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Amengual JL, Münte TF, Marco-Pallarés J, Rojo N, Grau-Sánchez J, Rubio F, Duarte E, Grau C, Rodríguez-Fornells A. Overactivation of the supplementary motor area in chronic stroke patients. *J Neurophysiol* 112: 2251–2263, 2014. First published July 30, 2014; doi:10.1152/jn.00735.2013.—Stroke induces a loss of neural function, but it triggers a complex amount of mechanisms to compensate the associated functional impairment. The present study aims to increase our understanding of the functional reshape of the motor system observed in chronic stroke patients during the preparation and the execution of movements. A cohort of 14 chronic stroke patients with a mild-to-moderate hemiparesis and 14 matched healthy controls were included in this study. Participants were asked to perform a bimanual reaction time task synchronizing alternated responses to the presentation of a visual cue. We used Laplacian-transformed EEG activity (LT-EEG) recorded at the locations Cz and C3/C4 to study the response-locked components associated with the motor system activity during the performance of this task. Behaviorally, patients showed larger variable errors than controls in synchronizing the frequency of execution of responses to the interstimulus interval, as well as slower responses compared with controls. LT-EEG analysis showed that whereas control participants increased their supplementary motor area (SMA) activity during the preparation of all responses, patients only showed an increment of activity over this area during their first response of the sequence. More interestingly, patients showed a clear increment of the LT-EEG activity associated with SMA shortly after motor responses as compared to the control participants. Finally, patients showed a hand-dependent inhibitory activity over motor areas ipsilateral to the response hand. Overall, our findings reveal drastic differences in the temporal dynamics of the LT-EEG components associated with the activity over motor and premotor cortices in chronic stroke patients compared with matched control participants during alternated hand responses.

stroke; supplementary motor area; brain plasticity; Laplacian EEG; motor system

STROKE IS THE SECOND LEADING CAUSE of death and the first cause of acquired disability in adults of developed countries (World Health Organization 2003). Frequently, stroke affects the motor function of the upper limb contralateral to the side where the vascular lesion occurs. It causes changes in the neural activation of both the ipsilesional and the contralesional hemisphere during the preparation and execution of movements performed with the affected side (Crofts et al. 2011; Wetter et al. 2005). Therefore, the study of the neural mechanisms underlying brain plasticity and functional reorganization is paramount to understand the motor recovery in stroke patients (Cicinelli et al. 1997; Marshall et al. 2000; Nudo and Milliken 1996; Sanes et al. 1988).

Prior studies have reported an altered activation of the motor system in stroke patients compared with controls. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have revealed bilateral activations over the primary motor (Johansen-Berg et al. 2002; Loubinoux et al. 2003) and premotor cortical areas (Willer et al. 1993) during movements performed with the paretic hand. Other studies have revealed a greater activation of the nonprimary motor areas such as premotor areas, the supplementary motor area (SMA), and parietal and insular cortex during simple movements in chronic stroke patients compared with controls (Chollet et al. 1991; Seitz et al. 1998; Willer et al. 1993). These observations have provided an important aspect in understanding the different mechanisms underlying the functional reshape of the motor system in stroke patients. However, the nature of these mechanisms responsible for such different patterns of activity found in stroke patients is still under debate. Indeed, during the acute phase of stroke these mechanisms seem to be related to the activation of other areas, partially due to compensation, diaschisis, or lack of inhibition produced by the lesion (Hallett 2001; Liepert et al. 2001). Conversely, during the chronic phase of the stroke, the mechanisms underlying these differences become more complex. In this context, it should be taken into account the spatial rearrangement of brain functions, which temporal dynamics is different in the chronic phase than during the acute phase of the stroke (Amengual et al. 2013; Takeuchi and Izumi 2013). Additionally, the role of the contralesional corticospinal pathway, as well as the role of ipsilesional cortical spinal projections originating in regions different from M1, are not completely clear (Traversa et al. 1998).

Electroencephalography (EEG) and magnetoencephalography (MEG) provide precious information about the neural dynamics among different regions of the motor cortex, since these techniques purvey an excellent temporal resolution that is lacking in other neuroimaging techniques (Cheyne et al. 1991; Kirsch and Hennighausen 2010). Indeed, knowing the specific

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time course and extent of the brain activity components associated with the planning, preparation, and execution of movements in chronic stroke patients would shed more light on the possible mechanisms underlying the functional reshape in cortical motor areas. Response-locked averages of EEG activity performed in motor studies typically show a negative motor-related potential over M1 contralateral to the movement side (contra-M1) (Deecke et al. 1976, 1980). This "Bereitschaftspotential" (BP; normally called "readiness potential") reflects the activity associated with the preparation and execution of a motor program. It has been demonstrated that, specifically during the preparatory stage of the movement, a central and nonlateralized component of the readiness potential arises mainly reflecting the activity over the SMA (Halsband et al. 1994; Mushiake et al. 1990). Particularly, Laplacian-transformed EEG (LT-EEG) activity (Perrin et al. 1989) has been widely used to study the temporal dynamics of neural activity emanating from premotor and motor areas during motor tasks (Carbonnell et al. 2004; Meckler et al. 2010; Meynier et al. 2009; Tandonnet et al. 2003; Vidal et al. 2003b). This spatial transformation of the EEG signal suppresses volume-conducted contributions of active cortical generators (Tenke and Kayser 2012). Therefore, LT-EEG is useful when an enclosed and well-characterized localization of an event-related potential (ERP) component is expected, as is the case of neural generators of ERPs located in motor or sensory structures (Tenke and Kayser 2012). Several prior studies have examined the SMA activity during the preparatory part of the readiness potential using LT-EEG (Carbonnell et al. 2004; Praamstra et al. 1996; Praamstra and Seiss 2005; Vidal et al. 2003b). In addition, LT-EEG has revealed a positive wave over the motor regions ipsilateral to the movement side (ipsi-M1) (Carbonnell et al. 2004; Meynier et al. 2009) coincident with the appearance of a negative wave on the contra-M1. This pattern of positive and negative activations between both hemispheres during the execution of motor tasks has been associated with opposite effects: the negativity over contra-M1 might signal an excitatory activation of this area, whereas the concomitant positivity over the ipsi-M1 has been related to an inhibitory process (Burle et al. 2002; Carbonnell et al. 2004; Meckler et al. 2010). Importantly, this inhibitory component could result from interhemispheric transcallosal projections whose influence has been already demonstrated (Ferbert et al. 1992).

Few studies have examined motor-related brain activity in stroke patients using electrophysiological recordings and have for the most part focused on the event-related synchronization/desynchronization of the EEG activity during finger movements (Babiloni et al. 1999; Graziadio et al. 2012). Consequently, the time course of the activity of the SMA, as well as ipsi-M1 and contra-M1 during the different stages of a movement (preparation and execution), has not been fully addressed in chronic stroke patients. In the present study we used LT-EEG during an alternating bimanual reaction time task (Osman et al. 2006) to analyze the activity of these cortical structures in a group of chronic stroke patients suffering from mild-to-moderate weakness of one upper limb. Alternated bimanual movements require the coactivation of the relevant motor areas from both hemispheres (Foltys et al. 2001), as well as a higher involvement of the SMA compared with unimanual movements (Sadato et al. 1996; Serrien et al. 2002). Indeed, performing sequences of alternating bimanual movements requires the engagement of premotor structures to coordinate the motor commands between both hands (Stephan et al. 1999). Therefore, it seems that motor tasks demanding a fast sequential coordination of both hands are suitable for the study of the temporal dynamics of the components related to the activity over the SMA, as well as the coordination between the ipsi- and contralateral motor cortex activity. On the basis of previous imaging and PET studies (Chollet et al. 1991; Seitz et al. 1998), we predicted a greater activation of the SMA in patients compared with controls during the execution of alternated bimanual movements. Indeed, this recruitment of nonprimary motor areas might reflect functional compensation in stroke patients with motor impairment as has been previously suggested (Ward et al. 2003; Willer et al. 1993). These previous studies have used neuroimaging techniques that provide a high spatial but reduced temporal resolution (Karakas et al. 2013). The use of EEG recordings, which are very sensitive in the time domain (Picton et al. 2000), might provide more insight about the exact contribution of these structures during the different phases of preparation and execution of movements in these patients. To pinpoint motor-related processed in closely adjacent cortical areas, we used current source density (CSD) waveforms, known to reflect predominantly cortical sources (Vidal et al. 2003b). This method is thought to provide a good estimation of the involvement of SMA in such processes. Additionally, because the alternation of movements demands the coordination between both hemispheres, we expect that our results will shed more light on the pattern of activity over the ipsi- and contra-M1 of these patients.

MATERIALS AND METHODS

Participants

Eighteen right-handed chronic stroke patients (15 men) with a mild to moderate hand paresis were recruited at the Hospital Universitari de Bellvitge and Hospital de L'Esperança in Barcelona. The average age was 59.6 ± 8.5 yr (mean ± SD). Handedness was measured using the Edinburgh Handedness Inventory (Oldfield 1971). Patients were required to have had a single stroke at least 6 mo before enrollment in this study and an overall Barthel Index >50 (van der Putten et al. 1999). Upper limb motor function was measured using the Action Research Arm Test (ARAT) with a maximum global score of 57 (Lyle 1981). The mean educational level of the patient sample was 7.7 ± 5.5 yr. History of seizures, marked cognitive impairment [mini-mental state examination (MMSE) score ≤25 (Folstein et al. 1975)], major comorbidity, and mirror movements were considered to be exclusion criteria. Table 1 provides additional demographic data for the patients.

Fourteen healthy participants [12 men; 57.5 ± 8.4 yr old], roughly matched by age [$t(30) = 1.15$, $P = 0.26$], sex [$\chi^2(1,N = 32) = 0.788$, $P = 0.59$], and educational level [8.1 ± 4.5 yr; $t(30) = 0.75$, $P = 0.72$], were recruited and included in this study as a control group. All participants from this group were right-handed and were free of neurological diseases, cognitive impairment, and major comorbidity.

The Committee of Ethics for Clinical Research of the Hospital Universitari de Bellvitge approved all procedures, and the experiment was carried out in conformity with the standards set by the Declaration of Helsinki. All participants gave written informed consent before their enrollment in the study.

Sequential Bimanual Task

We used an adapted version of the bimanual motor task reported by Osman et al. (2006). Participants sat in a comfortable armchair

Table 1. *Demographic data for each individual in the patient group*

Subject	Age, yr	Months Since Stroke	MRC Score	Lesion Location	Barthel Index	ARAT Score
1	42	20	4−	Left thalamus, posterior putamen and internal capsule	90	37
2	65	8	5−	Right frontal and temporal cortex and striatum	85	57
3	66	74	4−	Right internal capsule and striatum	95	46
4	60	11	5−	Left thalamus	100	48
5	59	71	4+	Right frontal, temporal and parietal cortex	95	49
6	65	14	4+	Left thalamus	70	42
7	63	50	5−	Left subinsular region and claustrum	100	38
8	68	10	4+	Right frontal and temporal cortex	75	38
9	51	59	4	Left pre-Rolandic region	100	31
10	68	8	5−	Right thalamus	80	56
11	71	8	3+	Right subinsular region and posterior frontal cortex	90	22
12	66	7	3+	Lenticulate nucleus, left external and internal capsule	70	40
13	49	10	4+	Left thalamus	100	57
14	44	9	5−	Right pons	100	40
15	60	55	4	Left putamen and external capsule	100	52
16	65	18	5−	Right caudate and cerebellum	95	35
17	57	20	5−	Right temporal cortex	95	48
18	65	13	4+	Left pons and occipital cortex	50	35

For each participant, the following data were obtained at the time the patient was included in the study: age, months since stroke, Medical Research Council (MRC) score, lesion location, Barthel Index, and Action Research Arm Test (ARAT) score.

looking at a 17-in. screen from about 1.1 m with their elbows resting on the armrest adjusted to the same height as a table in front of them. The left and right index fingers were located on response boxes fixed on the table at a comfortable distance along the line perpendicular to the midline of the body. The stimuli consisted of individual left- or right-pointing black arrows presented at the center of a monitor against a white background.

The task consisted of synchronizing taps to a series of visual pacing stimuli (above-mentioned black arrows) presented in sequences (Fig. 1). Each sequence comprised six arrow stimuli alternating toward the left and toward the right, presented serially at a constant rate of 1 per 1,500 ms (0.66 Hz). All sequences started with the left-pointing arrow. The participant's task was to synchronize taps with the left index finger to the left-pointing black arrow and taps with the right index finger to the right-pointing arrow.

Importantly, participants were instructed to respond as fast as possible to the corresponding stimulus, and they were requested to minimize blinking during the presentation of the stimuli. A 5-s break between 2 consecutive sequences allowed participants time to blink.

A total of 100 sequences were presented in 2 blocks of 50 sequences each. Two minutes of rest were given between the two blocks. Thus each participant performed 300 responses with each hand.

At the beginning of each sequence, a black cross on the center of the screen indicated to participants that they could blink during that time. One second before the onset of the first arrow of the sequence, this cross vanished so that participants would stop blinking.

Electrophysiological Recordings (EEG)

The EEG signal was recorded continuously (bandpass filtered, 0.01–250 Hz; analog-to-digital rate, 500 Hz) with a BrainVision system (Brain Products, Munich, Germany) and analyzed offline using MATLAB 7.5 (The MathWorks, Natick, MA). An electrode cap fitted with 29 tin electrodes (Fp1/2, F3/4, C3/4, P3/4, O1/2, F7/8, T3/4, T5/6, Fz, Cz, Pz, FC1/2, FC5/6, CP1/2, CP5/6, and PO1/2) was used. Two external tin electrodes were attached at the left and right mastoids. A tin electrode placed on the lateral outer canthus of the right eye served as an online reference. Subsequently, the recorded EEG signal was referenced offline to the algebraic summation of signal obtained from both mastoids. This reference method has been extensively used in prior studies (Amengual et al. 2014; Havas et al. 2012; Mas-Herrero and Marco-Pallarés 2013; Padrão et al. 2014). An additional external tin electrode was placed ~1 cm below the right eye to detect vertical eye movements (VEOG). All impedances were kept below 5 kΩ. Subsequently, data were bandpass filtered (0.01–45 Hz).

LT-ERP Assessment

Single-trial EEG data epochs time-locked to responses were extracted from the continuous EEG recording and used for averaging. For each participant, the electrical activity from all channels locked to affected and unaffected hand responses were averaged separately. For this study, two different data sets were obtained. One data set consisted of the averaged activity locked to the first response of each sequence. A second data set comprised all second and third responses of the sequences performed with the affected hand and the unaffected hand separately. In this second data set, electrode locations were mirrored offline by patients with left hemispheric lesions such that all lesions were mapped to the right hemisphere. This mirroring procedure was also performed in data from controls assigned to each patient with left hemispheric lesion. Therefore, despite the real side of the lesion, the data will show the lesioned hemisphere as the right hemisphere and the spared one as the left hemisphere. For both data sets, epochs were 2,300 ms long, beginning 1,300 ms before the response.

For this study, data were edited in three different steps. First, we only selected trials in which all responses were correct. Second, only trials with time responses longer than 150 ms and shorter than 3 SD above the mean were considered for the analysis. Third, trials for which activity exceeded ±200 μV were rejected. Only participants that showed at least 80% artifact-free trials were included in the statistical analysis.

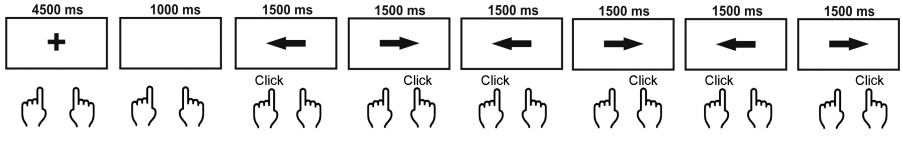

Fig. 1. Schema for 1 sequence of the bimanual reaction time task. Participants were asked to alternate taps with the left and right index finger synchronized to stimuli (arrows) presented every 1,500 ms.

ERPs were transformed into reference-free CSD waveforms using the spherical spline surface Laplacian algorithm with fourth-degree Legendre polynomials and a smoothing coefficient (λ value) of 10^{-5} (Perrin et al. 1989). The CSD waveforms were computed for each original ERP waveform using a CSD toolbox for MATLAB (Kayser and Tenke 2006). These estimates represent the radial current flow entering and leaving the scalp and are proportional to the direction, location, and intensity of current generators that underlie an ERP map (Kayser et al. 2012; Tandonnet et al. 2003).

Statistical Analysis

All statistical analyses were performed using SPSS 17 (SPSS, Chicago, IL).

Behavioral measures. Behavioral measurements of the task performance were as follows. Reaction times (RT) were calculated as the time between the stimulus presentation and the response. We measured RTs in two different types of trials. First, we measured the RT corresponding to the first response of each sequence, which was always performed with the left hand. We sought for between-groups differences in these RTs using independent *t*-tests. Second, we measured the RTs of the second and third responses performed with the affected and the unaffected hand. To seek hand differences in RTs between patients and controls in alternating responses, we conducted a repeated-measures analysis of variance (ANOVA) with hand (affected vs. unaffected) as a within-subject factor and group (patients vs. controls) as a between-subject factor. We also measured two different parameters concerning the synchronization of the responses with the stimuli along each sequence [interstimulus interval (ISI) = 1,500 ms]. First, the success in synchronizing responses to the stimuli was reflected by the constant errors, measured as the mean deviation from synchrony with the ISI. The sign of the constant error reveals whether responses are performed at higher (negative sign) or lower (positive sign) frequency than the stimulus presentation. Second, the cost in synchronizing the keystroke to the stimuli presentation was estimated with the magnitude of the variable errors, measured as the standard deviation of individual taps around the mean interval (Osman et al. 2006). We evaluated group differences in these two parameters by using independent *t*-tests for analysis.

Other measures of performance of the task included the percentage of missing trials (trials with no response) and error trials for each hand (right-hand response for left-pointing arrow, or vice versa). To seek hand differences between both groups in these parameters, we conducted repeated-measures ANOVA with hand as a within-subject factor and group as a between-subject factor.

For all statistical tests, the level of significance was set at $P = 0.05$. All P values from post hoc tests were corrected for multiple comparisons using the Bonferroni correction when necessary.

Electrophysiological measurements. Concerning the analysis of the EEG, we tested differences in the amplitude of the LT-ERPs in components associated with the activity in ipsi-M1, contra-M1, and SMA during affected and unaffected hand responses in both groups. We chose three channel locations for statistical analysis on the basis of previous studies: Cz was the channel location corresponding to the activity associated with the medial premotor cortex (SMA), and C3 and C4 were considered as the electrode locations corresponding to the affected and unaffected motor cortex (ipsi- and contra-M1, respectively) (Carbonnell et al. 2004; Meckler et al. 2010; Tandonnet et al. 2003; Vidal et al. 2003b). For each of these locations, mean current measures were obtained and entered into repeated-measures ANOVA with factors hand (affected vs. unaffected) and group (patients vs. controls) in corresponding time windows of interest (see RESULTS for a description of the selected time intervals of statistical analysis). The LT-ERPs were measured relative to the averaged activity from −1,300 to −1,200 ms. This baseline interval was selected to observe the evolution of the components associated with the activity in motor areas during the preparation of responses. In addition, we considered a second baseline interval (−150 to −50 ms) to observe the evolution of the related-SMA activity close to the response.

We also performed statistical analysis to test differences in the amplitude of the brain activity components between patients with cortical and pure subcortical lesions. Toward this aim, we split patients into two different subgroups as a function of the lesion location and performed repeated-measures ANOVA with factors lesion (cortical vs. pure subcortical) and hand.

With the aim to reduce the lateralization effect expected in controls (due to their right-handedness) and to obtain a more fair comparison between groups, we identified "affected" and "unaffected" hemispheres in each control participant by considering the corresponding patient. Post hoc comparisons were performed with paired and independent *t*-tests accordingly when significant group × hand interaction effects were obtained.

For all statistical tests, the level of significance was set at $P = 0.05$. All P values from post hoc tests were corrected for multiple comparisons using the Bonferroni correction when necessary.

Correlation between clinical scores vs. electrophysiological recordings and behavioral performance. In addition to the previous analysis, we sought for associations between the ARAT score and *1*) LT-ERP findings and 2) behavioral parameters. To this aim, we used Pearson correlation analysis between each pair of measures. The level of significance was set at $P = 0.05$.

RESULTS

From the initial sample of patients, three participants were not included in the analysis because of excessive blinking and movement artifacts. A fourth patient was not able to perform the task and was therefore removed from the final sample. Finally, 14 patients were included into the statistical analysis. From this final sample of patients, eight patients presented pure subcortical lesion and six patients presented a cortical lesion. The exact lesion location of each patient was inspected by a physician using available MRI and CT images. These patients showed a global ARAT score of 42.83 ± 9.56. All control participants were included in the analysis.

Behavioral Analysis

Before the statistical analysis, RTs were pruned such that trials with response times below 150 ms or greater than 3 SD of the individual mean were rejected. Results from the RT analysis are shown in Fig. 2. Controls responded faster than patients to the first stimulus of the sequence [controls vs. patients: $t(26) = -3.28$, $P < 0.001$; Fig. 2*A*]. The ANOVA showed a main effect of group for second and third responses [group effect: $F(1,26) = 11.98$, $P < 0.01$]. Figure 2*B* shows that controls responded faster than patients during second and third responses. A group × hand interaction [$F(1,26) = 4.61$, $P = 0.041$] was followed up by post hoc comparisons, which revealed that patients were faster responding with the unaffected hand [$t(13) = -2.89$, $P = 0.042$], whereas there was no hand difference in controls [$t(13) = -0.05$, $P > 0.5$].

We analyzed the task performance regarding the synchronization in alternating taps with arrows. Figure 3 shows the distribution of the intertap intervals relative to the ISI (1,500 ms) for patients and controls. Patients showed an average constant error (mean, range) of −12 ms [minimum (min) = −41 ms, maximum (max) = 18 ms] and an average variable error of 45 ms (min 25 = ms, max = 90 ms). Controls showed an average constant error of −14 ms (min = −34 ms, max = 8 ms) and an average variable error of 35 ms (min = 23 ms;

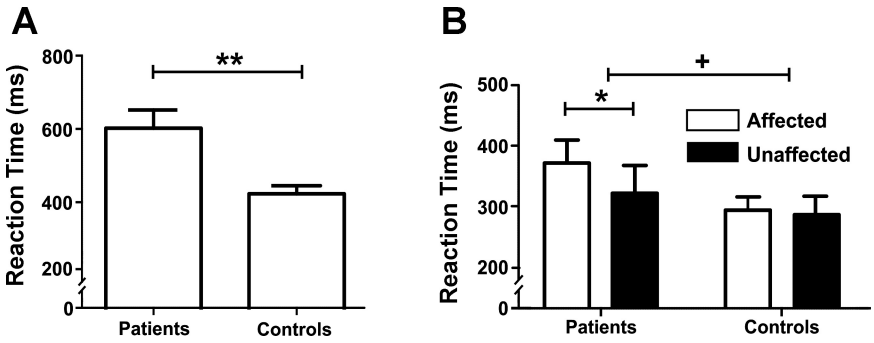

Fig. 2. Bar plots representing the mean reaction time of the first response of each sequence (*A*) and second and third responses performed with the affected and unaffected hand (*B*). Mean values for patients and controls are represented. Error bars represent the SE of each distribution. $*P < 0.05$; $**P < 0.01$. $+P < 0.05$, group effect.

max = 52 ms). Independent samples *t*-test analysis indicated that there were no differences between both groups in constant errors [$t(26) = -0.68$, $P > 0.1$], whereas a tendency toward larger variable errors in patients was revealed [$t(26) = -1.98$, $P = 0.057$].

Regarding the percentage of missing trials, there was neither a group main effect [group: $F(1,26) = 1.22$, $P = 0.28$] nor a group × hand interaction [$F(1,26) = 2.25$, $P = 0.14$]. A similar result was obtained for the percentage of erroneous responses [group: $F(1,26) = 1.86$, $P = 0.18$; group × hand, $F(1,26) = 1.63$, $P = 0.23$].

EEG Results

Figure 4 shows LT-ERPs recorded from locations C3 and C4. These LT-ERP deviations represent the evolution of the activity over contra-M1 and ipsi-M1 regions, accordingly. Figure 5 shows the LT-ERP traces obtained from the location Cz associated to the evolution of the activity over SMA. It represents the increase/decrease of activation relative to two different baseline time periods (−1,300 to −1,200 ms and −150 to −50 ms). During the preparatory phase of the response movement, LT-ERPs showed a greater negativity over the Cz in controls compared with patients for affected and unaffected hand responses (Fig. 4). Interestingly, we found a peak amplitude associated with the activation over the SMA after the response to be more prominent in patients than in controls (Fig. 5, *left*). Patients also showed a greater positivity in ipsi-M1 when the response was performed with the unaffected hand compared with the affected hand. In addition, controls showed a higher negativity than patients over the contra-M1 location at the response time. In the following sections we report the statistical comparisons of the LT-ERP amplitudes between groups and hands over each of these regions.

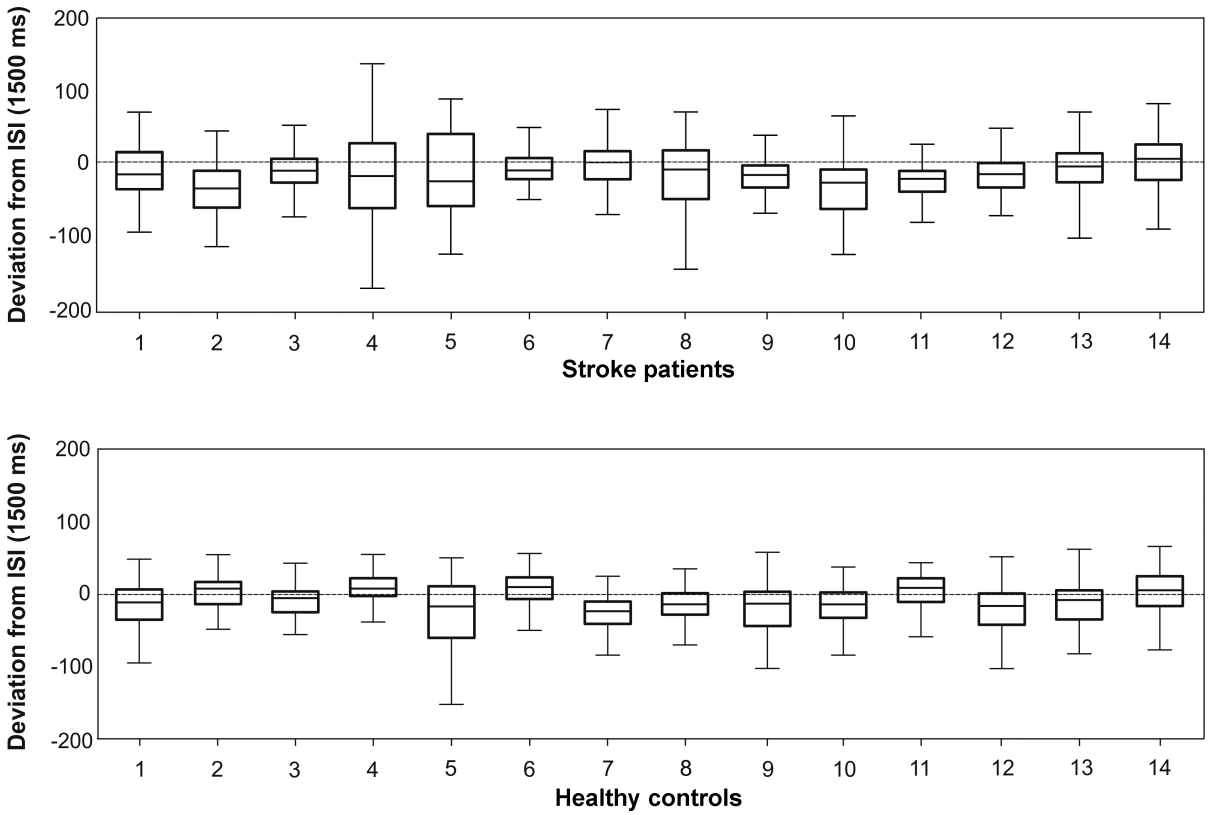

Fig. 3. Distribution of intertap intervals (time between successive taps) for each participant from the group of stroke patients (*top*) and matched controls (*bottom*). Each box represents the distribution of a single participant. The middle line, inner pair of lines, and outer pair of lines represent, respectively, the median and 25th and 75th percentiles. ISI, interstimulus interval (time between onsets of successive synchronization signals).

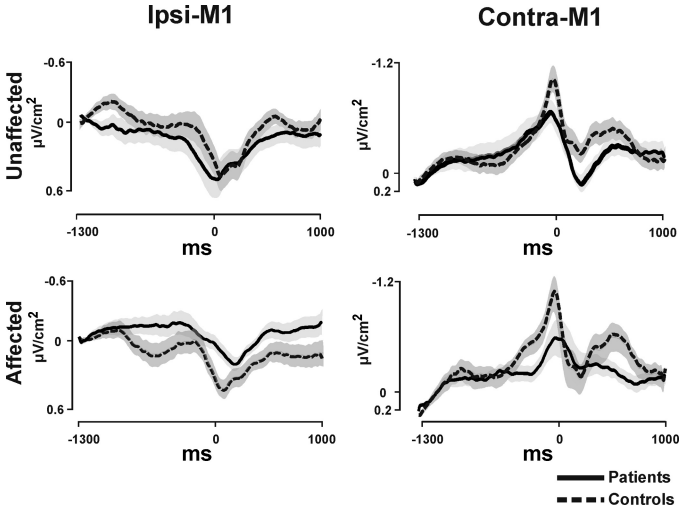

Fig. 4. Electroencephalogram (EEG) activity (grand averages for the 14 participants of each group) after estimation of the surface Laplacian recorded at C3 and C4 electrode sites corresponding to the activity over M1 contralateral (contra-M1) and ipsilateral (ipsi-M1) to the movement side. All traces were averaged while locked to the second and third responses of each sequences performed with the unaffected (*top*) and affected hand (*bottom*). Activity from controls is represented by dotted lines, whereas activity from patients is represented by solid lines. Gray shading represents the point-to-point SE of the amplitude in each Laplacian-transformed event-related potential (LT-ERP). Magnitude of the amplitude is given in $\mu V/cm^2$. The baseline time window was set at −1,300 to −1,200 ms.

Activity over the ipsi-M1. Figure 4, *left*, shows the evolution of the response-locked LT-ERPs recorded over the motor areas ipsilateral to the response hand (affected and unaffected) for each group. A characteristic feature of the controls' waveforms was a positivity starting at 150 ms before the response and peaking 60 ms after the response for both hand responses. Previous studies have suggested that these positive deflections in the ipsilateral cortex using LT-ERP correspond to an inhibitory process in this area (Burle et al. 2002). Data from patients showed a different picture. For both hand responses, we found a positive deviation starting around 300 ms preresponse, peaking around the response time (20 ms postresponse) for unaffected hand movements. However, and differently, this positive deviation clearly peaked after the response (190 ms) for affected hand responses (see Fig. 6 for the topographical representation of this component). This differential pattern of activation between both hand responses in patients was corroborated by the corresponding statistical analysis (peak-to-peak mean amplitude between −375 to −275 ms and 0 to 50 ms; see Fig. 4, *left*). A significant hand × group interaction was observed [$F(1,26) = 5.04$, $P = 0.033$]. Further pairwise comparisons showed a clear difference between affected and unaffected hand responses for patients [affected vs. unaffected, patient group: $t(13) = -3.29$, $P = 0.023$], whereas no differences were found in the control group [$t(13) = -0.52$, $P = 0.52$]. No differences were found in patients as either a function of the lesion location [$F(1,12) = 1.37$, $P = 0.71$] or interaction effects [hand × lesion: $F(1,12) = 0.33$, $P = 0.57$]. Therefore, these hand-dependent differences in amplitude and latency of these components might indicate an altered inhibition of the affected motor region during the preparation of movements performed with the unaffected hand.

Activity over the contra-M1. Figure 4, *right*, shows the evolution of the response-locked LT-ERP recorded over contra-M1 for both hand responses in each group. In controls, we found a characteristic long negative waveform starting around 360 ms preresponse, peaking at the response time for both hands. These negative deflections in the contralateral cortex have been largely reported, and they have been related with the preparation and execution of movements (see Shibasaki and Hallett 2006 for review). In patients, we found that this deviation started earlier for unaffected hand responses (300 ms) than for affected hand responses (240 ms). These differences between groups were statistically corroborated by a strong group effect [time window −275 to −225 ms, group: $F(1,26) = 15.26$, $P = 0.001$]. In addition, we found a group × hand interaction within the same time window [group × hand: $F(1,26) = 4.54$, $P = 0.043$]. Post hoc independent *t*-test analysis revealed that controls clearly showed an overall larger activation than patients during this time window [patients vs. controls, affected: $t(26) = 2.66$, $P = 0.049$; unaffected: $t(26) = 3.56$, $P = 0.006$].

The peak amplitude of this activation observed at the response time was different in controls than in patients for both affected and unaffected hand responses [time window −50 to 0 ms relative to the onset, group: $F(1,26) = 8.13$, $P = 0.008$; Fig. 4]. Post hoc independent *t*-test analysis revealed that patients showed an overall smaller amplitude than controls [merged activity from both hand responses, patients vs. controls: $t(26) = 2.85$, $P = 0.008$]. We did not find differences in amplitude as a function of the hand [hand: $F(1,26) = 0.03$, $P = 0.85$] or a significant interaction effect [hand × group: $F(1,26) = 0.078$, $P = 0.67$]. No differences in amplitude were found as a function of the lesion location [$F(1,12) = 0.003$, $P = 0.96$] or in the interaction hand × lesion [$F(1,12) = 0.12$, $P = 0.73$].

Activity over the SMA. The activity over the Cz location was analyzed while locked to two different events. First, we analyzed LT-ERPs locked to the first response of the sequences

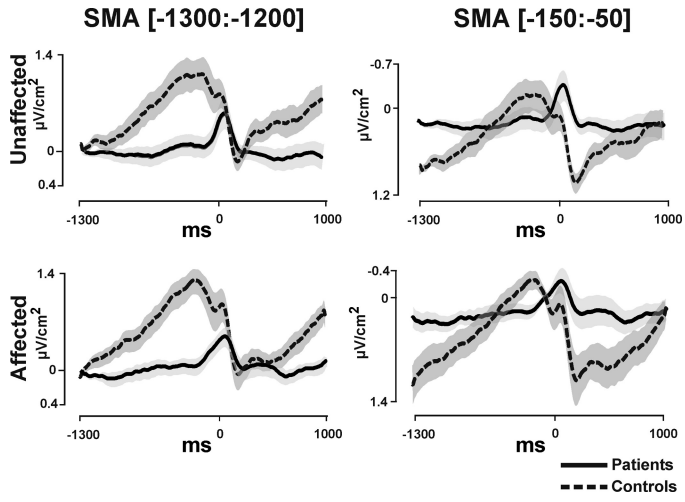

Fig. 5. EEG activity (grand averages for the 14 participants of each group) after estimation of the surface Laplacian recorded over the supplementary motor area (SMA) recorded at Cz electrode. All traces were averaged while locked to the second and third responses of each sequences performed with the unaffected (*top*) and affected hand (*bottom*). Activity from controls is represented by dotted lines, whereas activity from patients is represented by solid lines. Gray shading represents the point-to-point SE of the amplitude in each LT-ERP. Magnitude of the amplitude is given in $\mu V/cm^2$. The baseline time window was set at −1,300 to −1,200 ms (*left*) and at −150 to −50 ms (*right*).

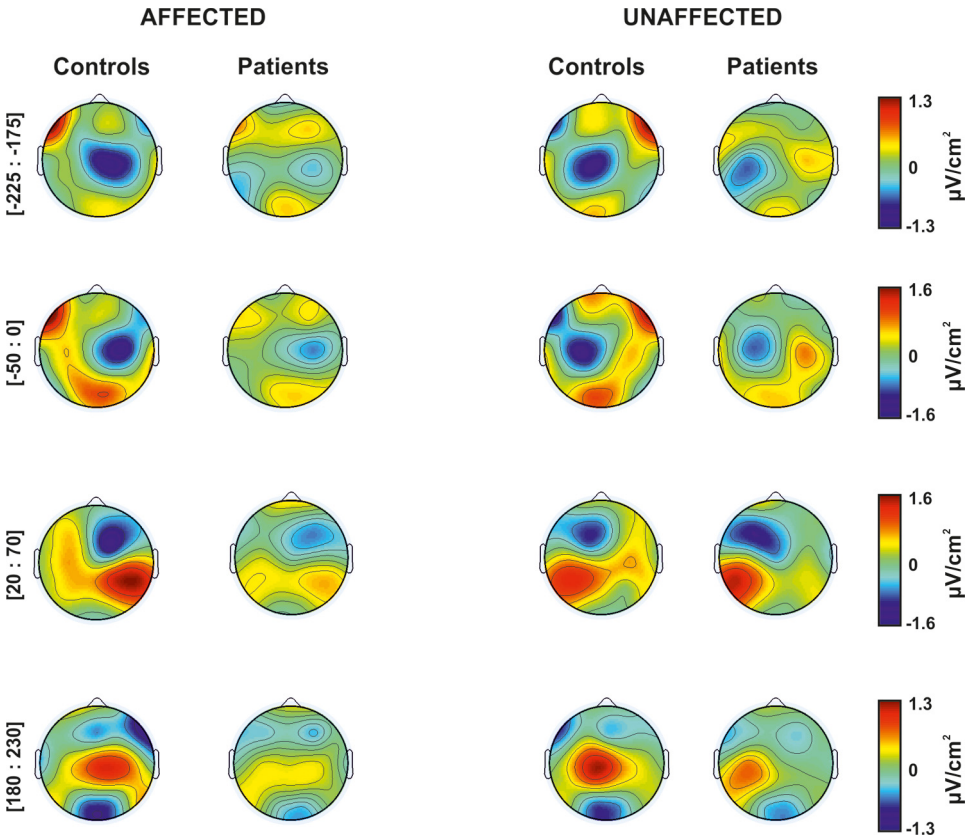

Fig. 6. Current source density (CSD) maps of the distribution of the Laplacian-transformed activity for each hand response and group. Warm colors represent sources of current, whereas cold colors represent sinks of current. Each time window corresponds to chosen periods from the statistical analysis.

(performed with the left hand). Second, we locked the LT-ERPs to the second and third hand responses as performed in *Activity over the ipsi-MI* and *Activity over the contra-MI*. These components have been largely attributed to the activation of the SMA during motor responses (Carbonnell et al. 2004).

Figure 7 shows the LT-ERPs locked to the first response of each sequence. Notably, this condition represents a pure simple RT task, since it is always known that all sequences begin with a left hand response. Controls showed a clear negativity during the preparatory phase of the movement, starting around 500 ms prior to the response and peaking around 80 ms preresponse. In this condition, patients showed a smaller but consistent negativity starting 100 ms later than in the control group. This different pattern was corroborated by statistical analysis [time window −400 to −300 ms relative to averaged activity within −1,300 to −1,200 ms, patients vs. controls: $t(26) = -2.19$, $P = 0.038$; Fig. 7, *left*]. These components also showed a different picture between patients and controls after the response. In this context, Fig. 7, *right*, depicts a clear negativity shortly after the response in patients (around 90 ms) that was smoothly decreasing until reaching baseline levels (500 ms after the response). Controls, conversely, showed a sudden decrease of amplitude. Independent *t*-test analysis corroborated this different pattern of activation [time window 100 to 300 ms relative to averaged activity within −150 to −50 ms, patients vs. controls: $t(26) = -2.67$, $P = 0.013$; Fig. 7, *right*].

Figure 5 shows the LT-ERP obtained from the Cz location for both affected and unaffected second and third hand responses in patients and in controls. Prominent differences between groups were observed. First, a ramp-shaped negativity, starting around −1,000 ms before the response and reaching its maximum at about −200 ms, was evident in the control group. This effect was observed for both hands and was similar to the pattern of activity described previously in healthy participants during the preparatory phase of movements (Shibasaki and Hallett 2006). However, patients showed a flat activity shape during the same period, which remained almost at baseline level until 100 ms before the response. Such differences between both groups were corroborated by a strong group effect [time window −225 to −175 ms relative to the average amplitude between −1,300 and −1,200 ms, group: $F(1,26) = 23.39$, $P = 0.0001$; see Fig. 6 for the topographical representation of this component]. We did not find a main

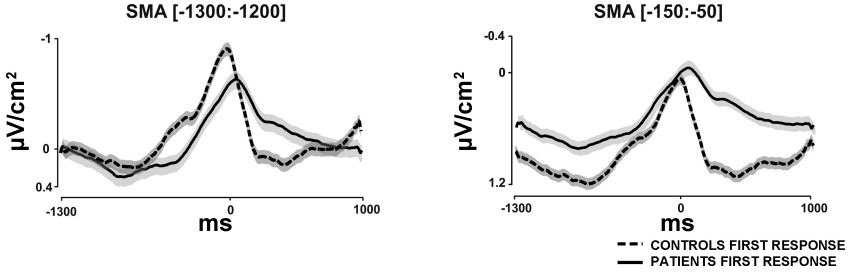

Fig. 7. EEG activity (grand averages for the 14 participants of each group) after estimation of the surface Laplacian recorded over the SMA at the Cz electrode. All traces were averaged while locked to the first response of each sequence. Activity from controls is represented by dotted lines, whereas activity from patients is represented by solid lines. Magnitude of the amplitude is given in $\mu V/cm^2$. The baseline time window was set at −1,300 to −1,200 ms (*left*) and −150 to −50 ms (*right*).

effect of hand [$F(1,26) = 1.07$, $P = 0.76$] or a group × hand interaction [$F(1,26) = 1.04$, $P = 0.75$] for this time window. Post hoc independent *t*-test analysis revealed significantly higher activation in controls compared with patients [merged activity from both hand responses, patients vs. controls: $t(26) = 4.83$, $P = 0.003$]. No differences were found in patients as a function of the lesion location [$F(1,12) = 0.03$, $P = 0.91$] or in the interaction hand × lesion [$F(1,12) = 0.09$, $P = 0.88$]. Therefore, we found an expected negative component during the preparation of responses associated with the activity of the SMA in controls (Shibasaki and Hallett 2006; Vidal et al. 2003a) that was nearly absent for patients.

Second, shortly after the motor response, a clear negativity was observed in both groups over this area. This sudden increase of negativity over central motor areas of the brain coinciding with the motor response has been extensively reported previously not only in EEG (see Shibasaki and Hallett 2006 for review) but also in LT-EEG (Vidal et al. 2003a, 2003b). Figure 5, *right*, shows the LT-ERPs from the Cz location relative to the averaged activity within the time interval −150 to −50 ms. We found that this activity peaked around 50 ms after the response for both groups. Interestingly, this negativity was larger in patients than in controls for both hand responses, suggesting an overactivation of the SMA in patients relative to controls after the response. Statistical analysis corroborated this differences between both groups [time window 20 to 70 ms relative to the averaged activity within −150 to −50 ms, group: $F(1,26) = 4.44$, $P = 0.045$]. Post hoc independent *t*-test analysis revealed that patients effectively showed a higher amplitude negativity in this time window than controls [merged activity from both hand responses, patients vs. controls: $t(26) = -4.83$, $P < 0.0001$]. In addition, we found that patients showed a different activation in unaffected compared with affected hand responses [group × hand: $F(1,26) = 5.36$, $P = 0.03$]. We did not find a significant hand effect in this time interval [$F(1,26) = 0.035$, $P = 0.55$]. No differences were found in patients as a function of the lesion location [$F(1,12) = 0.72$, $P = 0.41$] or in the interaction hand × lesion [$F(1,12) = 1.28$, $P = 0.27$].

Finally, a prominent positivity was observed in the control group which started at 80 ms and peaked at 200 ms. Conversely, the activity observed in patients returned at baseline levels (Fig. 5). Statistical analysis revealed a clear group main effect [time window 180 to 230 ms postresponse relative to the averaged activity within −150 to −50 ms: $F(1,26) = 13.1$, $P = 0.001$]. Post hoc independent *t*-test analysis revealed controls showed a larger activation than patients [merged activity from both hand responses, patients vs. controls: $t(26) = -3.6$, $P = 0.001$; Fig. 5]. We did not find a hand effect [$F(1,26) = 0.001$, $P = 0.98$] or hand × group interaction [$F(1,26) = 45$, $P = 0.50$]. Again, no differences were found in patients as a function of the lesion location [$F(1,12) = 0.01$, $P = 0.76$] or in the interaction hand × lesion [$F(1,12) = 0.62$, $P = 0.8$].

In summary, we found a clearly different LT-ERP activation corresponding to the SMA between patients and controls. This different activation was suggested by a nearly absent of activity of the SMA during the preparatory stage of the second and third responses of each sequence in patients. Additionally, patients showed an overactivation over the SMA after the response, whereas activity in controls suddenly decreased after the response.

Correlation Between Behavioral Parameters, Electrophysiological Recordings, and ARAT Score

We did not find a significant correlation between the scores on the ARAT and the RT of the responses performed with the affected or the unaffected hand ($P > 0.44$). The ARAT scores were also not significantly correlated with the amount of either constant or variable errors ($P > 0.31$ in all cases). Similarly, the correlation between the ARAT scores and the amplitude of the LT-ERPs in all time windows considered in the statistical analysis was nonsignificant ($P > 0.09$ in all cases).

DISCUSSION

The present work addresses the study of the behavioral performance and the electrocortical activity during alternating button presses executed with the affected and unaffected hand in a group of chronic stroke patients. We found differences between patients and healthy controls in execution parameters such as reaction time and synchrony of motor responses with the visual cue, suggesting a higher cost in patients in performing the alternating responses adequately. The analysis of the LT-ERPs recorded from different key areas of the motor system (associated to ipsi-M1, contra-M1 and SMA) suggests clearly different patterns of activation in these areas between both groups of participants. First, whereas controls showed an expected increase of the SMA activity during the preparation of the responses, patients only showed an increment of activity over this area in the first response of the sequence, showing a nearly absent activity during the other responses. Additionally, patients showed a clear increment of the SMA activity shortly after the response compared with controls in all responses. Second, the activity over the ipsi-M1 showed clear differences between patients and controls, specifically showing a different pattern in patients as a function of the responding hand. Last, the activity over the contra-M1 at the response time was higher in controls regardless of the responsive hand. The results reported in this work reflect a clearly different pattern of the temporal dynamics of the motor system activity in chronic stroke patients compared with matched controls participants in alternated hand responses.

Activity Over the SMA

A substantial number of studies have shown the involvement of the SMA during preparation and programming of unilateral (Hoshi and Tanji 2004; Matsuzaka et al. 1992) and bimanual movements (Serrien et al. 2002). Previous EEG and MEG studies have shown that activity of the SMA precedes that of contra-M1 (Cheyne et al. 1991; Cui et al. 1999; Deecke et al. 1980), indicating a hierarchical organization within the motor system in which contra-M1 might be subordinated to SMA (Carbonnell et al. 2004). This temporal succession of SMA and contra-M1 activity also has been shown by LT-ERPs (Vidal et al. 2003b). Our control group also showed that activity over the SMA precedes the activation over contra-M1. Patients, conversely, showed a clearly different dynamics of the components associated to the SMA activation. First, patients did not show an increased activation of the SMA during the preparation of responses, preceding the activation of contra-M1. Sec-

ond, they showed a higher increment of the SMA activity than controls shortly after the response that remained "overactivated" for a few hundred milliseconds, whereas this activity in controls suddenly decreased to baseline levels after the response.

One possible explanation for this apparent absence of activity in this area during the premovement period specifically in patients could be the high between-subject variability in this group, which could mask the activation when the activity is averaged into epochs. Indeed, this possibility must be taken into account due to patients showing higher variability in their performance than controls, as suggested by the higher average variable errors in synchronizing responses to the ISI. However, we found a strong group effect when comparing the amplitudes of LT-ERPs recorded from this location in both groups, as well as a clear negative peak in controls during this period. Contrary to these findings, we did not observe these components associated with the preparation of responses in patients. Hence, it seems unlikely that these results would be explained in terms of variability effects. A second explanation is based on the temporal dynamics of the components associated with the SMA activity in patients. Interestingly, SMA activity in patients before the first response of each sequence was increased, contrary to that observed during alternating responses. This may reflect a differential contribution of the SMA to the different types of response in the current experiment. Indeed, first responses of the sequence could be considered as a pure simple reaction time task, because *1*) no other responses (from the same sequence) have been performed first, and *2*) the information about the motor planning to execute the response is known. In addition, and contrary to what we observed in the EEG data in the control group, the SMA in patients remained activated after all responses. Because patients showed a persistent SMA activity during the between-response period, which served as the baseline for the subsequent response, we did not observe significant increases of the SMA activity during the preparation of the next response. It suggests that this group might have a problem in setting the correct activation/deactivation imbalance in the SMA requested for optimizing the performance in the bimanual task. This result is important and contrasts with the preserved increase of SMA activity observed during the preparation of the first response of the sequence. This finding is this line with Rosenbaum et al. (2007), who have suggested that an internal plan of an entire complex motor sequence could be generated before the execution of the first step, instead of planning each single step of the sequence separately. The excessive overactivation of the SMA in our patients could thus reflect a specific failure in the capacity to preplan the entire sequence. This excessive activation of the SMA in chronic stroke patients echoes previous findings of Vidal et al. (2003b) suggesting that sequential movements might be a more complex process in chronic stroke patients than in healthy controls.

In patients, the greatest increase of negativity over the SMA was observed immediately following the motor response. Previous studies have extensively discussed the role of the SMA and contra-M1 during the performance of reaction time tasks. Vidal et al. (2003b) found activation over SMA up to 40 ms before the muscular activation in a choice reaction time task, which was followed by the activation of the contra-M1 during the response in a group of healthy participants. This sequential activation between these two structures is consistent with a role of this area in programming and selecting the motor response. One possible explanation for this overactivation of the SMA observed in patients shortly after the response could be a higher complexity of the motor program. Indeed, corroborating evidence was reported by Carbonnell et al. (2004), who showed a diminished activation of the SMA in trials in which information was provided in advance to prepare a specific motor channel and, conversely, larger SMA activity in noninformative trials. This differential effect that they found was presumably because the motor preparation was necessarily performed after the presentation of the imperative stimulus, suggesting that the activation of the SMA might be influenced by the complexity of the motor program. Since the peak activity of the SMA in patients appears to have occurred after the activation of contra-M1, this explanation seems unlikely, however. After all, planning motor operations should develop before the execution processes. In addition, our task was highly predictive, because the timing of the stimuli was completely stable along the experimental session.

A second possible explanation for this postresponse activity found at the Cz location in patients relies on the sign (negative) and latency (~50 ms after the response) of the peak activity, which correspond to those of the error-related negativity (ERN; Ne). Classically, this negative potential has been interpreted as an index of error detection, as well as the neural signature of a compensatory mechanism to prevent further errors (Falkenstein et al. 1991; Gehring et al. 1993). However, in a series of studies, Vidal and colleagues found that this activity also can be observed after correct responses under certain conditions, challenging this specificity of the Ne as an "error-related" mechanism (Vidal et al. 2000, 2003a), and suggested that it might correspond to a response evaluation process. Gehring and Knight (2000) demonstrated that patients with lesions in the frontal lobe showed a very large Ne-like activity after correct responses, which was comparable to the homologous activation after erroneous responses. To explain this, they suggested that patients suffering from frontal lobe lesions would fail in elaborating accurate representations of the stimulus-response association, permitting the activation of multiple competing responses. Following these arguments, we could suggest that this activity shown by patients in the present study would be associated with an impaired representation of the movement effector, triggering the activation of medial frontal areas after the response as a neural signature of a sustained action monitoring. Indeed, Fang et al. (2007) suggested that a motor task, although simple, could be perceived by stroke patients as a difficult task requiring an elevated cognitive effort to monitor the motor performance responses. In addition, these engaged action monitoring mechanisms might also explain, at least partially, the overall slower responses that we found in patients. Indeed, many studies point out that triggering these processes might cause the coactivation of other areas of the frontal lobe, such as the prefrontal cortex, reducing the amount of excitatory input in primary motor areas (Marco-Pallarés et al. 2008; Ridderinkhof et al. 2004; van den Wildenberg et al. 2009). Such a reduction in the excitatory input might cause an increase of the time responses that we observed in our data from patients. However, because this rationale is not supported empirically by our data, we must remain speculative in this explanation. All in all, the increased activation at Cz observed

in chronic stroke patients echoes previous findings of Vidal et al. (2003a) suggesting that the performance movements might be a more complex process in chronic stroke patients than in healthy controls that would involve an overactivation of response monitoring mechanisms.

A remaining open question concerns the specific structure that would lead this activation. Many studies point to the anterior cingulate cortex as the key structure generating the Ne, at least when it is related to commission of errors (Botvinick et al. 1999; Kerns et al. 2004). However, other structures have been suggested to be involved in the generation of this potential, such as the SMA (Bonini et al. 2014; Hester et al. 2004; Vidal et al. 2000). Like Vidal et al. (2000, 2003a), we studied the Laplacian transformation of the activity, which is predominantly sensitive to superficial sources and relatively free of deeper ones (Perrin et al. 1989). Therefore, we would argue in favor of the SMA as the main source of this activity, although this argument is indirect due to the inability of Laplacians to solve the inverse problem (Tenke and Kayser 2012).

Activity Over the Ipsi/Contra-M1

The association of a negative contralateral deflection with motor activity has been previously described (Deecke et al. 1980; Shibasaki and Hallett 2006). This negative deflection starts slowly up to 2 s before the movement onset, called "early BP," showing a predominant central distribution over the scalp. This early component is followed by a steep increase of the negativity closely to the execution of the movement, called "late BP," which distribution over the scalp shows a contralateral preponderance to the movement side (see Shibasaki and Hallett 2006 for review of these components).

Previous studies have reported a reduction of the late-BP component in hemiparetic stroke patients (Battaglia et al. 2006). Similarly, data from patients in the present study showed a smaller LT-ERP over contra-M1 before the response. Interestingly, however, our results did not reveal statistical differences in the activation of contra-M1 as a function of the responding hand in patients. This result seems to be in line with previous studies suggesting bilateral plasticity after unilateral stroke associated with cortical poststroke reorganization in both hemispheres (Graziadio et al. 2012; Sanes and Donoghue 2000). Graziadio et al. (2012) reported reduced bilateral corticomuscular coherence in the beta-band frequency in chronic stroke patients compared with controls, suggesting bilateral reorganization rather than only changes of activation in the ipsilesional hemisphere. Our results seems to agree with the claim that certain stability within and between corticospinal systems is maintained during recovery, suggesting that these bilateral changes might be a signature of reestablishment of the balance in the activity between both corticospinal systems during the chronic phase of stroke.

Previous studies point to the premotor positivity (PMP) as the major feature of the waveform recorded over ipsi-M1 occurring before the motor response (Carbonnell et al. 2004; Meckler et al. 2010; Meynier et al. 2009; Praamstra and Seiss 2005; Shibasaki and Hallett 2006; Vidal et al. 2003b). The PMP has been interpreted as a reflection of suppression of the response with the non-intended hand. Data from the control group in the present study revealed a typical PMP starting 150 ms before the motor response that coincided in time with the negativity observed over contra-M1. However, we found a different pattern of inhibitory activity in this region in the patients group. Our data showed that the PMP over ipsi-M1 was quite large during preparation of responses of the unaffected hand but remained close to baseline values for responses with the affected hand, suggesting that the responses with the unaffected hand resulted in higher inhibition in the affected M1. As suggested by Carbonnell et al. (2004), such aberrant inhibition in ipsi-M1 during the preparation of these responses might indicate the recruitment of higher neural resources for the suppression of responses performed with the opposite (in this case, the affected) hand. A possible explanation for this inhibitory pattern in this region might be the avoidance of commission of errors during the actual response. In this context, using a double-choice reaction time task, Meckler et al. (2010) suggested that such ipsilateral inhibition is sensitive to the risk of commission of errors, being implemented in a gradual manner as the risk of committing errors increased. However, in the bimanual reaction time task there is no need to prevent this kind of errors, since choice errors are virtually impossible in this task. Indeed, there is no apparent competition between both hands since responses performed with the unaffected hand were always preceded by responses done with the affected hand and vice versa, which provides the information necessary to prepare adequate responses. Nonetheless, other errors such as the repetition of the response could be committed, and therefore the PMP observed in our data might reflect an inhibitory neural activity associated with the prevention of repetition of responses. Interestingly, this positivity over the ipsi-M1 is observed in patients essentially during the preparation of responses with the unaffected hand, indicating an imbalance of the inhibitory activity in ipsi-M1 as a function of the responding hand. We could argue that preventing repetitions in responses with the affected hand entails more difficulties, consequently triggering more neural demands in the affected M1 during responses with the unaffected hand in patients. However, we must remain cautious with this finding, and more studies are needed to confirm these explanations.

Plasticity of the Motor System in Chronic Stroke Patients

An important question is whether the alterations in the activity of the SMA and M1 regions in stroke patients are related to functional recovery and neural plasticity. Motor impairments in stroke patients result from a disturbance of the corticospinal tract. Transcranial magnetic stimulation (TMS) studies have found that the degree of corticospinal impairment is related to the clinical deficit (Heald et al. 1993; Pennisi et al. 1999; Stinear et al. 2007; Thickbroom et al. 2002). It has been demonstrated that different regions of the motor system, such as the contra-M1, SMA, and parietal areas, are connected at the cortical level and, in addition, can project directly to the motor neurons of the spinal cord (Dum and Strick 1991; Narayana et al. 2012; Rogers et al. 2004). Therefore, damage to the corticospinal tract might be compensated by activity in another pathway. Previous fMRI and PET studies have reported overactivation of the SMA in stroke patients and also excessive activation of other nonprimary motor regions such as the dorsolateral premotor cortex, ventrolateral motor cortex, cingulate motor areas, parietal cortex, and insula (Chollet et al. 1991; Seitz et al. 1998; Willer et al. 1993). It seems thus that

the recruitment of these regions is important for the patients' recovery. Interestingly, these same regions of the extended motor system are recruited in normal participants, if they engage in more complex motor tasks (Catalan et al. 1998), supporting that simple motor commands of the current task were more difficult for patients than controls.

Limitations of the Study

Despite the statistical significance and the clarity of our results, this study contains a set of limitations or caveats that require further discussion. First, the group of patients included participants with great differences in terms of the side and the lesion location that could cause a misinterpretation of data. Indeed, the cohort of patients recruited in this study present lesions in cortical and/or subcortical regions. This heterogeneity in the lesion location could explain the lack of relationship between clinical scores and both behavioral and electrophysiological measurements shown in our data. Other studies, differently, have reported such a relationship in patients suffering coma (Guérit et al. 1999), schizophrenia (Kayser et al. 2001), and also stroke (D'Arcy et al. 2003), but all of these studies included a cohort of clinical participants more homogeneous in terms of lesions and symptoms.

Globally, however, we did not observe effects of the location of the lesion in our findings (in terms of cortical and subcortical lesions), indicating that our results would not depend on the location of the lesion. Nonetheless, more studies are necessary to confirm the independence of the lesion location in this pattern of activation.

A second limitation refers to the interpretation of the high activation observed in the motor regions of the lesioned hemisphere during unaffected (ipsilateral) responses in patients. To our knowledge, there are no studies reporting similar activations in this type of patients, even during the acute phase of the stroke. Our main explanation is based on the specific motor commands that are triggered to perform this bimanual reaction time task, alternating affected and unaffected hand responses. However, more studies should be designed to confirm this finding.

There is a third caveat that concerns the interpretation of the overactivity observed over the SMA during responses in patients shortly after the response. In this sense, we have suggested that such a component might respond to an incremented action-monitoring process engaged during the execution of the whole motor sequence. However, the comparison of these data reported here with data obtained during the performance of more complex tasks such as a Flanker task or Stroop task would clarify the exact nature of these components. In this sense, further research including longitudinal experimental paradigms or testing of the LT-EEG in different motor tasks such as simple or choice reaction time in stroke patients would help to confirm our findings, shedding more light on the involvement of nonprimary motor areas as poststroke compensatory mechanisms during movements. Additionally, the rather low number of electrode locations in the present study might pose a problem for the accuracy of the Laplacian stimulation using spline interpolation functions, as suggested by Yao and Dewald (2005). However, other experimental studies in brain motor activity have reported CSD waveforms using the same number of electrodes or even fewer (Carbonnell et al. 2004; Meckler et al. 2010; Tandonnet et al. 2005). In this sense, it is important to bear in mind that ERP studies with neurological patients might have important methodological concerns that are motivated by the possible fatigue of the experimental EEG recording session. For this reason, sometimes it might not be possible to record EEG activity with more than 32 sensors (64 or 128). All in all, despite this methodological constraint, we believe our findings based on the CSD analysis allowed accurate measuring of brain activity in stroke patients.

Conclusion

In conclusion, LT-ERPs recorded during motor performance of a bimanual alternating reaction time task revealed clear differences in the pattern of activation within the motor system of chronic stroke patients compared with a matched group of controls. Importantly, we found in patients a possible neural signature of a higher recruitment of frontal regions, which might attributable to the engagement of monitoring processes associated with higher complex tasks. Additionally, we report evidence of excessive inhibition of the ipsilateral motor cortex, particularly for the unaffected hand responses, which might be associated with the avoidance of performing erroneous responses. In summary, these results shed more light on the functional reshape of the motor system in stroke patients, pointing to an increment of action monitoring-related processes that presumably leads to compensation for a loss of the movement representation. Nonetheless, more studies are needed to confirm our findings.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.L.A., T.F.M., N.R., F.R., E.D., C.G., and A.R.-F. conception and design of research; J.L.A., N.R., and J.G.-S. performed experiments; J.L.A. analyzed data; J.L.A., T.F.M., J.M.-P., and A.R.-F. interpreted results of experiments; J.L.A. prepared figures; J.L.A. drafted manuscript; J.L.A., T.F.M., J.M.-P., and N.R. edited and revised manuscript; J.L.A., T.F.M., J.M.-P., N.R., J.G.-S., F.R., E.D., C.G., and A.R.-F. approved final version of manuscript.

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