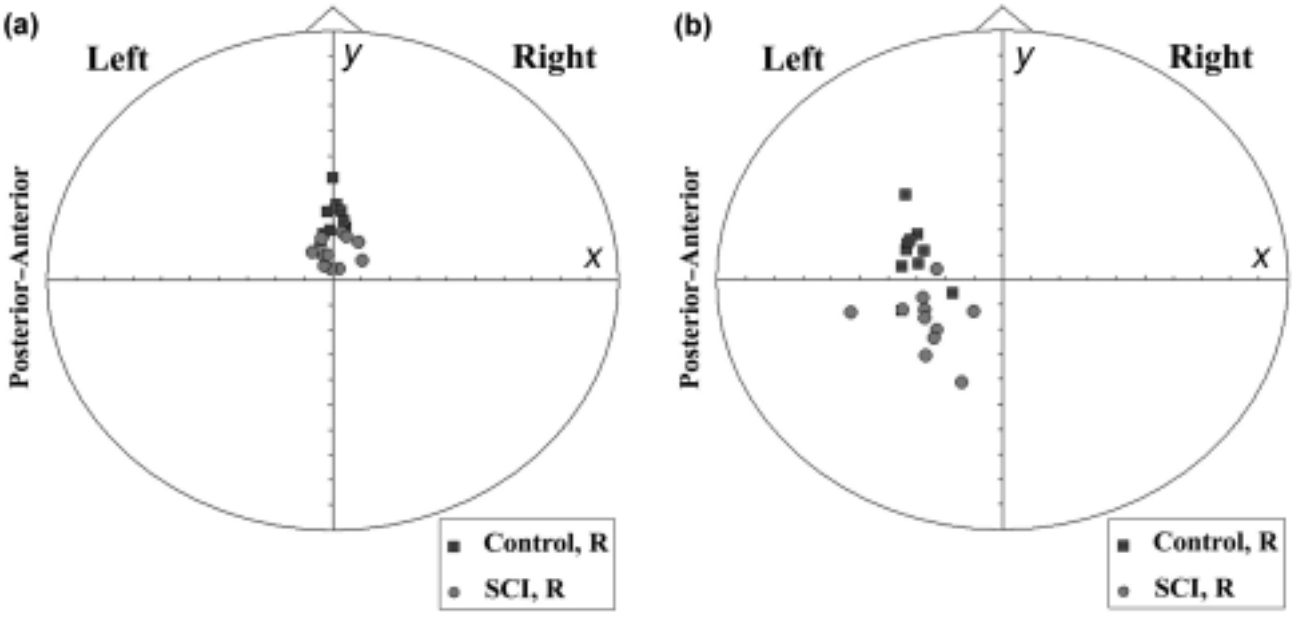

Figure 1.
Normalized coordinates on an *x*-*y* grid demonstrating SMA and M1 dipoles (statistically significant posterior shift of SCI versus controls). **(a)** SMA activation; *p* value along *x*-axis = 0.37 and *p* value along *y*-axis = 0.0003 and **(b)** M1 activation; *p* value along *x*-axis = 0.15 and *p* value along *y*-axis = 0.0002.

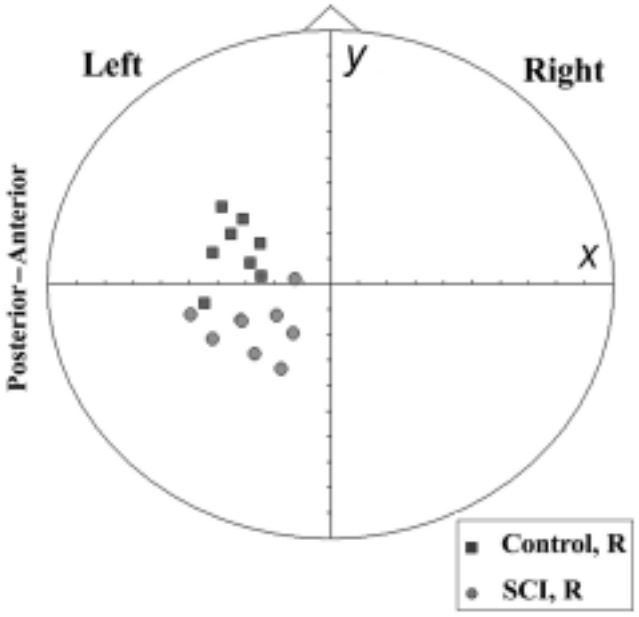

Figure 2.
Normalized coordinates on an *x-y* grid demonstrating M1 dipoles (statistically significant posterior shift of SCI versus controls). Passive movement; *p* value along *x*-axis = 0.23 and *p* value along *y*-axis = 0.00005.

movements). All subjects were right-handed and used the fingers of the right hand in the tasks. Subjects were instructed in how to move the right middle or index finger briskly and how to flex and extend the finger. Of the 16 SCI patients, 1 was a female, and of the 10 control subjects, 3 were females.

Electromyogram (EMG) to detect voluntary movement was used and monitored in all subjects. The joints moved in the finger flexion-extension task included the middle metacarpophalangeal, the middle proximal interphalangeal, and the middle distal interphalangeal. The duration of movements in the SCI group was in the time range of 300 ms to 600 ms, and the duration of movements in the controls was from 200 ms to 450 ms. Duration was measured from the EMG (flexor digitorum sublimus) onset until baseline recovery. This onset of the EMG was used as a trigger for the epoching process in averaging responses.

High-Resolution Electroencephalogram

Each patient and control subject was examined with a 128-electrode Hr-EEG with the use of NeuroScan Laboratories equipment (El Paso, Texas). MRCPs were recorded, and the MP was selected for mapping and DSL studies. An electrode cap was used, made from stretchable fabric and contained 121 scalp electrodes encased in plastic holders. The cap was put on the head with reference to the landmarks of the nasion, inion, and preauricular notches and stretched to properly position the electrodes. The estimated average interelectrode distance was 2.25 cm. We used two channels (four electrodes) to monitor horizontal and vertical eye movements. Additionally, one electrode was used as a ground and one channel (two electrodes) was used for EMG recording. We arranged EMG electrodes on the active forearm, centered on the flexor digitorum superficialis, to detect muscle activity that was generated during executed movement. EMG served to indicate the onset of movement. Individual scalp sites were slightly abraded through the hole in the top of each electrode and conducting gel injected. Electrode impedances were lowered to below 5,000 Ω.

We used an electromagnetic digitizer (Polhemus) to sample the surface of the head and the electrode positions on the scalp to establish the accurate location of electrode coordinates in 3-dimensional (3D) space. Electrode coordinates in 3D space were referred to scalp landmarks (nasion, left and right preauricular points). We obtained 5,000 to 7,000 points and entered them into the host computer as an individual file, which was interfaced with magnetic resonance imaging (MRI). The 128-channel direct current (DC) amplifier system (Neuroscan) was calibrated. Data acquisition parameters were set at a 500 Hz digitization rate for continuous recording. The bandpass filter was DC to 100 Hz. At a gain of 1,000, the dynamic range was 5 mV, with a resolution of 0.084 μV/bit. Scalp electrodes were referred to the ear electrodes during data acquisition and were rereferenced to an average reference. The Neuroscan electric source imaging (ESI) system digitizes 128 channels simultaneously and can display topographical maps. Each epoch of EEG recorded at 121 electrodes was individually scrutinized for artifact and either included in the average or rejected. An epoch of EEG was 3 s (2 s before and 1 s after onset of EMG activity).

Subjects were seated on a reclining chair or wheelchair, or were placed prone on a bed. The subject was asked to rapidly flex and extend the middle finger (or index finger if movement of the middle finger was not possible) every 5 s to 10 s; i.e., the movements were self-generated. Movements were brisk enough so as not to

exceed 500 ms from EMG onset to baseline. The average was triggered by a rectified EMG signal that was recorded by bipolar surface electrodes placed over the appropriate muscles in the forearm. For each digit tested, three blocks of 80 movements were recorded for off-line averaging. Additionally, a person trained in the proper finger movement accomplished other recordings of the subject's digits (passive movements).

Dipole Source Analysis

We accomplished the dipole source analysis (DSA) using a current reconstruction and imaging software package known as CURRY (3.0) Multimodal Neuroimaging [8]. This package used several reconstruction algorithms (single-dipole, multiple-dipole, current density distribution, etc.) with subject-specific MRIs to restrict the volume conductor geometry to the individual anatomy. Segmenting or separating the skin, skull, and brain surfaces from the MRI determined the shape of the optimum volume conductor model. We modeled these compartments using the boundary element method (BEM), by assigning different appropriate conductivity values for each surface (skin, skull, etc.). This method allowed accurate localization of cortical activity by restricting the model to neurophysiological appropriate source locations, such as the cortex. Calculations were based on a window of 50 ms before and after the MP peak for DSA. There are important theoretical objections to comparisons of dipoles across subjects, namely comparing point sources at different latencies, each of which represents one of an infinite number of possible inverse solutions. We have therefore limited our use of DSA to comparing the MP distribution fields with their putative sources in individual subjects. The spatial localization of dipole sources of MRCPs has been shown to be accurate, and with self-paced finger movements, a single dipole can be found with low residual variance (i.e., <10 percent).

Magnetic Resonance Imaging Scans

All subjects and controls were asked to undergo an MRI scan. A General Electric 1.5 Tesla Horizon MRI scanner was used, with a special protocol fitting the CURRY program. The staff of the Memphis Veterans Affairs (VA) Medical Center Magnetic Imaging Center screened each subject and control for any contraindications for MRI and then placed supine on the table, with the head secured in the head coil with padding. The MRI protocol consists of a 3-plane localizer (3SPGR T1 gradient) with 124 individual slices in the sagittal plane at 1.5 mm thickness apiece (field of view (FOV) = 281 mm; voxel = 1.1 × 1.1 × 1.5 mm^3). The MRI data were coregistered with the electrophysiological data derived from patient measurements (fiduciary and scalp) and the CURRY DSL program.

Analysis of Electrophysiological Data

We used a distance metric, in millimeters, to define changes in the location of the maximum of the scalp field MP distribution (as well as the Laplacian) to determine if a relationship existed between the condition and the location of the MP. Comparisons can be made at baseline or at any given point in time. The distance metric, often referred to as the "norm" or absolute value of z, is defined to be

$$|z| = \sqrt{x^2 + y^2}$$

and measures the distance between any point (x,y) and the origin, C_z. In our application, C_z is the center of the electrode array defined by the scalp landmarks of the inion, nasion, and auricles. The distance between any two points, $z_1 = (x_1,y_1)$ and $z_2 = (x_2,y_2)$, may be determined by

$$|z_1 - z_2| = \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2} \ .$$

The maximum of the scalp field MPs and MP Laplacian transforms was defined by the maximum scalp voltage value and the maximum scalp current density, respectively, of the MP. If a set of equal maximum values was found, then the spatial center of the cluster of equal values was defined as the center of the voltage distribution of the MP and/or Laplacian. The location of the nasion was computed at baseline. Using the equation just given, we then calculated the distance between the two locations. This result provided a referential control value in which differences in cortical excitability and variations in the anatomy of the motor cortex could be compared with respect to the nasion. Next, the mean distance between the nasion and finger MPs was computed separately. This distance provides a referential metric with respect to the nasion. Last, the distance between the average spatial locations for the finger MPs was computed relative to C_z.

We accomplished comparisons by normalizing head size using the greatest distance between electrodes. Using this method, comparisons between subjects of different head sizes and electrode locations were compared with arbitrary units.

RESULTS

Time Sequence

To illustrate the findings, we used an MRI scan to photograph a time sequence series of 25 images on one individual over the course of 100 ms, from –70 ms to 120 ms at 10 ms intervals. The SMA was activated early (**Figure 3**) and took a direction toward an anterior position just above the cingulate gyrus (see arrows shown in figure). Upon onset of the SMA activation, a faint indication of electronegativity appeared, predicting where the M1 (previously the MP) would eventually appear. The MP-M1 was posterior to the SMA, pointing to the opposite direction, and had increased in size (see arrows). The SMA became smaller, until it was barely visible (**Figures 3** and **4**).

In the **Table**, normalized coordinates of the study population are shown. Numbers represent the activation dipoles for the SMA, M1, and passive movements.

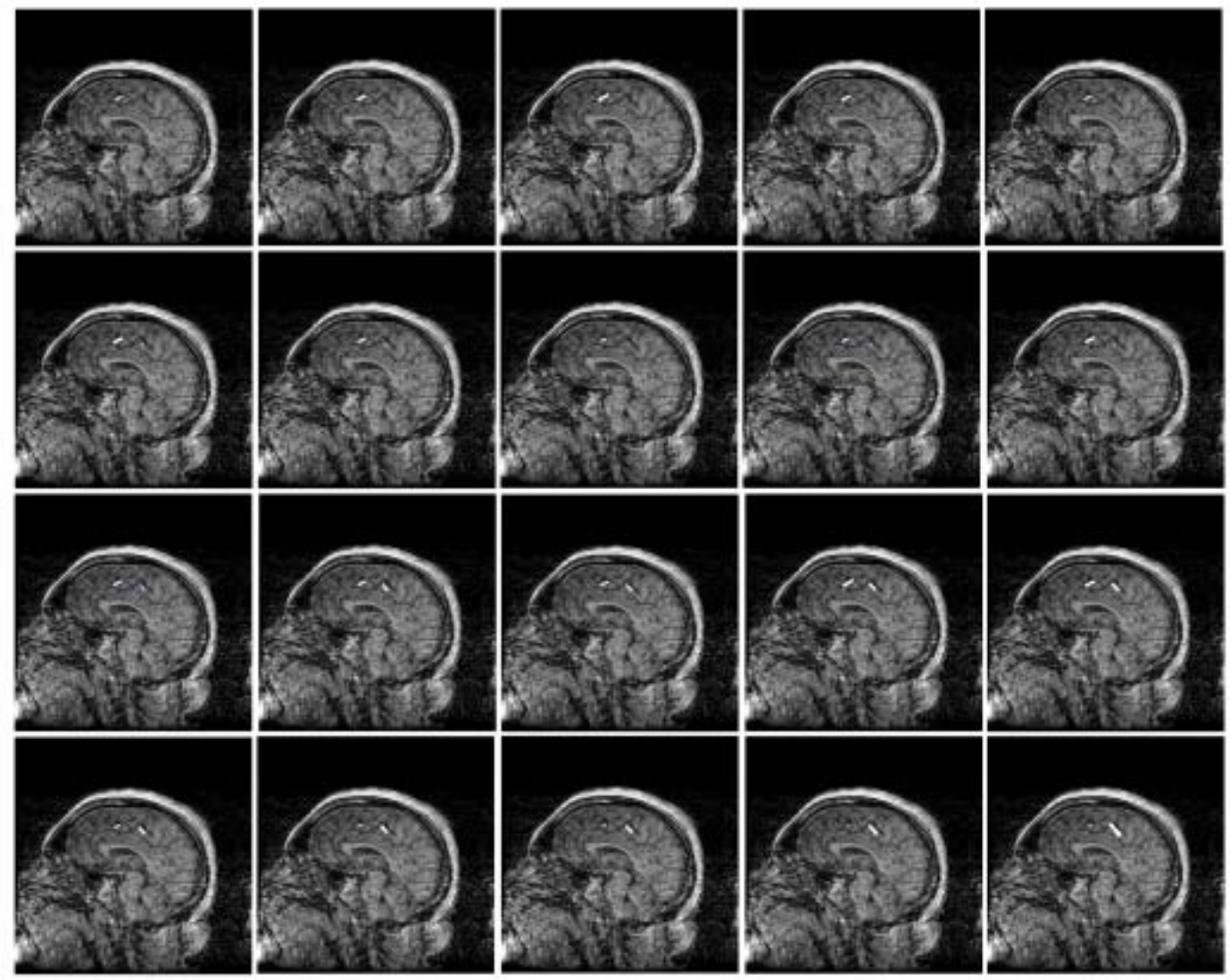

Figure 3.
SMA and MP-M1. A time series from –70 ms to 120 ms.

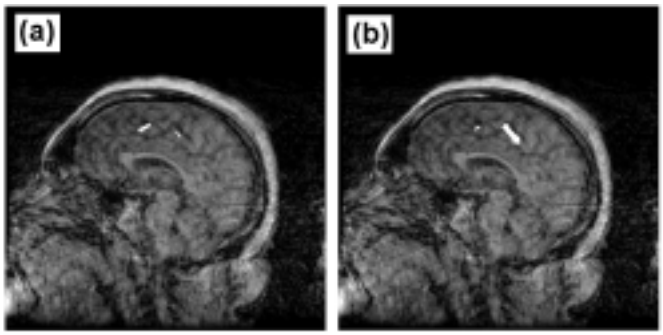

Figure 4.
Selected images demonstrating initial SMA activation with subsequent M1 activation and their inverse relationship. **(a)** –70 ms and **(b)** 120 ms.

Figures 1 and **2** (distance metrics) show normalized coordinates on *x*-*y* grids, demonstrating the SMA, active MP-M1 potentials, and passive movement dipoles. Note the posterior displacement of these dipoles in SCI patients with respect to the controls (see the **Table** and **Figures 1** and **2**). A significant posterior shift is shown in SCI patients in SMA, MP-M1, and passive movement.

SMA location differed between controls and paraplegics with respect to the *y*-axis, i.e., anterior to posterior ($p < 0.0013$). When activation occurred, it was of the ventrocaudal SMA with few exceptions. This was not the case for tetraplegics, but there were only five such patients, $p < 0.2825$. Self-paced MP-M1 also displayed the difference between all spinal cord patients and controls with respect to the *y*-axis, i.e., $p < 0.0001$ for paraplegics and $p < 0.0066$ for tetraplegics. Both the SMA activation and MP-M1 activity confirm the anterior-posterior relocation of MPs in SCI, previously reported by our group.*

DISCUSSION

Posterior Location of MP-M1 in Spinal Cord Injury

We previously reported that this posterior shift of dipole locations in SCI patients was reversible because the potentials occasionally returned to the normal anterior position with recovery. A group of investigators at Long Beach VA Medical Center in California recently confirmed our EEG studies [9]. Using an entirely different method, i.e., functional magnetic resonance imaging (fMRI), they also found that moving or attempting to move fingers caused cortical activation, which was more posterior than in controls.

The pathophysiology of the posterior "reorganization" of MPs in SCI is unclear. It seems unlikely to be explained by a reafferent discharge from the somatosensory cortex because the posterior potentials develop before EMG activity are produced and occur in paralyzed patients without movement. New posterior cortical connections can be formed rapidly after denervation; this has been demonstrated in normal human subjects after ischemic nerve block [10]. However, reinforcement of an already existing pathway may be more likely.

The results of DSL have suggested that the generator of the posterior location of the MP is S1. S1 normally contributes to the generation of the MP. There may be a relative preservation of S1 axons in incomplete SCI. Pyramidal axons originating in S1 may be spared because their course in descending the spinal cord is more posterior and medial than that of M1 axons within the spinal cord. These S1 pathways are deeper within the spinal cord anatomy, rendering them less vulnerable to trauma. Axons originating from M1 may be more peripherally located within the spinal cord anatomy, rendering them more vulnerable to trauma. Moreover, the S1 neurons synapse on propriospinal neurons. Shown in studies on monkeys, cortical somatic areas S1 and S11 have well-organized motor outflows that can function months after ablation of the precentral motor area [11]. However, this finding does not entirely explain the association in some patients of reversal of the MP to an anterior position with variable rates of recovery. Possibly, the posterior MPs may reverse only in incomplete cases or within a short time of onset of new lesions.

We demonstrated that passively moving a subject's finger or toe also produces MPs, similar, but not identical in location to those produced by actual movement. MPs also accompany attempts to move paralyzed limbs in the absence of movement. We have shown that MRCPs, such as the MP, are generated by the somatosensory cortex and resemble a "set of plans" used by the cortex in generating and controlling movement. The plan itself requires a final trigger to activate the pyramidal tract and its descent down the spinal cord. Our results emphasize the role of somatosensory cortex in movement; we have found that

*Green JB. SMA and MP-M1 activity confirm the anterior-posterior relocation of motor potentials in spinal cord injury. Unpublished observation.

Table.
Normalized coordinates representing study populations. Numbers represent activation dipoles for SMA, M1, and passive movements. Note posterior displacement of these dipoles in SCI patients with respect to controls.

Patients	SMA		M1		RFPM	
	x	*y*	*x*	*y*	*x*	*y*
Paraplegic	0.035	0.191	–0.227	0.039	–0.125	0.017
	0.024	0.045	–0.277	–0.073	–0.315	–0.145
	0.106	0.078	–0.230	–0.204	–0.132	–0.194
	–0.036	0.165	–0.270	–0.122	–0.314	–0.146
	–0.004	0.043	–0.350	–0.123	–0.269	–0.277
	0.093	0.150	–0.100	–0.129	—	—
	–0.026	0.054	–0.271	–0.154	–0.190	–0.126
	0.051	0.175	–0.141	–0.412	–0.173	–0.334
	–0.03	0.095	–0.239	–0.235	—	—
	–0.069	0.112	–0.529	–0.132	–0.495	–0.120
	–0.014	0.100	–0.269	–0.308	–0.416	–0.216
Tetraplegic	0.0	0.233	–0.239	0.019	–0.259	0.018
	0.038	0.193	–0.167	–0.022	–0.142	–0.278
	–0.014	0.387	–0.239	–0.054	–0.254	–0.077
	0.084	0.113	–0.189	–0.038	–0.242	0.122
	0.015	0.184	–0.284	–0.184	–0.518	0.072
Control	–0.030	0.185	–0.34	0.341	–0.383	0.301
	0.046	0.210	–0.353	0.050	–0.245	0.029
	–0.041	0.151	–0.353	–0.125	—	—
	0.015	0.288	–0.296	0.181	–0.352	0.195
	0.016	0.304	–0.334	0.117	–0.446	–0.079
	–0.019	0.272	–0.323	0.160	–0.308	0.256
	0.0	0.411	–0.333	0.143	–0.416	0.122
	0.030	0.276	–0.294	0.061	–0.284	0.081
	0.042	0.235	–0.257	0.115	–0.248	0.159
	–0.007	0.200	–0.174	–0.057	—	—

SMA = supplementary motor area
M1 = primary motor area
RFPM = right-finger passive movement

activation of the SMA parallels the BP during and through movement. Indeed, the activation of the SMA may be the triggering mechanism for actual movement. [12]. However, at this time, separating the contributions of the premotor area, anterior-SMA, and posterior-SMA from the SMA dipole and the overall MRCP is difficult. More study is needed, particularly why, in our results, SMA activation did not occur with passive movements.

Supplemental Motor Area

The SMA is perhaps the most important contributor to the early phase of the BP [13]. Self-initiated movements

strongly activate rostral and caudal SMA, adjacent cingulate cortex, and dorsolateral prefrontal cortex (DLPFC). Activation of the caudal SMA per se reflects the primary involvement of this area in movement execution, rather than the preparation of movement by the rostral SMA [14,15]. A negative cortical potential developed in the BP up to 1.5 s before self-initiated movements with maximum amplitude at the vertex, and it involved the SMA [16]. This result suggests that the SMA was active long before self-initiation of a simple task, paralleling the BP. The SMA started 1200 ms prior to initiation of voluntary movement of the right thumb at the same time the initial component of the BP was recorded [17]. The BP included a long-lasting phase (600 ms to several seconds) and a short phase of <600 ms, depending on processes of motor preparation. SMA activity contributed a signal about the order of forthcoming multiple movements and was useful for retrieving appropriate actions according to a memorized order. Caudal SMA was activated when subjects performed simple repetitive movements of hand or arm or over-learned sequences with automatic movement of the fingers. PET and fMRI have been used to record active movements involving flexion-extension movements of the right middle finger (the same paradigm we used). Passive movement activated only sensory areas S1 and S2 (left) [18]. We found passive movement also activated MP-M1.

Investigators have reported that both imagined and actual movements could activate most of the entire motor system [19]. The rostral part of the SMA was activated by imagining movements; the caudal SMA and dorsal anterior cingulate cortex were additionally activated upon execution of the movement. Basal ganglia were also activated during movements. Segregation of afferent somatosensory input and motor output function was found between rostral SMA, caudal posterior SMA, and dorsal cingulate. The same authors reported that "passive movement had a focused maximum movement in the depth of the central sulcus, within the bank of the Sylvian fissure (S11)—a relay area for sensation without a direct connection to the executive motor system." These authors suggested that passive movements might qualify as "pars pro toto" activations. The tight coupling between afferent somatosensory and motor output in the primary cortices suggested passive movements might also be useful in studying the reorganization of the brain in stroke patients.

The two motor areas in the SMA, i.e., rostral and caudal, correspond to 6ab and 6aa of Vogts [17]. Phasic responses to visual cues indicated the direction of forthcoming arm-reaching movement and involved the rostral SMA. Only the caudal part has reciprocal connections with M1. The rostral SMA receives massive projections from the prefrontal cortex around the principal sulcus. The rostral part differed in activity depending on how the selection was made, whereas the caudal was similarly active in different conditions. The SMA neurons are involved, not M1, if the preparatory process is more complicated. The SMA is active long before self-initiated digit movement, even if the motor task is simple. SMA neurons send activity to M1 neurons. Orbitofrontal and mesial prefrontal cortices in humans generate slow potentials and direct corticospinal projections and somatosensory input [19,20].

Several investigators have opted to use various systems of stimulation of the digits and/or elbows [21]. Movements have been initiated by auditory cues, and the planning and/or execution of volitional movement can be separated from the afferent input by a servomotor system. PET studies have been done using a torque motor and guide hinge. Flexion-extension of the elbows caused an increased blood flow in contralateral S1-M1, SMA, cingulate, and the inferior parietal lobe and basal ganglia bilaterally. Passive elbow movements caused an increased flow in inferior SMA, dorsal anterior cingulate, and precuneus and posterior putamen. Activation was found bilaterally in the depth of the S11. These results differed from ours because, unlike our cases, the SMA could be recorded with passive movements, but was much stronger during active movements. The investigators found that the ventrocaudal area of the posterior SMA [21], behind the anterior commissure and dorsal cingulate cortex, seemed closely related to motor output force, whereas more rostral areas were involved in complex aspects of motor function. The SMA and cingulate motor areas possess complete somatotopic representation.

CONCLUSIONS

Interest in a direct linkage from the brain to a prosthetic device is keen as evident by the Neural Prosthesis Programs at National Institutes of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH) and many universities [22,23]. In our own studies, Hr-EEG has been shown to yield a surprising degree of direct information about brain signals not previously

appreciated. Furthermore, the full potential of this modality has yet to be achieved. The advantage of Hr-EEG is in its capability to identify and follow the BP to its outcome without electrodes being placed invasively in large brain areas. The outcome itself is represented by the averaged MP, which triggers the contralateral voluntary movement activity. The terminal event of the BP is comparable to the terminal SMA discharge, and it carries important proprioceptive information from S1 and S2. The data at that point have already been processed by the brain and are essential to all voluntary movement. Improved quality in Hr-EEG, combined with new signal analysis techniques and other new methods, will enable a greater understanding of the brain signaling requirements for movement, and a means then to directly drive prostheses from the brain. The SMA may be important in this connection. For our patients with SCI, the ability to manipulate objects in their environment directly via a brain-computer interface could immediately improve the quality of their lives.

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