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Abnormal Motor Preparation in Severe Traumatic Brain Injury with Good Recovery

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ABSTRACT

Movement-related cortical potentials (MRCPs) were examined in seven patients with severe traumatic brain injury (TBI) and 12 matched control subjects. All patients had clinically established good recovery by the time of testing. Flexion movements of the index finger of the left or right hand were recorded in two (alternating and repetitive) self-paced conditions and in one externally triggered condition. In control subjects, the bereitschaftspotential (BP) component of MRCP was detected approximately 2000 msec prior to movement onset in the self-paced conditions and was larger and earlier in the alternating compared to the repetitive condition. The BP component was absent in the externally triggered condition. In TBI patients, the BP was greatly reduced and no difference between the alternating-repetitive conditions was detected; in contrast, only small differences were present in the controls for the negative slope (NS) and MP components and no difference for the reafferent positivity (RAP) component. A dipole analysis indicated the supplementary motor area and the premotor area as the likely generators of BP and NS′ components, respectively. Gradient-recalled echo magnetic resonance imaging allowed the detection of a number of small hypointense lesions primarily located in the frontal lobes, as in diffuse axonal injury. This pattern of results indicates a selective deficit in motor preparation and a relatively spared pattern of activation during and following movement in these patients. Imaging data appear generally consistent with the pattern of MRCPs observed in the patient group. Implications of these results for the problem of slowness in TBI patients are discussed.

Key words: MRCP; readiness potentials; source analysis; TBI

INTRODUCTION

EVEN AFTER A LONG TIME post trauma and despite a good clinical recovery, closed traumatic brain injury (TBI) patients respond slowly (van Zomeren and Brouwer, 1994; Leclercq and Azouvi, 2002). This deficit has important consequences in the patient's social and work life (Brooks et al., 1986).

Much research has focussed on the cognitive characteristics of this deficit. For example, it has been repeatedly reported that differences in reaction times between TBI and controls increase as a function of the number of

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stimulus/response alternatives in the task (Norrman and Svahn, 1961; Miller, 1970; van Zomeren and Deelman, 1976). By separating reaction time from movement times, it was shown that this effect is probably cognitive in nature and independent from the motor component of the task (Ponsford and Kinsella, 1992). However, this observation does not rule out the possible contributing role of motor components in the genesis of response slowness (Gray et al., 1998). In fact, severe TBI patients may show a transitory or persistent extrapyramidal syndrome (Gerstenbrand, 1967) that includes symptoms such as bradykinesia, rigidity, and parkinsonian posture.

Some studies have used Sternberg's paradigm to distinguish among the various components that may contribute to response slowness. This allows segregating different stages, such as stimulus encoding, memory comparison, decision-making, response selection and execution. Shum and colleagues found that chronic TBI patients were selectively impaired in response selection and execution, that is, in movement times (Shum et al., 1990 and 1994). Recently, we examined the influence of stimulus complexity on reaction times and of distance on the movement times of severe chronic TBI patients with good clinical recovery (Incoccia et al., 2004). Confirming previous evidence (e.g., Miller, 1970; van Zomeren and Deelman, 1994), TBI patients were slow in discriminating targets from non-targets (go/no-go paradigm) but not in responding to simple unstructured visual targets. Concerning movement times, regardless of the complexity of the target TBI patients were slow compared to peer control participants; however, their movement times increased with distance to the same degree as those of control subjects. This finding seems to indicate a deficit in motor planning rather than in motor execution per se. Overall, the reviewed evidence indicates that (a) slowness in chronic TBI may depend partly on cognitive factors related to stimulus complexity and partly on the motor components of the task; and (b) the nature of motor deficits is still unspecified but a deficit in motor planning may be hypothesized.

Lesion identification in TBI has always been problematic and many patients do not show single (or multiple) identifiable lesions on standard MRI examinations. In these cases, diffuse axonal injury (DAI) is commonly hypothesized. DAI is one of the most common types of primary brain injury in severe TBI patients. It has been estimated that DAI not accompanied by an intracranial mass lesion occurs in almost 50% of patients with a severe head injury and is the most common cause of persistent vegetative state and severe disability in TBI (Graham, 1996). This peculiar lesion pattern is characterized by widespread disruption of axons that occurs at the time of an acceleration and deceleration injury. DAI lesions tend to be multiple and small (Parizel et al., 1998). The radiological recognition of DAI can be of critical importance for understanding the clinical syndrome and for predicting TBI patients' outcome. However, DAI is frequently underestimated by computer tomography or conventional MRI (Wardlaw and Statham, 2000). The MRI appearance of DAI lesions depends on several factors including time from injury, presence of hemorrhage or blood-breakdown products and type of sequence used. Conventional T2-weighted spin echo (SE) and fluid-attenuated inversion recovery (FLAIR) MRI sequences can depict small nonhemorrhagic shearing injury as a hyperintense lesion. Because of their sensitivity to susceptibility changes, gradient-recalled echo (GRE) MR images permit identification of hemorrhagic iron deposits in the white matter due to disruption of the penetrating blood vessel, which is often undetected using conventional T1- and T2-weighted images alone (Kuzma and Goodman, 2000). Moreover, Fazekas and colleagues provided histopathological evidence that focal areas of signal loss on (GRE) T2*-weighted MR images correspond to hemosiderin deposits (Fazekas et al., 1999). In order to fully document the areas of cortical involvement, several kinds of MR images were used to allow anatomo-clinical correlations with the expected motor planning deficit of severe TBI patients.

In the present study, we investigated TBI patients' motor activity to determine the stage at which this deficit arises. An effective paradigm to tease apart planning from execution is the analysis of movement related cortical potentials (MRCPs). Self-paced voluntary movements are preceded by MRCPs caused by the neural processes involved in preparing and executing commands to move. MRCP is composed of a series of components obtained by averaging the electroencephalogram (EEG) with respect to movement onset when a subject makes voluntary movements in a self-paced manner. Although latency and scalp topography of MRCP components are well known (Shibasaki et al., 1980; Tarkka and Hallett, 1991), the generators of the MRCP in the brain and the timing relationships of their activation have been investigated only in the last decade (Bötzel et al., 1993; Toro et al., 1993; Tarkka, 1994; Toma et al., 2002). The MRCP reflects the summed post-synaptic potentials of large numbers of cortical neurons; these neurons are arrayed perpendicular to the cortical surface, thereby producing dipolar currents orthogonal to cortical gray matter (Niedermeyer and Lopes da Silva, 1993). The major sources of the MRCPs active prior to the movement were identified in the supplementary motor area (SMA) and in the premotor area (PMA). The post-movement potentials (PMP) sources were found in the primary motor area (M1) and

in the primary somatosensory area (S1) (Bötzel et al., 1993; Tarkka, 1994; Toma et al., 2002).

Complexity of motor action appears to modulate MRCPs. It was shown that MRCPs were larger when subjects alternated between flexion of their left and right index fingers (alternating condition) than in a control condition when they used a single hand repetitively (Dirnberger et al., 2000, 2002). These findings were attributed to the higher preparatory demands of alternating movements. For repetitive movements, it is conceivable that some part of the pre-movement activity remains in place between two identical actions and is still available for the next movement.

In the present study, we examined MRCPs to self-paced voluntary movements in severe TBI patients. The patients selected were in the chronic stage and had clinically established good recovery. Based on the previously reviewed evidence (Dirnberger et al., 2000, 2002), we compared conditions favoring the emergence of large MRCPs, that is, alternating conditions, and compared them to conditions expected to produce smaller MRCPs (repetitive condition). As a control condition, we also examined MRCPs to movements triggered by an external (auditory) stimulus. In this case, we expected activation in M1 and in S1 but limited or no activity prior to the movement in SMA and PMA. Based on our previous findings (Incoccia et al., 2004), we expected the TBI patients to be impaired in the preparatory phases of the MRCPs and less (or not) in the components concomitant to the movement. In the patients' sample we also replicated our previous observations on reaction and movement times as a function of target distance.

MATERIALS AND METHODS

Subjects

Selection criteria for patient recruitment were the following:

- A single traumatic brain injury at least 6 months before testing
- Age 17–60 years
- Diagnosis of severe TBI (Glasgow Coma Scale score of <8 for at least 6 h; Jennett and Teasdale, 1974)
- Absence of cerebellar tremor
- Good recovery on the Glasgow Outcome Scale by the time of testing (Jennett et al., 1981)
- Good motor recovery according to the Adams Scale (Adams et al., 1987)
- Absence (or withdrawal) of dopaminergic drugs (anti-Parkinson), anti-epileptic medications and any other drugs affecting the CNS, including myo-relaxant agents, minor and major tranquilizers (i.e., benzodiazepines and neuroleptics), and nootropic agents or antidepressant drugs

Seven severe post-acute TBI patients (mean age 29.7 ± 5.7 years, five males) participated in the study (TBI patients are usually young males). All participants were right handed. Mean interval from injury was 39.5 months (SD = 47.3), the cause of injury was car accident for all patients. Average coma duration was 40 days (SD = 30.4). Mean post traumatic amnesia (PTA) was 66 days (SD = 10). Individual socio-demographic data are presented in Table 1. All patients enrolled complained of slowness of movement. During the first recovery phase after coma, a parkinsonian posture with reduced swinging of upper limbs during gait was present in all patients together with hypersalivation and seborrhea in A.C. and M.S. By the time of testing, a mild extrapyramidal dysarthria and non extinguishable glabellar tapping (Meyerson sign) were present in all patients. Rigidity and hypomimia were present in some patients (Table 1).

Motor recovery in proximal and distal movements was established by using the Adams scale, which measures motor impairment of upper and lower limbs, not functional disability. All patients showed good motor recovery (score of 6 or 7 for both proximal and distal movements) at least in the arm used for testing (range, 26–28). No patients had invasion of neurosurgical procedures.

A standard neuropsychological examination was given to all patients. Individual patients showed varying degrees of impairment in memory, verbal fluency and constructional apraxia (Table 1). In contrast, all patients were within the normal range on Raven's Progressive Matrices test and the Wisconsin card sorting test (WCST), and had normal verbal and visuo-spatial short-term memory (Corsi and Digit span test); finally, no sign of language disorder or hemineglect was present (not shown).

All patients underwent a brain MRI study on a 1.5-Tesla scanner (Vision, Siemens). The imaging protocol included the following:

- Conventional spin-echo (SE) T1-weighted images (TR/TE/ excitations/flip-angle 650/14/2/70)
- Double echo Turbo SE (TSE) proton density (TR/TE/excitations 3800/22/1) and T2-weighted (TR/TE/excitations 3800/90/1) images
- Fluid attenuated inversion recovery (FLAIR) T2-weighted images (TR/TE/inversion-time 9000/119/2470)
- GRE fast low-angle shot (FLASH) (TR/TE/excitation/flip-angle 777/15/2/15)

Table 1. Individual Socio-Demographic, Neurological, and Neuropsychological Data of the Patient Group

Test	*G.B.*	*C.D.*	*A.C.*	*G.F.*	*E.D.*	*M.S.*	*M.D.*
Age (years)	30	30	25	29	22	40	32
Sex	M	F	F	M	M	M	M
Time from trauma (months)	42	11	76	7	6	129	6
Coma duration (days)	15	74	60	25	15	80	10
PTA (days)	40	120	90	40	21	120	30
Bradykinesia	P	P	P	P	P	P	P
Rigidity	N	N	P	P	N	P	N
Hypomimia	P	N	P	N	P	P	P
Adams scale	28	28	27	28	28	26	28
Rey AVLT (immediate recall)	N	P	N	N	P	P	P
Rey AVLT (delayed recall)	N	P	P	N	P	P	N
Prose memory	N	P	N	N	P	P	N
Verbal fluency (phonemic)	N	P	N	N	N	N	N
Verbal fluency (semantic)	N	P	N	N	N	N	N
Constructional apraxia	N	N	N	N	N	P	N

Rey AVLT, Rey Auditory-Verbal Learning Test; Ps and Ns, pathological and normal scores, respectively.

Twenty-one axial, coronal and sagittal 5-mm-thick sections with an intersection gap of 1 mm, a 23–24-cm field of view, and a 256 $\times$ 256 matrix were obtained with all MR imaging techniques. The axial, sagittal and coronal sections ran respectively parallel and perpendicular to the line that joins the anterior and posterior commissure (AC-PC line). A middle section in the axial and coronal planes was placed on the AC-PC line in all patients. An experienced investigator (U.S.) reviewed all images. DAI was recognized as hypointense lesions on the T2-weighted sequences. The lesion locations were ascertained and they were grouped as follows: lobar (frontal, temporal, parietal), deep (basal ganglia, corpus callosum) and infra-tentorial (cerebellum, brainstem) regions.

Ten healthy control participants (mean age 27.5 $\pm$ 6.2 years, four males) also took part in the study. All participants were right handed. This group was closely matched with the TBI patients for age and sex (all p values were nonsignificant). Control participants had no history of psychiatric or neurological disease.

Written informed consent was obtained from all participants after the procedures had been fully explained to them. The experiment was approved by the local research ethics committee.

Design

Participants made self-paced or externally-triggered flexion movements with the index finger of their left or right hand by pressing one of two response buttons. There were three conditions: alternating self-initiated, repetitive self-initiated, and repetitive externally triggered. In the alternating condition, the participants pressed two buttons in a strictly alternating fashion, i.e., the left index finger response button on the first trial, the right index finger response button on the second trial and so on.

In the repetitive condition, the participants had to press a given button repetitively across trials. There were two types of series in the repetitive conditions: one for the left index finger, one for the right index finger. In the externally triggered condition, the participants had to press a button repetitively across trials as soon as possible in response to an auditory tone. There were two types of condition series: one for the left index finger, one for the right index finger. Before each block the participants were told which finger or which pair of fingers they should use.

The condition order was counterbalanced within and between subjects so that each condition was executed equally often in each serial position.

Procedure

Participants were comfortably seated with their arms resting on a pillow placed on their laps. Two buttons (of a response pad) were placed at a distance that allowed the subjects to reach them comfortably with their index fingers. The inter-button distance was 6 cm. Subjects were instructed to always rest their two fingers on the appropriate buttons. Before starting the task, and during its execution, subjects had to fixate on a point straight ahead

in order to minimize eye movements and avoid looking directly at their hands. Subjects were instructed about the type of movement (alternating, repetitive or externally triggered condition) and the fingers they should use in the next block. Blocks lasted about 20 min or until a minimum of 120 movement repetitions were executed. In the alternating and repetitive conditions, subjects were required to make self-paced brisk flexion movements irregularly but not earlier than 4.0 sec after the previous movement. They were told not to count or to engage in any other rhythmic activity during the entire session; the subjects' inter-movement interval was verified during preliminary warm-up trials. The subjects' average inter-movement interval was 5.6 sec. The total time taken to complete the tasks was about 2 h. Between blocks, the subjects were allowed to have a rest break. They had two breaks of approximately 10 min during the course of testing. The observations were "blind" to clinical data.

Electrophysiological Recording and Data Analysis

The EEG was recorded from a 64-channel amplifier (Brain Products™ München, Germany) using part of the 10–10 electrode montage (Fp1, Fp2, AF3, AFz, AF4, F7, F3, Fz, F4, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, M2, TP7, CP5, CP3, CP1, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, PO1, POz, PO2, PO4, PO8, O1, Oz, O2, I5, I3, Iz, I4, I6, SI3, SIz, and SI4). All scalp channels were referenced to the left mastoid (M1) and grounded to CPz. Horizontal eye movements were monitored with a bipolar recording from electrodes at the left and right outer canthi. Blinks and vertical eye movements were recorded with an electrode below the left eye, which was referenced to Fp1. The EEG from each electrode site was digitized at 250 Hz with an amplifier bandpass of 0.005–60 Hz together with a 50-Hz notch filter and was stored for off-line averaging. Computerized artifact rejection was performed prior to signal averaging in order to discard epochs in which deviations in eye position, blinks, or amplifier blocking occurred. In addition, epochs with inter-movement intervals that were too short were not included in further analysis. On average, about 18% percent of the trials were rejected due to violation of these artifact criteria. Blinks were the most frequent cause of rejection.

For each trial, the EEG was averaged with reference to movement onset. The period used for statistical analysis started 1500 msec prior to movement onset and lasted until 200 msec after movement onset. The baseline was calculated from 3500 to 2500 msec before movement onset. Pulses generated by pushing buttons (NeuroScan™ STIM pad system, USA) served as triggers. MRCPs were averaged separately for hand and condition (100–120 trials). To further reduce high-frequency noise, the averaged MRCPs were low-pass filtered at 10 Hz. MRCPs were classified into two components: bereitschaftspotential (BP) and negative slope (NS′), the PMP, according to Becker and Kristeva (1980) were classified in motor potential (MP) and reafferent positivity (RAP). For simplicity, in present paper the term MRCP will refers to all four components. The amplitude of each component was measured (usually C3 and C4 for BP and NS′, and FC1 and FC2 for MP and RAP). BP amplitude was defined as the mean amplitude in the time window between −1500 msec and −500 msec from the baseline; the BP peak was defined as the largest negativity of the initial slope; the NS′ amplitude was measured between −500 msec and −50 msec minus the BP peak; the MP amplitude was measured from the NS′ peak to the MP peak; the RAP amplitude was measured at the peak. The amplitudes and onset latencies of these components were submitted to separate ANOVAs with group (TBI vs. controls) as unrepeated factor, task (alternating, repetitive and externally triggered movements) and finger (left vs. right) as repeated measure. The Greenhouse-Geisser correction was applied to the results. The significance level was set at $p < 0.05$.

Modeling of MRCP Sources

Maps of scalp voltage were obtained for the MRCPs in all movement conditions. Estimation of the dipolar sources of MRCP components was carried out using Brain Electrical Source Analysis system (BESA 2000 v. 4.4). The BESA algorithm estimates the location and orientation of multiple equivalent dipolar sources by calculating the scalp distribution that would be obtained for a given dipole model (forward solution) and comparing it to the original MRCP distribution. Interactive changes in the location and in the orientation of the dipole sources led to minimization of the residual variance (RV) between the model and the observed spatio-temporal MRCP distribution (Miltner et al., 1994). In these calculations, BESA made a realistic approximation of the head with the radius obtained from the average of the two groups of subjects (patients, 90 mml; controls, 91 mm). The realistic model of the head represents an improvement of the classical spherical approximation (Toma et al., 2002). Single dipoles were fit sequentially over specific latency ranges (given below) to correspond to the distinctive components in the waveform. Dipoles accounting for the earlier portions of the waveform were left in place as additional dipoles were added. The reported dipole fits remained consistent as a function of the starting position. A Polhemus spatial digitizer was used to record the three-dimensional coordinates of each electrode and of three fiducial landmarks (the left and right preauricular points and the nasion). A computer algorithm was used to cal-

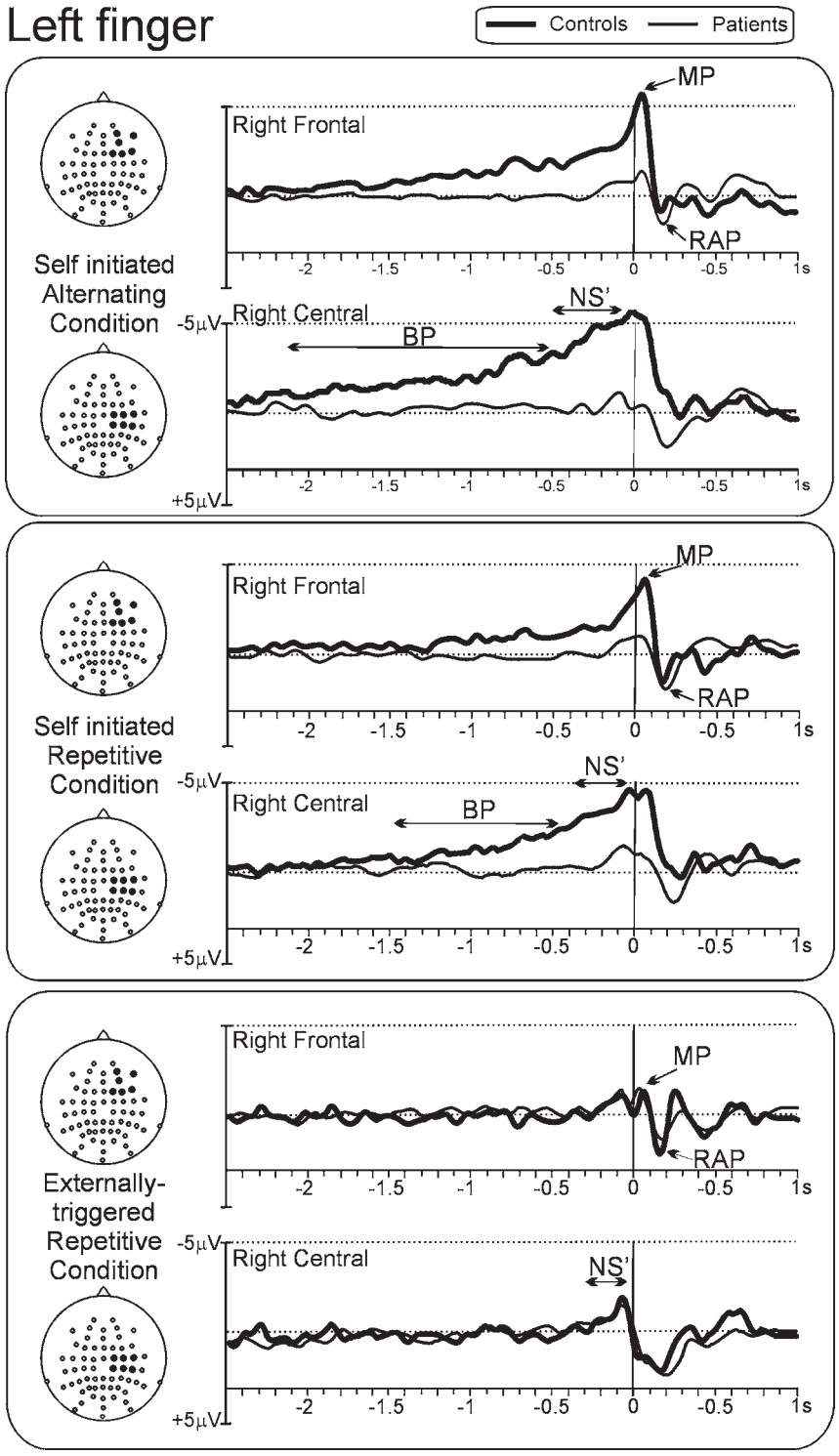

FIG. 1. Grand average movement-related cortical potential (MRCP) for the two groups performing flexion of the left index finger. The MRCP waveforms are presented for the three conditions and superimposed lines represent the two groups of participants. Data are from frontal and central pools of electrodes shown in the left side of the figures. The alternating, repetitive, and externally triggered conditions are represented separately.

culate the best-fit sphere that encompassed the array of electrode sites and to determine their spherical coordinates. The mean spherical coordinates for each site averaged across all subjects were used for the topographic mapping and source localization procedures. In addition, individual spherical coordinates were related to the corresponding digitized fiducial landmarks and to fiducial landmarks identified on the standardized finite element

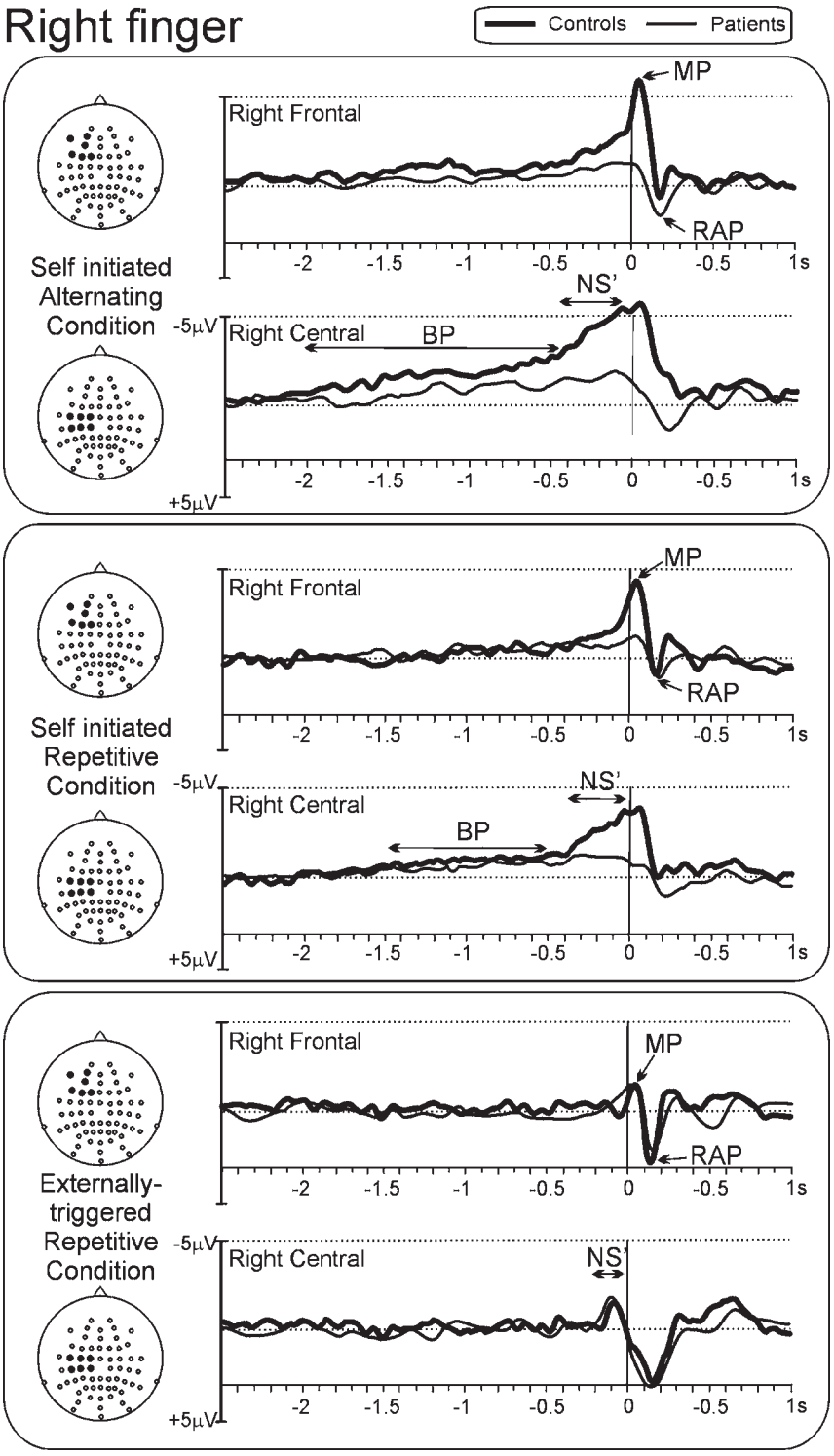

FIG. 2. Same as Figure 1, except this is for the right index finger.

model (FEM) of BESA 2000. The standardized FEM was created from an averaged head using 24 individual MRIs in Talairach space. The averaged head is used for the standard MRI displays and shows a three-dimensional brain. Major sulci can be identified. The standardized FEM model provides a realistic approximation of the average head.

Behavioral Test

A yellow square (3.5 × 3.5°) was presented in the center of a PC screen located 70 cm from the observer. A response button (4 cm diameter) was placed close to the subject (20 cm). A second button was placed further away at three distances (34, 46, and 58 cm from the subject; hereafter short, medium and long). Buttons were placed perpendicularly between the subject and the screen on a plywood base. The observer placed his right index finger on the closest button triggering the appearance of a fixation point in the center of the screen. After randomly varied intervals (between 2 and 6 sec), the visual stimulus was presented for 50 msec and the subject was required to leave the first button and reach for the second one as

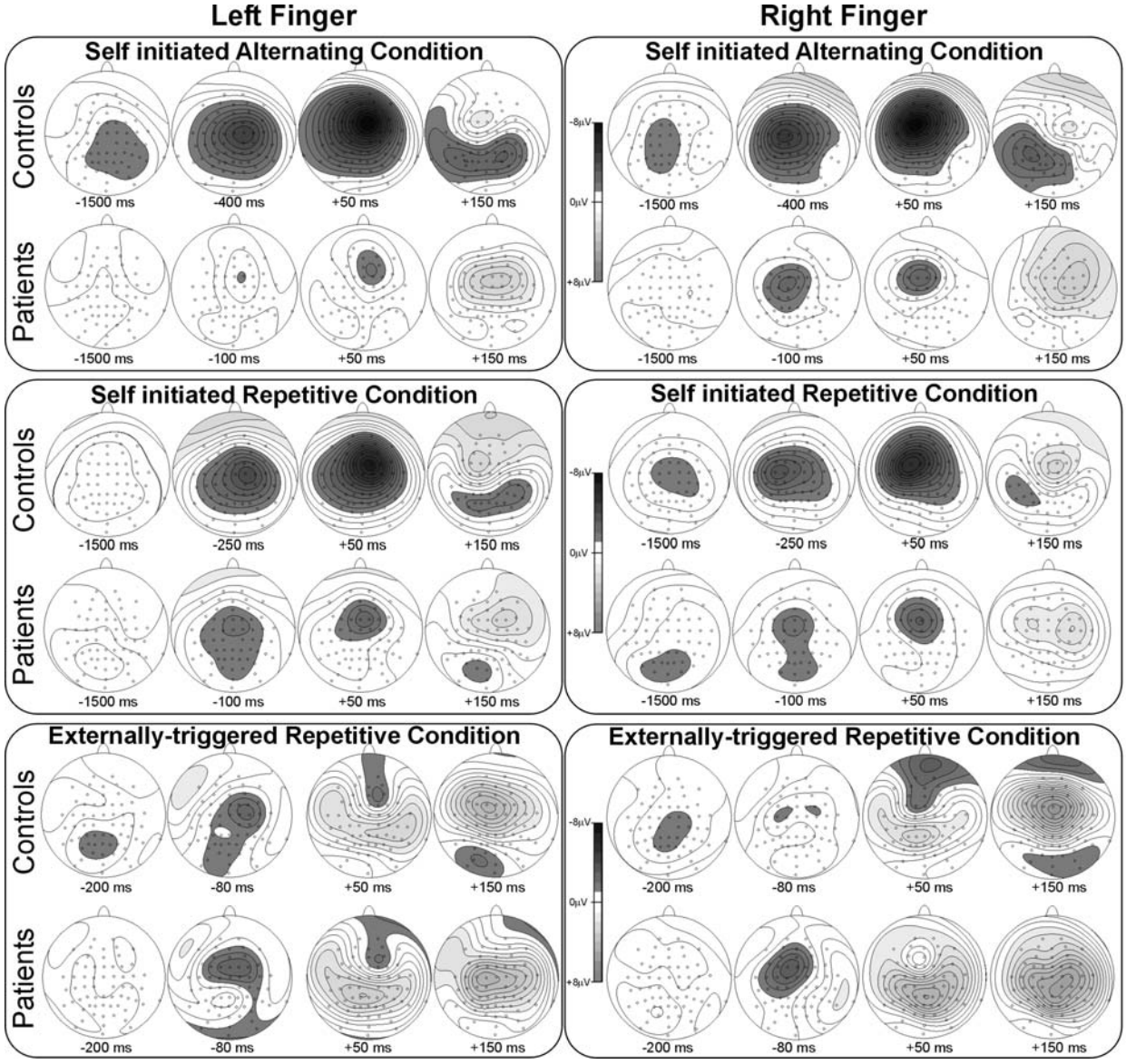

FIG. 3. Spline-interpolated voltage maps of MRCP components elicited by left (left panels) and right (right panels) finger movement in the three conditions. The first row of each panel shows controls' data, the second row patients' data. The dark and light grey areas represent negative and positive polarity, respectively.

quickly as possible. After each trial, the subject returned to the initial button thus triggering the beginning of a new trial. A block of 30 stimuli for each of the three inter-button distances was presented for a total of 90 stimuli. Median reaction time (from stimulus onset to release of first button) and median movement time (from release of first button to depression of second button) was measured. The inter-button distance (short, medium and long) was randomized across subjects. Separate ANOVAs were performed on median reaction and movement times with group (TBI, controls) as unrepeated factor and movement length (short, medium, long) as repeated measure.

RESULTS

Movement-Related Cortical Potentials

Figures 1 and 2 show the grand MRCP average in the three conditions for left and right finger movements, respectively.

Control group. In the control group, the MRCPs of the two fingers were quite symmetrical; no significant differences in terms of latency and amplitudes were detected; therefore, the data were averaged for statistical analysis. The general shape of the potentials was the same for both repetitive and alternating conditions. Alternating movements were associated with larger MRCPs than repetitive movements. This difference appeared to begin about 2000 msec before movement and increased until movement onset. As typically reported (Dirnberger et al., 2000 and 2002), the initial gentle negativity, that is, the BP started rising about 2000 msec prior to movement onset in the alternating condition, significantly before that of the BP in the repetitive condition (onset -1500 msec, $p < 0.001$). In the externally triggered condition, the BP was not present. The NS′ was present with a steeper rise in the last 500 msec before movement in the alternating condition, significantly later than the NS′ of the repetitive condition (onset -365 msec, $p < 0.001$). An NS′-like potential was also visible in the externally triggered condition starting about -200 msec, significantly later than the NS′ of the first two conditions ($p < 0.001$). The MP was observed around movement (peaking at $+45$ msec) in all conditions. The positivity, called RAP, was present in all conditions, peaking at about $+150$ msec.

The BP amplitude in the alternating condition was significantly larger (-2.3 μv, $p < 0.05$) than that in the repetitive condition (-1.3 μV). The NS′, the MP, and the RAP did not differ between the two self-paced conditions (mean amplitude -2.6, -3.1, and $+1.7$ μV, respectively). In the externally triggered condition, the NS′ and the MP potentials were smaller (-0.5 and -1.5 μV, $p < 0.001$) than in the self-paced conditions. The RAPs were larger ($+5.3$ μV, $p < 0.001$) in the externally triggered condition than in the self-paced ones.

The first row of each panel in Figure 3 shows a top flat-view (125° view) of the scalp potential distribution for the left and right fingers in the -1500 to 150 msec time window. The BP showed widespread symmetrical distribution over the centro-parietal areas, whereas the NS′ was contralaterally predominant over the centro-frontal areas. The MP showed focal distribution in the contralateral sensorimotor area. The RAP showed tangential activity with the positive pole centered over the frontal areas and the negative pole over the occipito-parietal areas.

Patient group. In the patient group, the BP was either not clearly visible or was absent in some patients (see thin lines in Figs. 1 and 2). In any case, in the group grand-average small activity was present starting at about 1600 msec prior to movement onset of the right finger in the alternating condition, significantly before that in the repetitive condition (onset -1200 msec, $p < 0.001$). In the externally triggered condition, the BP was not present. The NS′ was visible in the last 300 msec before movement of both fingers in the alternating and repetitive conditions. The NS′ was also visible in the externally triggered condition starting at about -220 msec, significantly later than in the other two conditions ($p < 0.001$). The motor potential (MP) was observed around movement (peaking around $+35$ msec) in all conditions. The RAP peaked in all conditions at about $+180$.

The BP amplitude in the alternating condition did not differ from the BP amplitudes in the repetitive condition (mean value, -0.7 μV). The NS′ amplitude did not differ between conditions (mean value, -0.6 μV). No significant differences were found between conditions for the MP (mean amplitude, -1.2 μV). The RAP amplitude did not differ between the self-paced conditions (mean amplitude, $+2.5$ μv), but it was larger ($+4.7$ μV, $p < 0.001$) in the externally triggered condition than in the self-paced ones.

The second row of each panel in Figure 3 shows the patients' scalp potential distribution. In the BP time window, small widespread symmetrical activity was barely visible over the parietal areas. The NS′ was clearly visible over the contralateral centro-parietal areas. As in the control group, the MP showed focal distribution in the contralateral sensorimotor area. The RAP showed strong activity with the positive pole centered over the frontal areas and the negative pole over the parietal areas.

Control–patient comparisons. The main difference between the two groups is in the BP amplitude ($p < 0.001$), which is almost absent in the patients. The BP onset in

the patients was significantly delayed in both the alternating (400 msec delay, $p < 0.001$) and repetitive conditions (300 msec delay, $p < 0.001$). In the self-paced conditions, the NS′ and MP amplitudes were significantly reduced ($p < 0.001$) in the patients. The NS′ onset was significantly delayed in both alternating (175 msec delay, $p < 0.001$) and repetitive conditions (65 msec delay, $p < 0.05$). In the externally triggered condition, the NS′

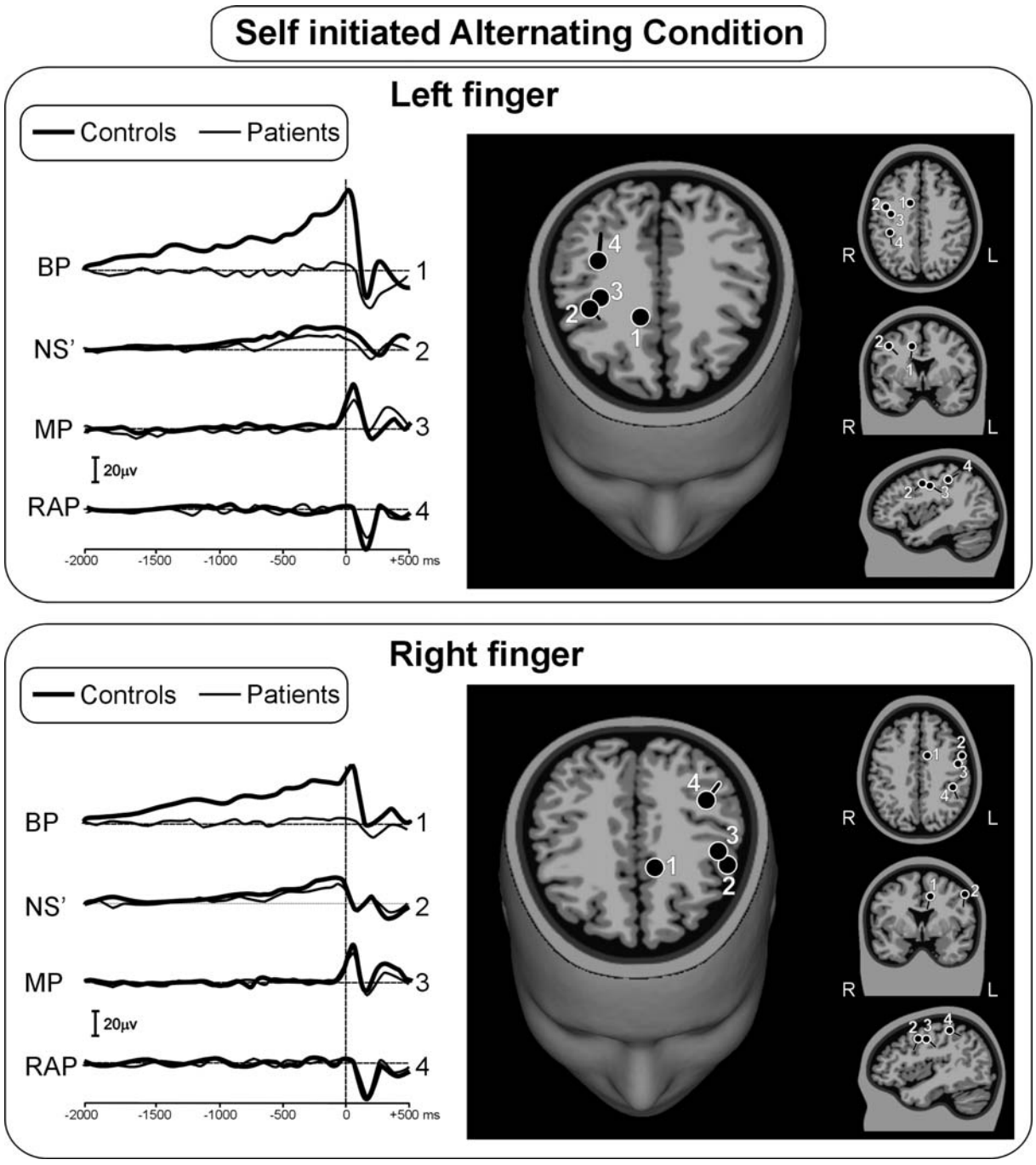

FIG. 4. BESA dipole models fitted to the grand-average MRCPs in the alternating condition. Waveforms at the left of each model show the time course of source activity for each of the modeled dipoles. Dipole #1 corresponds to the BP component, dipole #2 to the NS′, dipole #3 to the MP, and dipole #4 to the RAP.

and the MP did not differ in terms of amplitude or latency. The RAP amplitude did not differ in terms of amplitude, but was significantly delayed with respect to the control group ($p < 0.01$) in all conditions, with an average delay of 30 msec.

Source Analysis

Control group. MRCPs obtained in all conditions were decomposed in four time windows corresponding to the BP (−1500 to −500 msec), NS′ (−500 to −50 msec), MP (0 to +100 msec), and RAP (+100 to +200 msec) components. In the alternating condition (Fig. 4), the BP time window was fitted with a radial dipole (dipole #1) located in the medial frontal cortex, slightly contralateral to the midline. The source activity, starting at −2000 ms, was quite similar to the BP recorded on the scalp. The NS′ time window was fitted with a radial dipole (dipole #2), which was contralaterally situated in the anterior motor cortex; the source activity of this dipole peaked just before the movement, as did the NS′. The MP time window was fitted with a slightly tangential dipole (dipole #3), located in the contralateral motor cortex; the source activity, peaking after the movement was quite similar to the MP. The RAP time window was fitted with a clearly tangential dipole (dipole #4) with a frontal pos-

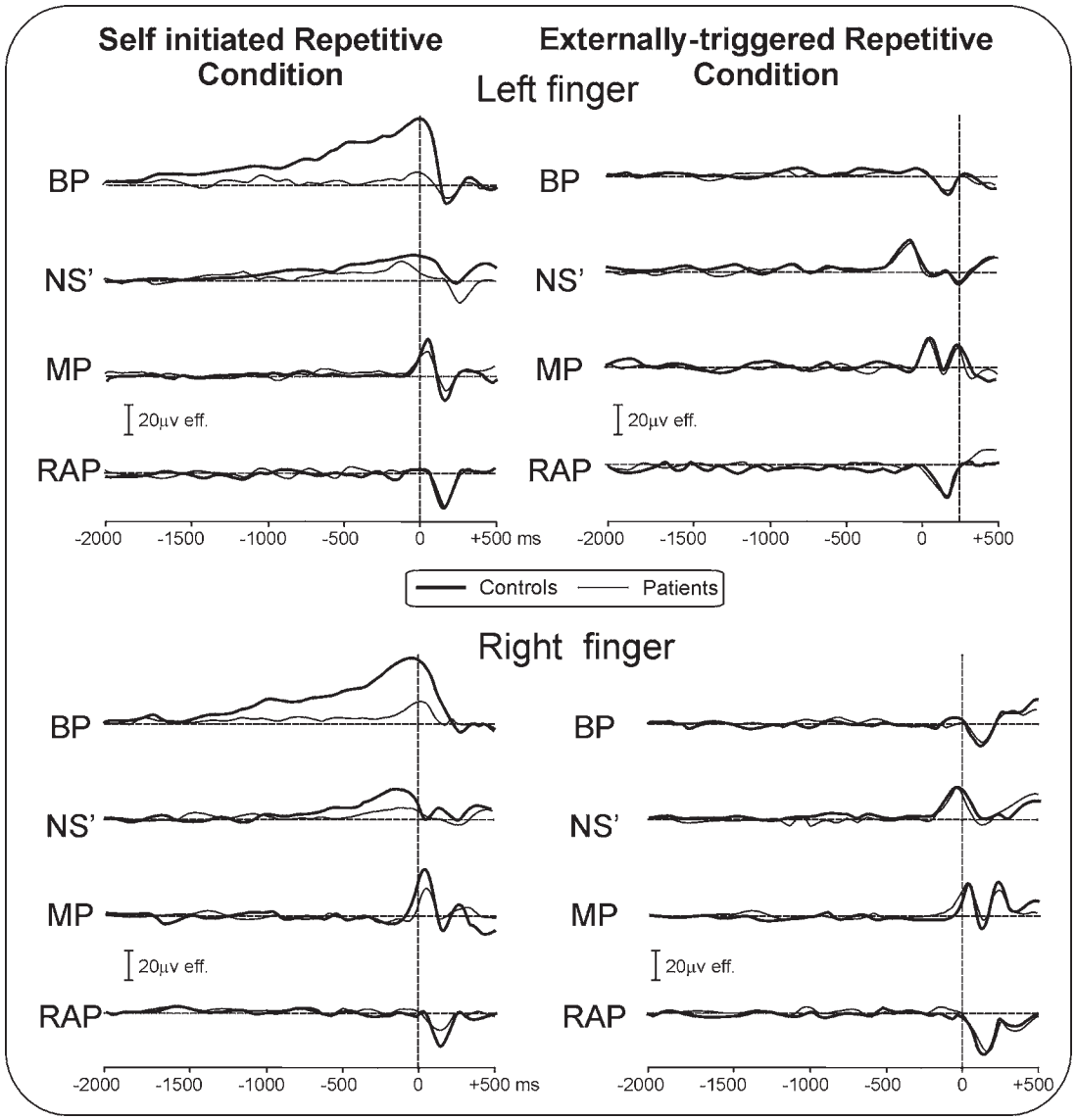

FIG. 5. Dipole model source activity as a function of time fitted to the grand-average MRCPs in the repeated and externally triggered conditions.

itive pole and a posterior negative pole; the resulting location was in the contralateral somatosensory cortex and the source activity was quite similar to the RAP. The residual variance of the model was 3.14% for left finger and 4.05% for right finger movement in the −1500 to +150 msec time window. This four-dipole model was fitted on the MRCPs obtained in the repetitive condition (left side of Fig. 5) keeping the dipole location fixed. Compared to the alternating condition (Fig. 4), the major difference was in the smaller amplitude of the source waveforms explaining the BP wave. The residual variance of this model was 3.61% for left finger and 3.88% for right finger movement in the −1500 to +150 msec time window. Then, the same model was applied on the MRCPs obtained in the externally triggered condition (right side of Fig 5). Compared to the self-paced conditions, the major difference was the absence of the source waveforms explaining the BP component. The residual variance of this model was 4.16% for left finger and 4.42% for right finger movement in the −1500 +150 time window.

Patient group. The four-dipole model was applied to the patients' data keeping the dipole locations fixed and fitting the orientations in the four time windows. The resulting source waveforms (thin lines in Figs. 4 and 5) were similar to those of the control group except for the BP dipole activity. Prior to movement onset, the strength of the BP dipole was close to zero in all conditions and showed only small activity around the movement. Overall, the residual variance of the dipole models resulted less than 5.3%.

Behavioral Data

Reaction times. The ANOVA showed a main effect of the group factor ($F_{(1,16)} = 14.4$, $p < 0.002$), with faster RTs in the control (310 msec) than in the patient (399 msec) group. The main effect of movement length and the interaction between movement length and group were not significant. No errors were made.

Movement times. The ANOVA showed a significant main effect of the group factor ($F_{(1,16)} = 8.1$, $p < 0.02$): movement times were slower in the TBI patients (358 msec) than in the control participants (265 msec). The movement length factor was also significant ($F_{(2,32)} = 111.8$, $p < 0.0001$): movement times increased monotonically with movement length, with each distance (248, 321, and 366 msec) differing significantly from the others ($p < 0.0005$). No interaction proved significant. In other words, the TBI patients were slower but their movement times increased with distance to the same degree as those of the control subjects. No errors were made.

Imaging Data

Diffuse axonal injury was observed in all seven patients. Using the four sequences described in the method section, we detected a total of 79 hypointense brain lesions in the patient group (Table 2). Considering the number of lesions located in the different anatomic regions, a high concentration of DAI lesions were located in the frontal lobe ($n = 38$). We further identified 14 in the temporal lobe, five in the parietal lobes, 17 in the deep (nine in the basal ganglia, eight in the corpus callosum), and eight in the infra-tentorial regions (two in the cerebellum, six in the pons-mesencephalon). DAI lesions were not associated with other intracranial abnormalities of signal intensity as provided by conventional SE, TSE and FLAIR T1, proton density and T2-weighted images. Figure 6 shows some typical DAI lesions in patient E.D. Several DAI lesions (hypointense lesions) are visible in the axial GRE T2-weighted images located in the subcortical frontal white matter and in the right thalamus (small arrows).

Table 2. Number of DAI Lesions at Different Locations in the 7 TBI Patients

	G.B.	*C.D.*	*A.C.*	*G.F.*	*E.D.*	*M.S.*	*M.D.*	*Total = 7*
Whole brain	17	6	2	17	26	4	7	79
Frontal lobe	3R,2L	1R,1L	1L	6R,6L	9R,6L	1R,1L	1R,1L	38 (21R,18L)
Temporal lobe	27,7L	—	—	1R	3R,1L	—	1R	14 (6R,8L)
Parietal lobe	—	1L	1R	2L	—	1R	—	5 (2R,3L)
Basal ganglia	—	1R,2L	—	—	2R,1L	—	1R,2L	9 (4R,5L)
Corpus callosum	—	—	—	2	4	1	1	8
Cerebellum	2L	—	—	—	—	—	—	2 (2L)
Brainstem	1L	—	—	—	2R,2L	—	1L	6 (2R,4L)

[a]R, right hemisphere; L, left hemisphere.

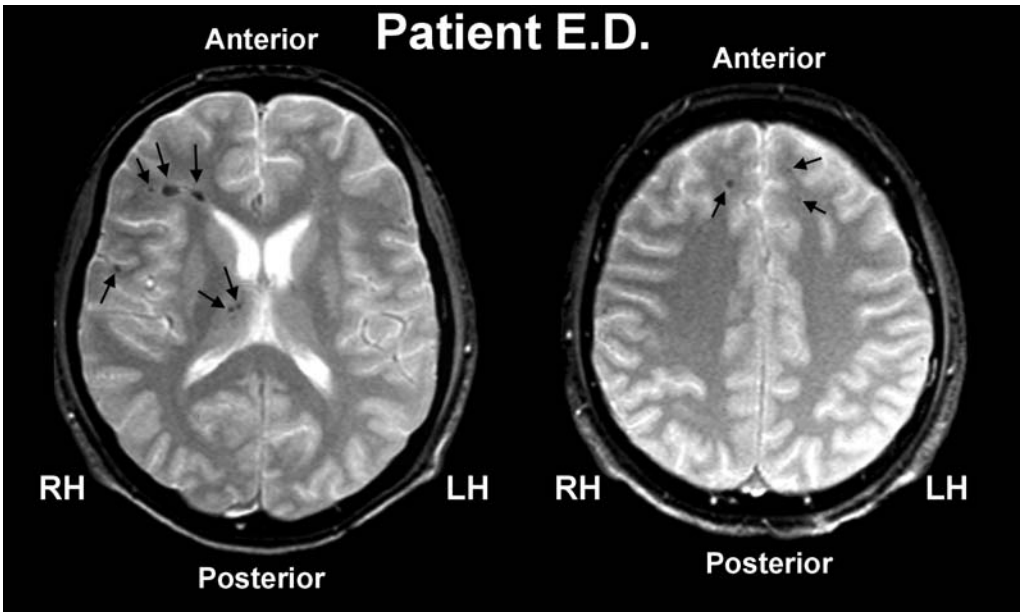

FIG. 6. Axial MRI GRE T2-weighted slices from patient E.D. Diffuse axonal injury is defined as areas of abnormal low signal intensity. Hypointense lesions are indicated by small arrows located in the subcortical frontal white matter and in the right thalamus.

DISCUSSION

In the present study, we tried to segregate the different components of motor preparation and execution to evaluate their possible role in the characteristic slowness of TBI patients. The results were straightforward. The BP potentials were strongly reduced and delayed in the TBI patients. This finding indicates that these patients have a selective deficit in the preparatory components of movement. In contrast, differences in NS′ and MP potentials were small although some differences in latency and amplitude were detected. The RAP amplitude was essentially normal, but the latency was delayed in the TBI patients. Therefore, at least in the case of chronic TBI patients showing good clinical recovery, motor deficits may be rather selective. Motor execution per se is largely spared and a deficit is detected only if experimental conditions require preparatory activation prior to the movement. According to the paradigm developed by Dirnberger and colleagues (2000, 2002), we asked patients and controls to self-generate finger movements at irregular intervals. In controls, this produced the expected BP activation about 1500 to 500 msec prior to the movement. Replicating the observations of Dirnberger et al. (2000, 2002), this effect was significantly enhanced in alternating compared to repetitive movements. This differentiation was absent in the TBI patients. Moreover, no difference was found between controls and patients in responses to externally triggered signals. In this case, BP potentials were not detected in either group. Therefore, examining MRCPs to an imperative stimulus is not an effective manipulation for detecting electrophysiological differences between patients and controls. Overall, the pattern indicates a selective deficit in motor preparation and a relatively spared pattern of activation during and following movement in these patients.

The dipole analysis generally confirmed the pattern of MRCP activation hypothesized on the basis of previous evidence (Tarkka and Hallett, 1991; Toro et al., 1993). Replicating previous studies (Toro et al., 1993; Bötzel et al., 1993; Tarkka, 1994; Toma et al., 2001), the supplementary motor area, the premotor area, the primary motor area and the primary somatosensory area were the likely generators of the scalp-recorded BP, NS′, MP, and RAP components, respectively. This analysis indicates that SMA activity is deficient in these patients. MRI data were generally consistent with this electrophysiological finding. In our study using a GRE sequence, DAI lesions were detected in all patients. The GRE sequence has been reported to be more sensitive than conventional T2-weighted sequences to the magnetic susceptibility induced by static field inhomogeneities arising from paramagnetic blood breakdown products (Patel et al., 1999). In agreement with previous neuroimaging studies, in our patients DAI lesions, appearing as small areas of hypointense signal on GRE T2-weighted images, are consistent to hemorrhagic iron deposits in the white matter, caused by disruption of the penetrating blood vessels oc-

curring at the time of brain injury. While damage was spread across many cortical and sub-cortical areas, a greater involvement of the polar frontal areas was detected in all patients in the present series. It is common knowledge that DAI lesions are frequently located at the gray-white matter junction in parasagittal areas and deep periventricular white matter, especially in the frontal areas. Moreover, in our patients DAI lesions were not associated with other intracranial lesions as indicated by conventional MRI. Thus, the lesion pattern is compatible with the hypothesis suggested by the MRCP source analysis of a deficit in frontal areas and in particular in the SMA, which is responsible for motor preparation.

Behavioral data confirmed the presence of slowness in these patients. TBI patients showed slowed reaction times to visual stimuli and slowed movement times on a simple visuo-motor task. In general, these observations confirmed previous evidence (van Zomeren and Deelman, 1978) indicating that, in spite of good clinical recovery, in the chronic stage slowness may be a pervasive characteristic of these patients. As for movement times, TBI patients were delayed but showed an increase in time with increasing distance similar to that of control patients. These data confirm our previous observations on a similar patient population (Incoccia et al., 2004).

Although TBI slowness is a well established fact, it has been interpreted in different ways, with some hypotheses advancing more specific and others more generalized interpretations. One view refers to the presence of a selective cognitive deficit in response selection (Shum et al., 1990, 1994). Another more general hypothesis, advanced by van Zomeren and Brouwer (1994), proposes that mental slowness may depend upon a reduction of the signal-to-noise ratio in information processing; general axonal damage may be the underlying anatomical correlate of this proposal. The idea that motor components may contribute to slowness has a long history, going back to the bradykinesia/bradyphrenia dichotomy (Gray et al., 1998). However, recent neuropsychological studies have controlled motor factors primarily to avoid sources of confusion for cognitive interpretations (Ponsford and Kinsella, 1992). In contrast, both the behavioral and the electrophysiological data of the present research call attention to the idea that a deficit in motor preparation may contribute to the genesis of slowness in TBI patients.

Motor characterization of severe chronic TBI patients is a controversial issue. Some authors have noted similarities with the motor deficit shown by patients suffering from Parkinson's disease (PD) (Gerstenbrand, 1967); however, this proposal has also been severely criticized in the past, particularly in the case of focal TBI (Adams and Victor, 1976). Especially in the first phases of coma recovery, survivors of traumatic coma with MR features of DAI may show extrapyramidal signs similar to those present in vascular parkinsonism secondary to multi-infarct encephalopathy. In particular, akinesia and rigidity (Lindemberg, 1964; Jellinger, 1966) are common symptoms and may be secondary to multiple lesions either in the substantia nigra or in the caudate-putamen area (Morsier, 1960; Nayernouri, 1985). It should be noted that motor disabilities in this population are the consequence of traumatic lesions at the level of the extrapyramidal pathway and not the effect of systemic dopaminergic degeneration (Peppe et al., 1998). Indeed, our young patients' history was unremarkable; no extrapyramidal symptoms were reported before the brain injury. In the small series of patients investigated in the present study, some association between extrapyramidal symptoms, such as bradykinesia or motor slowness, and DAI was confirmed.

The results of the present study indicate some continuity also at the electrophysiological level. Previous research with MRCPs on pre-frontal lobe patients (Singh and Knight, 1990) and PD patients (Dick et al., 1989; Filipovic et al., 1997) demonstrated reduced BP amplitudes, indicating diminished preparatory activity in the SMA. As stated above, this structure determines the earliest amplitude of the MRCP (Toma et al., 2002), an origin confirmed by the present study. However, it should also be observed that this similar deficit may have different origins in the two types of patients. In PD patients, the reduction of the BP component is thought to result from inadequate basal ganglia activation of SMA (Dick et al., 1989); this is also confirmed by functional MRI studies (Sabatini et al., 2000). In fact, it is well known that the basal ganglia provide a major source of afferent input to this structure. In the present series of severe TBI patients, reduced SMA activity was associated with lesions in several important stations of the extrapyramidal pathway, such as the frontal lobe, basal ganglia, and brainstem.

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