Motor-Related Cortical Dynamics to Intact Movements in Tetraplegics as Revealed by High-Resolution EEG

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Abstract: We explored the cortical dynamics during movements of an unaffected body part in tetraplegic subjects with chronic spinal cord injury (SCI). The aims were to find out whether the intact movements were associated with a physiological time-varying pattern of activity in the motor-related cortical areas and whether the primary motor area (MI) activation followed a somatotopic distribution. Event-related potentials to self-initiated lip movements were analyzed by means of cortical source imaging of EEG recorded from seven tetraplegic subjects and seven control subjects. Regions of interest (ROIs) were selected on individual MRI and the time-varying electrophysiologic activity (cortical current density, CCD) was estimated on these ROIs and subjected to across-subject analysis. A significant, bilateral movement-related pattern of MI activation was detected during motor task execution in SCI patients as well as in controls. The site of local maxima activation displayed a symmetrical discrete distribution within MI, consistently with a putative somatotopic lip representation, in all the subjects. The supplementary motor area proper (SMAp) was always coactivated with MI and coactivation was characterized by a time course with typical premotion and motion phases over both motor areas. A clear-cut temporal delay between the SMAp and MI activation did not occur either in SCI patients or in controls. These findings obtained with noninvasive neuroelectrical source imaging document that in chronic SCI subjects "executive" motor areas are engaged with a preserved temporal and spatial pattern during preparation and execution of intact movements. *Hum Brain Mapp* 27:510–519, 2006. © 2006 Wiley-Liss, Inc.

Key words: high-resolution EEG; spinal cord injury; cortical current density; intact movements

INTRODUCTION

Patients with traumatic spinal cord injury (SCI) suffer from an acquired neurological disorder with functional deficits (para/tetraplegia) caused by a loss of the supraspinal control.

This disconnection between a part of the body and the brain structures generates a condition in which patients are unable to perceive sensation or to execute movements with that part of the body below the spinal cord lesion, although the cortical sensorimotor areas associated with the sensation and movement of the body below the lesion are still intact.

This neurological condition has been the subject of several neuroimaging studies providing evidence for a functional reorganization of the motor cortical-subcortical networks that occurs with a variable degree after SCIs [Bruehlmeier et al., 1998; Curt et al., 2002b; Green et al., 1999; Lotze et al., 1999; Mikulis et al., 2002; Roelcke et al., 1997; Topka et al., 1991]. In this regard, it is still undefined how far this reor-

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ganization affects the motor system functions. For instance, functional magnetic resonance imaging (fMRI) data stand for a preserved gross somatotopy in the activation of the primary motor areas (MI) observed during overt movements performed by SCI patients with unaffected body segments or even with body parts that underwent late partial motor recovery [Corbetta et al., 2002; Curt et al., 2002a; Shoham et al., 2001].

Considering the low temporal resolution intrinsic to the hemodynamic measurements (blood oxygenation-dependent effect delayed for 3–10 s), questions remain undressed about the temporal dynamics of the motor cortical activation patterns in SCI patients. A first question to be posed is whether in SCI subjects simple and well-controlled movements of the intact body parts are related to patterns of motor cortical activity with a physiological time course. If this is so, a second question would regard whether the movement-related cortical dynamics maintain a topographic distribution within MI. Answering these questions could play a critical role to draw appropriate pattern recognition algorithms able to automatically detect the presence of selected cortical activations and this would represent an ultimate step in the creation of a communication channel which can bypass the damaged motor pathways in severely paralyzed subjects [Birbaumer et al., 1999; Wolpaw et al., 2002].

It is well known that scalp EEG or MEG are good techniques to investigate the dynamic properties of movement-related cortical reactivity, due to their excellent temporal resolution (millisecond scale). The application of these techniques in humans has revealed how event-related brain activity to movement preparation and execution originates from the contribution of a variety of motor cortical areas whose activation takes place with a temporal-specific sequence [Ball et al., 1999; Cheyne and Weinberg, 1989; Erdler et al., 2000; Ikeda et al., 1992; Praamstra et al., 1996; Toro et al., 1993; Urbano et al., 1996].

In the present study the motor cortical dynamics related to execution of movements involving a nonaffected body part were explored noninvasively in subjects with tetraplegia resulting from stabilized SCIs. In order to answer the above questions, we analyzed scalp event-related potentials to simple self-initiated lip movements (pursing) with the aid of an advanced cortical source reconstruction analysis that remarkably improved the spatial resolution of the scalp data collected with high-resolution EEG recordings. This source reconstruction analysis was based on a distributed, cortically constrained source model whose shape is based on individual MRIs. Regions of interest (ROIs) in the adopted source model were segmented by means of anatomical information to represent the activity of relevant patches of motor cortices. The whole procedure allowed quantification of the time-varying electrophysiologic activity (cortical current density, CCD) of selected cortical regions. A dataset was also obtained from healthy subjects performing the same motor task and it served to test the adopted body of methodology.

SUBJECTS AND METHODS

Subjects

Seven healthy subjects (five males, two female, mean age 26.2 ± 1.5 years; subjects S1–S7) and seven subjects with spinal cord injury (SCI; six males, one female, mean age 25.3 ± 2.8 years; subjects S8–S14) participated to the study. Informed consent was obtained from each subject after explanation of the study, which was approved by the local institutional ethics committee. The SCIs were all of traumatic etiology and located at the cervical level (S10–S14 had lesions at level C6; S9 at level C5; and S8 at level C7). All patients had a stabilized lesion (mean distance from trauma 18.4 ± 6.1 months). Neurological status was assessed according to the American Spinal Injury Association (ASIA) standards [Maynard et al., 1997]. Lesion was complete in four patients (ASIA-A: complete motor and sensory loss below the lesion level in S9, S10, S12, S14) and incomplete in the remaining three (ASIA-C: less than half of the muscles below the lesion level with a strength grade ± 3 in S8, S11, and S13). None of the SCI patients had suffered from a head or brain lesion associated with the trauma leading to the injury. Neither uncontrollable body movement-induced spasticity nor dysesthetic pain syndrome were reported by the patients. All subjects were right-handed as assessed by the Edinburgh inventory [Oldfield, 1971].

Task and Data Acquisition

For the EEG data acquisition subjects were comfortably seated on a reclining chair in an electrically shielded, dimly lit room. They were asked to perform a brisk protrusion of their lips (lip pursing). The task was repeated every 6–7 s in a self-paced manner. The subjects were asked to avoid any other movements and to fix their gaze on a central fixation point. To ensure proper and reproducible task execution, movements were practiced before data acquisition. Verbal instruction was given to the subjects whenever their performance was found to be poor (low electromyographic signal or intertrial interval significantly different from instructions).

A 96-channel EEG system (BrainAmp, Brainproducts, Germany) was used to record electrical potentials from 58 electrodes disposed on the scalp according to an extension of the 10–20 international system. EEG data sampling frequency was 200 Hz and signal was bandpass-filtered between 0.1 and 70 Hz before digitization. Bipolar electromyogram (EMG) was recorded with surface electrodes from m. orbicularis oris on the right and left corner of the mouth in order to detect the onset of lip movements. One hundred single EEG trials were recorded for each subject in two acquisition blocks lasting ~5 min each. EEG data were continuously acquired.

For the structural MRI, magnetization prepared rapid gradient echo T_1 -weighted images (256×256 matrix, 182 slices, 1 mm isotropic voxels, repetition time 11.4 ms, echo time 4.4 ms, flip angle 15°) were obtained with a Siemens 1.5 T Vision Magnetom MR system (Germany).

Data Preprocessing

After the acquisition the EMG channels were rectified and the envelope of the waveform was extracted. A first semi-automatic procedure was run to capture the “first-guess” EMG onset as the time point when the rectified EMG overcame a given threshold. A carefully offline visual analysis was then performed to minimize false positives and negatives. Thereafter, a second automatic procedure was applied to avoid the position of the identified markers reflecting an overcoming of a rather high threshold, and thus resulting in a delayed marker position with respect to the actual EMG signal onset. This second automatic procedure operated by moving the marker back to the time point when the envelope signal definitively overcomes a potential level defined as twice the “baseline noise”; this latter is equal to the envelope standard deviation in a period ranging from -2.0 s and -1.0 s before the “first guess” marker.

For the purpose of artifact rejection, a second segmentation (from -4.0 s to $+4.0$ s) was used. This wider segmentation enabled the electroencephalographers, who performed artifact rejection, to identify and discard those trials where the previous or the following movement execution was too close (less than 4 s) to the current. On average, about 70 trials were considered artifact-free.

Head Models and the Cortical Source Estimation

Three-shell realistic head models were generated with the help of Curry 4.6 software (Compumedics Neuroscan, El Paso, TX). The cortical sources were modeled by using a distributed source model with realistic cortical shape [Dale, 1993; Grave de Peralta and Gonzalez Andino, 1999; Pascual-Marqui, 1995]. With this approach the cortical surface is tessellated into triangles so that the relevant geometric features are preserved and a dipolar source is modeled at each vertex of the tessellation (yielding $\sim 3,000$ source locations). The orientation of each dipole is constrained to be perpendicular to the surface to model the alignment of the pyramidal neurons with respect to the cortical mantle.

The actual strength of these sources was then estimated using a linear inverse procedure according to a weighted-minimum norm approach [Dale, 1993; Uutela et al., 1999]. The detailed procedure for estimation of current density strength waveforms has been reported elsewhere [Babiloni et al., 2004]. By iterating the solution of the linear inverse problem at each time point, we obtain the CCD waveforms relative to each employed current source [Babiloni et al., 2005].

Cortical Regions of Interest

Three cortical ROIs were defined on the adopted cortical model according to anatomical and functional criteria: the primary motor lip (MI-lip) area, the primary motor hand (MI-hand) area, and the supplementary motor area proper (SMAp) on the medial aspect of the frontal lobe. The procedure to determinate the ROIs within MI is illustrated in Figure 1 for one representative subject (S1 in Tables I, II).

We first depicted the MI-hand ROI by exploiting widely recognized anatomical landmarks for this area within the MI. Accordingly, the precentral gyrus was bilaterally identified on the individual MRI with respect to its anatomical landmark [Yousry et al., 1997]: a “knob-like” structure, shaped as an inverted omega on the axial plane (left panel, bottom) and as a hook on the sagittal plane (left panel, top). The precentral knob is known to correspond to the representation site of the hand area within MI. The MI-hand ROI included the posteriorly convex region of the anterior bank of the central sulcus in the “omega”-shaped area, from its fundus to the crown of the precentral gyrus (Fig. 1, right panel, solid circle). The center of gravity (COG) and the area of the selected ROI were estimated for every subject after spatial normalization of the MRI into the Talairach atlas coordinates [Talairach and Tournoux, 1988].

Since it is not possible to anatomically define a “motor lip” area due to the variability in the configuration of the inferolateral segment of the central sulcus and the precentral gyrus, the MI-lip ROI was depicted on the basis of the known relative positions of the hand and face representations within the MI [Penfield and Boldrey, 1937]. In detail, a first “guess” of the lip motor representation was considered to lay in spatially normalized brain, about 4 cm laterally to the “hand-knob” (i.e., MI-hand ROI in our cortical model) along the dorsolateral course of the precentral gyrus. This distance between hand and lip relative positions was inferred from previous fMRI findings on the somatotopic organization of MI [Lotze et al., 2000a]. Thereafter, this quasi “a priori” defined lip motor area was reevaluated taking into account the information derived from the EEG recordings to achieve more accurate estimation of the definitive MI-lip ROI. For this purpose the peak position of the lip movement-related potential closest to the first “guessed” lip motor location was detected from the topographic map of CCD distribution obtained at movement onset (e.g., Fig. 3) and utilized to eventually segment the MI-lip ROI. The extension of the MI-lip ROI was chosen to be similar to the MI-hand ROI (Fig. 1, right panel, dotted circle); the COG of MI-lip ROI obtained in the Talairach coordinates are reported in Table II.

Finally, the SMAp was depicted bilaterally on the medial frontal wall by following the anatomical landmarks recommended by Picard and Strick [1996]. Namely, the anterior border of the SMAp corresponded to a plane perpendicular to the anterior–posterior commissure (AC-PC) line at the level of the AC (VAC) while a perpendicular plane at the level of the posterior commissure (VPC) represented the SMAp posterior border.

The degree of involvement of the ROI in the experimental task is measured by the average CCD in the region. To measure this quantity, those dipoles of the source model that are geometrically comprised in a given ROI are grouped in a subset of the source space, one subset per each ROI. By averaging the estimated dipole moment within each subset, the time course of the activity on the ROI can be computed:

Figure 1.

Illustrations from the scheme procedure to identify the cortical region of interest (ROI) within the primary motor area (MI) in one representative subject (S1). Left panel shows the rendering obtained from the MPRAGE sequences in the sagittal and axial planes of the right hemisphere. Axially (bottom) the precentral knob-like structure is omega-shaped (elliptical), whereas sagittally it is identified as a posteriorly directed hook (square). In right panel the

cortical hand and lip ROIs are identified on the segmented right MI of the segmented head: solid circle and dotted circle encase the MI-hand ROI (coded in blue color, Hand MI) and the MI-lip ROI (coded in red, Lips MI), respectively. The COG of the MI-Lip ROIs in this subject are reported in Table II. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

$$r_k(t) = \text{mean}\{\hat{x}_j(t)\}_{j \in \text{ROI}_k} \quad (1)$$

These ROI waveforms, relative to the event-related changes of the CCD, can be successively averaged across the subjects of the studied population.

TABLE I. Average cortical current density (CCD) values ($R_k^{(7)}$) estimated for the selected ROIs in the last 100 ms before EMG onset

Subjects	Group	Left MI-lip	Right MI-lip	SMAp
S1	H	-0.207	-0.279	-0.113
S2	H	-0.208	-0.185	-0.069
S3	H	-0.118	-0.106	-0.095
S4	H	-0.122	-0.231	-0.046
S5	H	-0.222	-0.198	-0.172
S6	H	-0.115	-0.106	-0.103
S7	H	-0.067	-0.127	-0.049
S8	SCI	-0.022	-0.059	-0.015
S9	SCI	-0.130	-0.059	-0.050
S10	SCI	-0.083	-0.313	-0.182
S11	SCI	-0.238	-0.100	-0.013
S12	SCI	-0.355	-0.428	-0.018
S13	SCI	-0.044	-0.040	-0.010
S14	SCI	-0.100	-0.163	-0.092

Values are expressed in arbitrary units (homogeneous to nA · mm).

In the case of CCDs estimated for the ROIs corresponding to the right and left SMAp, their values were pooled for further analysis, since no interhemispheric asymmetry was expected in the SMAp activity during simple self-initiated lip movements.

Dynamic Statistic Parametric Maps

In order to assess the significance of EEG inverse solutions, a statistical approach to the problem and a measure of the signal-to-noise ratio in the modeled cortical activity were designed as follows: an estimate of the noise that affects the scalp recording was used to compute the intensity of the noise affecting the CCD estimations. The ratio of the CCD estimates over the noise estimate quantifies how much the estimated source strength is above the noise level and, thus, it is reliably participating in the generation of the recorded potentials.

According to a previously proposed approach [Babiloni et al., 2005; Dale et al., 2000], a normally distributed Z-score estimator can be obtained for each cortical location and for each time point considered. Values of Z exceeding a given threshold represent the levels of estimated cortical activity unlikely due to chance alone, but related to task performing. To avoid the effects of the increase of Type I error due to the multiple tests performed, the results were Bonferroni-corrected.

TABLE II. Position of the COGs of the MI-lip ROIs in Talairach coordinates

Subjects	Left hemisphere	Right hemisphere
	x, y, z	x, y, z
S1	-47.3, -12.0, 39.3	51.3, -15.2, 32.7
S2	-48.0, -8.7, 35.0	63.4, -7.0, 28.6
S3	-49.4, -16.1, 33.6	41.9, -10.4, 41.5
S4	-52.1, -17.3, 39.6	51.8, -8.1, 45.0
S5	-48.5, 1.1, 34.3	63.4, -1.5, 22.9
S6	-55.4, -5.9, 26.3	47.1, -12.0, 42.5
S7	-52.4, -13.4, 40.3	52.4, -9.1, 42.8
S8	-54.4, -8.0, 41.8	63.4, -6.2, 38.7
S9	-47.2, -5.6, 33.9	63.9, 9.2, 29.5
S10	-61.4, -11.7, 28.4	58.5, -11.1, 34.5
S11	-48.8, -35.8, 26.6	46.7, -25.2, 32.4
S12	-60.3, -16.4, 35.5	46.2, -12.6, 42.9
S13	-51.3, -22.0, 29.8	47.7, -14.1, 33.3
S14	-64.2, -12.8, 33.4	49.7, -9.5, 39.6

Statistical Evaluation

To investigate the temporal course of activation of the selected motor areas during motor task, we addressed the statistical evaluation as follows. We first tested with the Z-score analysis whether the current densities estimated in the different cortical ROIs were substantially different from the noise level during the period preceding lip movement onset. To this purpose, we set a threshold $z_{thr} = 3$, equivalent to a significance lower than 0.001. When the estimated CCDs in the time period of interest resulted in significantly higher levels than the noise level, waveforms were successively submitted to analysis of variance (ANOVA). Given a time period of interest spanning the last 100 ms before EMG onset, the mean values of significant CCD waveforms were computed as:

$$R_k^{(T)} = \text{mean}\{r_k(t)\},$$

$t \in T$

$$T \equiv \{t \in [-100..0] \text{ ms} \ \& \ t | z_k(t) \geq 3\} \quad (2)$$

The resulting values were entered as dependent variables into the ANOVA. The main factors considered in the ANOVA were: the between-factor GROUP, with two levels (CONTROLS and SCI) to distinguish the normal and the SCIs subjects; the within-factor ROI, with three levels: RIGHT MI-lip ROI, LEFT MI-lip ROI, and the SMap ROI.

A similar statistical procedure was utilized for the group analysis of the source localization in Talairach coordinates. The ANOVA was performed by using the main between-factor GROUP with two levels (CONTROLS, SCI) and the two within-factors SIDE (two levels, LEFT and RIGHT) and COORD (three levels: x, y, z). Absolute values of the Talairach x coordinate were considered in the analysis, since its sign solely indicates that the voxel belongs to the right or left hemisphere and this was taken into account by the factor SIDE. Duncan's test was used as a post-hoc test at the 5% significance level.

RESULTS

Scalp Event-Related Potentials (ERPs)

Figure 2 shows the grand average waveforms of the ERPs obtained from all subjects ($n = 14$) executing self-paced lip movements. This figure was designed only for visualization of the EEG signals as they appeared from the scalp before applying the linear inverse procedure to estimate the current density waveforms on the defined motor ROIs. All later findings are based on the adopted cortical source model. In both groups of subjects (Fig. 2, Control, black solid line; SCI, white solid line), task execution was preceded and accompanied by an average negativity which slowly increased from about 1.6–1.5 s prior to the movement onset, with the steeper rise in the last 500–400 ms before movement onset. The maximum negativity was observed close to movement onset, bilaterally over the centromedian, frontocentral, and centroparietal electrodes. The time course and the scalp topography of the observed ERP components resemble the Bereitschafts potential (BP; or readiness potential), the negative slope (NS') and the motor potential (MP), which are widely recognized as electrophysiological markers of motor preparation and execution of voluntary self-initiated move-

Figure 2.

Scalp topography of grand average mean of the event-related potentials (ERPs) associated with self-paced lip movements in Control ($n = 7$, black solid traces) and SCI ($n = 7$, white solid traces) subjects. The shaded area indicates the confidence interval (at ± 1 standard error). The arrangement of the traces reflects the arrangement of representative electrodes on the subject's head. The vertical scale represents the potential ($-15/+5 \mu\text{V}$); up is negative, down is positive. The horizontal scale represents the time period from 2 s before to 500 ms after the EMG onset ($-2,000/+500 \text{ ms}$); the intersection between calibration bars indicates the 0 time equivalent to the EMG onset. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 3.

Cortical current density (CCD) map relative to lip movement execution for one Control subject (S7) and one SCI subject (S12). Rendering of the segmented realistic head and cortical mantle viewed from above (axial) and right/above (lateral). The CCD maps estimated at the EMG onset (average of the last 100 ms before EMG onset), are coded by yellow color for maximum negativity and by blue color for the maximum positivity (linear, color scale -0.4 , $+0.4$ arbitrary units). The segmented left and right central sulci are indicated by the dotted line; open triangles indicate the right precentral omega (MI hand area).

ments [Kornhuber and Deecke, 1965; Shibasaki et al., 1980]. Hence, the scalp ERPs to lip-movement performed by our sample of control and SCI subjects appear analogous to those typically recorded during other self-generated movements. The components following the movement onset could not be clearly identified because of postmotion artifacts. Indeed, lip pursing produced in all subjects a brisk EMG activity maximally detected by frontopolar channels.

Finally, while the “BP” activity for lip movements was comparable for control and SCI subjects, the later NS’ phase displayed a smaller increase of its slope in the SCI subjects with respect to that of controls (Fig. 2). However, this intergroup difference in amplitude of the late ERP components was no longer evident when a cortical source reconstruction analysis was applied to the scalp data.

Estimated Cortical Current Density (CCD)

Figure 3 shows the CCD map reconstructed on the realistic head-and-cortical model utilized for the solution of linear inverse problem, and relative to one representative subject for both Control (S7 in Tables I, II) and SCI (S12 in Tables I, II) groups. In control subject (right panel, CONTROL), the CCD map estimated at EMG onset reveals significant sources of

cortical activity distributed bilaterally (axial view) along the pre- and postcentral gyrus with a location site within the precentral gyrus consistent with primary motor (MI) lip area (lateral view). Significant EEG sources were also found in the bilateral mesial and dorsolateral aspects of the SMA (axial view). When the SCI subject executed lip pursing (left panel, SCI), the pattern of significant source location agreed with what observed in the control subject: bilateral sources of activity were found within the precentral (and postcentral) gyrus consistently with MI-lip area (axial and lateral view) and over the SMA (axial view). Note that no significant sources of activity were observed over the bilateral MI-hand areas, corresponding to the precentral “omega,” in both representative subjects (Fig. 3, open triangles). The overall pattern of sources was consistent across subjects.

Table I summarizes the average values of the CCDs estimated by applying the linear inverse procedure, taking into account the cortical ROIs selected in each Control ($n = 7$) and SCI ($n = 7$) subject. The group analysis performed on $R_k^{(T)}$ values revealed that the overall CCD amplitudes relative to lip movement execution did not differ significantly between Control and SCI subjects (GROUP, $F_{(2,24)} = 0.28$; $P = 0.60$); this intergroup similarity was also evident for the

Figure 4.

Left panel: position of centers of gravity (COGs) of cortical regions of interest (ROIs) corresponding to the left and right lip motor area (MI-lip), and to supplementary motor area proper (SMAp), in Control (top) and SCI (bottom) group. Color of cones identifies single subject, the vertex indicates the local direction of the perpendicular to the cortical mantle (as derived from MRI-based single subject cortical model). A representation of the average cortical model in the Talairach frame is superimposed to the COGs to provide an anatomical reference. Right panel: grand average waveforms of cortical current densities (CCD) on the ROIs—left MI-lip, SMAp, and right MI-lip, respectively. Time series are displayed from 2.5 s before EMG onset to 0.5 s after. Shaded areas beyond waveforms represent the confidence interval at ± 1 standard error.

CCD amplitudes of the individual right and left MI-Lip ROIs and the SMAp, as indicated by the no significant interaction $\text{GROUP} \times \text{ROI}$ ($F_{(2,24)} = 0.99$; $P = 0.38$). The significant ROI factor ($F_{(2,24)} = 5.98$; $P < 0.0078$) and the successive post-hoc test performed at the $P < 0.05$ significance level showed that in both groups the SMAp source of activity was significantly weaker than what occurred for the bilateral MI Lip ROIs. The activity of the right MI-Lip ROI was slightly greater as compared to the left, but this difference did not reach statistical significance in either group of subjects (see also Fig. 4, left panel).

Analysis of the location of the COG relative to the right and left MI-Lip ROIs in Talairach coordinates (Table II) did not reveal significant intergroup differences in the site and side of the motor task-induced MI activity (GROUP , $F_{(1,12)} = 0.4$; $P = 0.55$, $\text{GROUP} \times \text{SIDE} \times \text{COORD}$, $F_{(2,24)} = 1.2$; $P = 0.315$, respectively). This finding of a comparable location of activity within MI between control and SCI subjects can be appreciated in the right panel of Figure 4, where the individual COGs relative to right and left MI-Lip ROIs are superimposed on an average anatomic image in Talairach space. The distribution of the individual COGs of the SMAp ROI was also similar between groups (Fig. 4, right panel).

The time course of the CCDs estimated for the considered ROIs is illustrated in the right panel of Figure 4. The grand

average of the CCD waveforms showed that activity in the bilateral MI-Lip ROIs and the SMAp was characterized by a negative gradient typically starting between 2,000 and 1,000 ms before the EMG onset (with the left MI-Lip ROI activity occurring earlier than contralateral ROI), slowly rising until ~ 300 ms before the EMG onset and eventually peaking close to the movement onset. This temporal pattern was found to be similar between control and SCI subjects (red and blue solid lines, respectively), thus suggesting that the engagement of the primary motor and the mesial aspect of supplementary motor areas maintained an expected temporal course for simple self-paced movements performed by the SCI subjects.

Finally, the cortical activity underlying lip movements was also estimated on the MI-hand ROIs in order to verify the selectivity of the CCD estimated on the lip representational areas within MI. As shown in Figure 5, no relevant activity was found on the bilateral MI-hand ROIs, either in Control or in SCI representative subjects (S1 and S12, respectively), whose bilateral MI-Lip ROI time course was in agreement with the average data shown in Figure 4.

DISCUSSION

The present study was designed to noninvasively investigate the dynamics of the cortical motor responses to the

Figure 5.

Time course of the CCD estimated on the MI-Lip and MI-Hand ROIs related to lip movements in Control (S1) and SCI (S12) subject. Left and right panels: CCD waveforms estimated on the bilateral Lip and Hand cortical ROIs which are depicted on a section of the segmented cortical mantle of the subjects. The

segmented left and right central sulci are indicated by the dotted line and the cortical ROIs are shown bilaterally along the precentral gyrus in both subjects. The COG of the selected ROIs are reported in Table II. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

execution of simple voluntary movements of nonaffected body parts (lips) in patients with tetraplegia caused by a spinal cord injury (SCI) and in healthy controls. For this purpose, event-related potentials (ERPs) recorded by high-resolution EEG were analyzed with respect to their time course and cortical sources taking into account the individual brain morphology.

The overall findings indicate that preparing and executing intact movements in presence of chronic SCIs are still able to engage “executive” motor areas, like the primary motor area (MI) and the supplementary motor area proper (SMAp), with preserved spatial and temporal features.

Cortical Current Density (CCD) Analysis

The CCD maps estimated in healthy subjects executing lip movements provided evidence for EEG sources located in the bilateral MI and SMA areas. The EEG sources were significantly confined in discrete MI regions consistently with a putative somatotopic site for the lip movements, as revealed by source modeling based on individual normalized brain. Despite the intersubject variability, the group analysis unveiled no significant interhemispheric asymmetry in the activation maxima of the bilateral MI-lip areas. This functional inter-side symmetry is quite understandable because both hemispheres control lip movements like other movements of the facial muscles [Kuypers, 1958].

The current neuroelectrical detection of the cortical representation sites of simple lip movements parallel the hemodynamical evidence of a lip movement-induced activation, which is situated on the inferior aspect of the precentral gyrus with a high degree of interhemispheric symmetry [Lotze et al., 2000a,b]. The execution of mouth movements and their related cortical activity detected by electromagnetic techniques (EEG, MEG) have been previously investi-

gated in the context of verbal vs. nonverbal task-paradigms [Nishitani and Hari, 2002; Salmelin and Sams, 2002; Tarkka, 2001]. Based on these studies, the execution of neutral (no linguistic content) lip movements elicited a modulation of the cortical activity either in the time or the frequency domains located symmetrically in the precentral areas (Brodmann’s area 4), where the face representation is expected. The consistency between these previous findings and the present electrophysiological relation between MI and lip movement execution confirms the accuracy of the EEG source localization model adopted in the present study to assess task-related modulation of the MI activity.

In addition to the somatotopic MI activation, execution of lip movements was time-related with significant activity of the mesial aspect of the SMA, anatomically identified as SMA proper in all control subjects. This movement-related coactivation of MI and SMAp also preceded the motor execution itself. Indeed, analysis of the time course of the CCD waveforms estimated for the different motor areas revealed that both the MI-lip areas and the SMAp were systematically active, since 1.8–1.5 s before lip movement execution, this latter being concomitant with the peak of the observed premotion activity. Furthermore, we did not find a clear delay between MI and SMAp activation in any of the analyzed subjects. Taken together, these data extend to internally paced labial movements of the interwoven temporal recruitment of the MI and the more “executive” SMA substructure (SMA proper, also identified as posterior SMA) as previously suggested for hand-finger movements of variable complexity [Ball et al., 1999; Cunningham et al., 2003; Erdler et al., 2000; Lee et al., 1999; Weille et al., 2001]. Overall, the cortical dynamics underlying lip movement preparation and execution fit well with the general view of a more “executive” role of SMA proper as compared to other “premo-

tor" areas like the pre-SMA and/or the cingulate motor areas [for review, see Picard and Strick, 2001; Rizzolatti et al., 1996].

When the adopted model of EEG source reconstruction was applied in subjects with tetraplegia caused by SCIs, we found that the preparation and execution of lip movements were correlated with a spatiotemporal pattern of activation of the selected motor ROIs (MI-lip ROIs and SMAp) that did not significantly differ from that observed in healthy subjects. With respect to the movement-related MI activity, the congruency between groups was expressed either for the site of activation maxima that was compatible with a bilateral somatotopic representation of the lips, and for the interhemispheric symmetry of the activation itself. In addition, MI activity appeared as early as ~ 1.8 s prior to lip movement execution, as indicated by the time course of the estimated CCD waveforms. Thus, the findings herein indicate that the MI subtends movement execution of an unaffected body part in tetraplegic subjects, preserving its physiological somatotopy and timing.

As mentioned in the Introduction, the activation of MI related to upper limbs and tongue movements in paraplegic patients with SCI occurs with a maintained somatotopic order, without any shift of the activation towards the de-efferented and de-afferented MI foot area [Curt et al., 2002a]. Similarly, a preserved MI somatotopy has been observed in quadriplegic SCI patients moving or attempting to move several body parts (including lips) [Shoham et al., 2001]. In line with these hemodynamic data, our novel EEG findings on the cortical dynamics related to intact movements in SCI patients can be viewed as an additional functional indicator of a preserved segregation in the different representational sites within MI, and they further extend this evidence by assessing preservation of the temporal course of MI recruitment under this neurological disorder.

According to our experimental design, the hand motor areas were considered as anatomical landmarks in the identification procedure of the ROIs within MI. Nevertheless, the observation that in tetraplegic subjects (like in controls) performing lip movements, no significant activation occurred in the adjacent hand motor areas would also be in favor of a normal spatiotemporal activation of MI in response to movements of different muscular segments, despite the SCIs.

Another considerable finding of our study is the significant engagement of the SMA proper that preceded and accompanied the execution of intact movements in SCI subjects. The involvement of the SMAp was time-related with that of the MI and, as discussed above in the case of controls, indicates that MI and SMA proper maintain their predictable concomitant contribution in (late) preparation and execution periods of brief self-timed movements performed by SCI subjects with nonimpaired body parts. The finding of a preserved electrophysiological relationship between intact movement and the more "executive" motor areas may indicate that the activity of these motor areas cannot be primarily influenced by the cortical reorganization phenomena occurring after chronic spinal cord damage (see Introduction). In this regard, an enhancement of the activity in several "higher-order" motor areas (like PMd,

cingulate, pre-SMA), and posterior parietal areas (also in subcortical motor regions) has been revealed in patients with chronic SCIs during execution of intact hand and face movements whose motor representation maintained its topography [Curt et al., 2002a]. fMRI data reported in a tetraplegic patient with late recovery of some motor function have led to a similar conclusion for the motor cortex network activated by overt finger and tongue movements, despite the profound reorganization of the somatosensory map observed for the same movements [Corbetta et al., 2002]. Reasonably, reorganizational changes of the movement-related dynamics of "higher-order" motor areas with respect to those more "executive" investigated in the present study are not excluded in our sample of SCI patients. Although this possibility remains to be addressed, the initial divergence between control and SCI subjects observed in the scalp ERPs may be a preliminary indication that other sources of premovement and movement-related activity can be the target for the functional changes occurring in the SCIs while the "executive" part of the SMA and MI retain their patterned contribution in generating intact movement-related cortical activity.

CONCLUSIONS

The present use of neuroelectric source imaging of EEG data revealed the motor cortical dynamics related to voluntary execution of intact movements in subjects with tetraplegia caused by SCIs. Under this experimental condition, a stable functional topography of the "executive" motor areas concomitantly with a preserved temporal course of their activation occurred. The possibility to depict the motor functional representation in these subjects with high temporal- and spatial resolution may open a future trend in the basics of development of neural-interface technology.

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