Defective sensorimotor integration in preparation for reaction time tasks in patients with multiple sclerosis

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SLOWNESS OF MOVEMENT IS A common observation in patients with central nervous system disorders. This is the case in multiple sclerosis (MS), where delayed movement execution in reaction time tasks has been mainly attributed to decreased alertness, fatigue, and slowness of cognitive processing (De Sonneville et al. 2002; Godefroy et al. 2002; Kail 1998; Kujala et al. 1995; Morgante et al. 2011). However, these may not be the only factors responsible for disordered movement execution. A delay in simple reaction time (SRT) tasks could theoretically be due to slowness of conduction in motor or sensory pathways or to defective sensorimotor integration, i.e., the activation of the required synaptic circuitry that leads to execution of a preprogrammed motor act in response to a sensory cue (Abbruzzese and Berardelli 2003; Swayne et al. 2006). In fact, the characteristic multifocal involvement of MS makes these patients likely candidates for defective sensorimotor integration. We hypothesized that MS patients may have abnormal integration of sensory inputs in circuits that are often a target of MS lesions. Therefore, we devised SRT paradigms involving conduction through the corpus callosum and activation of brain stem motor circuits.

For the functional assessment of conduction through the corpus callosum, we used a special case of an SRT paradigm, i.e., the unilateral limb reaction to a contralateral somatosensory stimulus or crossed SRT task (Kennedy et al. 2013; Schieppati et al. 1984; Schulte et al. 2005). This should certainly involve interhemispheric transfer of sensorimotor information, which has been shown to be impaired in MS. An established neurophysiological means to evaluate interhemispheric connections indirectly is the assessment of the ipsilateral silent period (iSP) to focal transcranial magnetic stimulation (TMS) (Meyer et al. 1995), which is indeed often abnormal in MS (Jung et al. 2006; Llufriu et al. 2012; Schmierer et al. 2000). We hypothesized that crossed SRT tasks in MS patients should reflect the hypothesized delay of the interhemispheric sensorimotor transfer of the information needed for integration of sensory inputs into motor commands for fast reaction time. We also considered the possibility that the differences between crossed and uncrossed SRTs would correlate with iSP-derived measures of conduction time in the corpus callosum.

For the assessment of the brain stem functions related to execution of motor tasks, we examined the contribution of reticulospinal tract activation via a loud startling auditory stimulus (SAS) to the execution of a task in an SRT paradigm. Motor preparation is a key factor for fast execution of voluntary ballistic movements. In SRT, healthy subjects are able to prepare the motor program fully in advance before the imperative signal (IS) is issued, since they have all of the information needed for task execution (Hallett 1990; Henderson and Dittrich 1998; Pascual-Leone et al. 1992a, b). Motor preparation implies enhancement of excitability in cortical and subcortical structures to facilitate activation of the motor system (Brunia 1993; Valls-Solé et al. 1995). The preparation-related enhancement of excitability in subcortical motor tracts probably accounts for the StartReact effect, i.e., the significant shortening of reaction time that takes place when an SAS is applied together with the IS (Carlsen et al. 2004a, b; Siegmund et al. 2008; Valls-Solé et al. 1995, 1999). We reasoned that...
defective motor preparation of subcortical structures would be reflected in an abnormal StartReact effect.

Therefore, in healthy subjects and MS patients, we investigated SRT tasks involving the corpus callosum (using crossed SRT tasks) and the brain stem (using the StartReact effect).

METHODS

Subjects

The present study was part of an extensive neurophysiological study of a cohort of 20 patients with relapsing-remitting MS, prospectively selected from the outpatient MS clinic of the Hospital Clinic of Barcelona. Other features of the same patients have been reported elsewhere (Cabib et al. 2014; Llurru et al. 2012) or are under preparation. Patients were diagnosed according to the criteria of Polman and Rudick (2010) and recruited if they were ambulatory, had low-to-moderate scores on the Expanded Disability Status Scale (EDSS; 0–6.0) (Kutzke 1983), had no clinically relevant limb paresis, were under stable immunomodulatory treatment, and were relapse and steroid free for at least 1 mo before inclusion. They were also excluded if they had any clinically relevant sensory deficit in the arms or absence of evoked potentials to somatosensory stimuli. Their mean age was 37.0 ± 7.0 yr (ranging from 27 to 53 yr). Patients were 11 women and nine men, with a median EDSS of 2.0 (range between 0 and 6.0) and a median score for brain stem in the evaluation of functional systems of 1.0 (range between 0 and 3.0). Seventeen of them were right handed (85%), with a score in the Edinburgh scale <25 (Oldfield 1971). We also examined 13 age- and sex-matched healthy volunteers used as a control group. They were eight women and five men, with a mean age of 35.2 ± 8.0 yr, ranging from 26 to 52 yr. Nine were right handed (69.2%). The Hospital Clinic Research Ethics Committee approved the study, and all participants gave written, informed consent.

Experimental Settings

Subjects were sitting comfortably with both forearms and wrists fixed to a metallic platform in such a way that only the wrist joint could move freely along the complete flexo-extension range of motion. SRT was measured at the onset of electromyographic (EMG) activity, recorded from the wrist-extensor (WE) muscles (band pass 10–2,000 Hz) using a conventional electromyograph (Mystro5Plus; Vickers Medical, Surrey, UK). Surface-recording electrodes were attached over the right and left extensor digitorum communis muscles and over the right orbicularis oculi (OOc) and sternocleidomastoid (SCM) muscles.

Reaction Time Task and StartReact Effect

Subjects were requested to perform unilateral ballistic wrist-extension movements in the context of an SRT paradigm and were told that there could occasionally be a loud auditory stimulus (the SAS) accompanying the IS. The movement requested was an open-loop movement, i.e., with no specific target to reach, to make it as simple as possible. The IS consisted of an electrical pulse, applied to the index finger with ring electrodes, with an intensity set at two times the individual’s sensory-perception threshold. The SAS was obtained by discharging the magnetic coil of a magnetic stimulator (Novametrix 200; MagStim, London, UK) over a metallic platform at an intensity of 100% of the stimulator’s capacity. The auditory stimulus of 130 dB (sound-pressure level) is able to elicit the auditory startle response (ASR), which we recorded from OOC and SCM.

All participants had a few trials of training, and the experiments began only when they were confident with the task. In all trials, subjects were requested to perform the task by the ipsilateral (uncrossed) or by the contralateral hand (crossed) to stimuli to the right or the left index finger. Therefore, according to the site where the IS was applied and the hand requested to move, subjects were presented with two stimulus-response congruous trials—right stimulation-right reaction and left stimulation-left reaction—and two stimulus-response incongruous trials—right stimulation-left reaction and left stimulation-right reaction. For each stimulus-response combination, we obtained eight baseline trials, in which only the IS was presented (baseline-SRT trials) and four trials in which an SAS was presented simultaneously with the IS (SAS-SRT trials). The two types of trials were intermingled randomly. We never applied two SAS-SRT trials in sequence. Trials were repeated online in case of an occasional absence of the ASR.

TMS Studies

Focal TMS was applied over the left or right primary motor cortex (M1) with a figure-of-eight coil connected to the magnetic stimulator and the responses recorded from the first dorsal interosseous muscle in both sides. We set the stimulus intensity at 1.2 times the resting motor threshold, determined as the lowest intensity needed to obtain a motor-evoked potential (MEP) of at least 50 μV amplitude in at least three out of five trials (Kobayashi and Pascual-Leone 2003). We first recorded the MEPs at rest, and then, subjects were requested to maintain a voluntary muscle contraction (index abduction) of 20% of their maximum, while we applied TMS to the ipsilateral hemisphere to obtain the iSP. We repeated the procedure four times.

Somatosensory-Evoked Potentials

The somatosensory-evoked potentials (SEPs) were recorded with conventional techniques (Cooper et al. 2004) to stimulation of the median nerves. Patients were lying relaxed on the examination bed with electrodes placed over the contralateral parietal cortex with reference to the two earlobes. Electrical stimulation frequency was 5 Hz, and stimulus duration was 0.2 ms. The intensity was adjusted to the one eliciting a slight motor twitch in the thenar eminence. Trials were repeated twice (after averaging 500 traces each) to replicate the responses consistently.

Data Analysis

Data were analyzed offline and blindly by one of the authors (C. Cabib). Reaction time (milliseconds) was measured as the onset of the EMG activity in the WE muscles to the somatosensory IS. We considered latency of the reaction at the time that the EMG burst became consistently >0.1 mV above background. For between-group comparisons on both experimental conditions (baseline-SRT and SAS-SRT trials), we analyzed data from all trials to calculate the mean reaction time of each subject in each stimulus-response combination. However, for correlation analyses of reaction time values, we considered the shortest reaction time in each group of trials.

To examine the effects of stimulus-response congruence on reaction time, we pooled together data from right and left sides for uncrossed (stimulus-response, congruous trials) and crossed (stimulus-response, incongruous trials) reaction time tasks. This was done for both baseline-SRT and SAS-SRT trials. To examine the StartReact effect, we grouped SAS-SRT trials and represented reaction time values as a percentage of the baseline trials. We also measured the latency of the ASR elicited in the OOC and SCM. We considered ASR to be present when a burst with amplitude >0.05 mV was present in both muscles at the expected latency (Brown et al. 1991). We excluded online the trials in which subjects did not have an ASR to SAS.

With TMS, we considered MEP to be present when a response >0.1 mV was obtained, whereas a reduction >80% of the prestimulus EMG activity was considered significant for iSP to be present. We measured onset latency of the MEP and latency and duration of the
iSP. From all trials, we considered the shortest latency of the MEP and iSP, as well as the mean duration of the iSP for further analysis. For SEPs, we considered responses to be present when the N19 peak amplitude was >0.5 μV. We measured the latency of N19 and P22 components recorded in C3’ or C4’ (depending on the side of the stimulus). Data from each hand were used independently for correlation analysis.

Data Reduction

After data analysis, we produced the following variables: uncrossed and crossed baseline-SRT, uncrossed and crossed SAS-SRT, MEP latency, iSP latency and duration, SEP latency (N19 and P22), and ASR latency for OOc and SCM. For each individual, we calculated the interhemispheric reaction time difference (IHRTd) by subtraction of the shortest uncrossed from the shortest crossed SRT in baseline trials. We also calculated the interhemispheric conduction time (IHCT) as the difference between the MEP latency and the iSP latency (Schmierer et al. 2000, 2002).

The StartReact effect was estimated in each subject by calculating the percentage reaction time shortening in SAS-SRT trials with respect to baseline trials, as follows: StartReact effect (%) = 100 × [shortest reaction time in baseline SRT trials (milliseconds) − shortest reaction time in SAS-SRT trials (milliseconds)]/shortest reaction time in baseline SRT trials (milliseconds). This analysis was done separately for uncrossed and crossed trials to estimate the degree of effectiveness of subcortical preparation.

Statistical Analyses

All of the statistical analyses were performed using SPSS for Windows (version 18.0). The 2 × 2 correlation test ($\chi^2$) was used to examine differences in data distribution. As inferred from above and because there was a normal distribution of data, mean values for shortest and mean reaction times were obtained in healthy subjects and patients. Data were grouped according to stimulus-response congruence (crossed and uncrossed) and experimental condition (baseline-SRT and SAS-SRT). Within-group differences between crossed and uncrossed reaction time, as well as between baseline-SRT and SAS-SRT, were analyzed using paired Student’s t-test. An overall analysis was carried out with two-way ANOVA for each group of subjects to examine the interaction between response congruence and experimental condition, whereas one-way ANOVA was used for comparison between healthy subjects and patients. Statistical significance was set at $P < 0.05$.

To assess the contribution of possible effenter and afferent conduction abnormalities on reaction time, we examined the correlation between the uncrossed SRT and the MEP or SEP latencies. Also, to examine whether reticulospinal pathways contributed to the StartReact effect, we correlated the SAS-SRT and the ASR latencies. Furthermore, to assess the contribution of functional abnormalities in the corpus callosum to crossed SRT, we examined the correlation between IHCT and IHRTd. We used the Pearson’s test for all correlation analysis.

RESULTS

Data on conduction time for MEPs and SEPs are summarized in Table 1, together with all other data on conduction time gathered from TMS studies. One factor is that ANOVA showed significant differences between groups in the MEP and SEP latency ($F[1,31] = 8.963, P = 0.005$ for MEP; $F[1,31] = 5.048, P = 0.028$ for N19; and $F[1,31] = 4.675, P = 0.034$ for P22), which were longer in patients than in healthy subjects. There were also statistically significant differences in iSP latency ($F[1,31] = 19.593, P < 0.001$) but not in SEP duration ($F[1,31] = 8.963, P = 0.005$). ANOVA also showed shorter SEP latency ($F[1,31] = 0.897, P = 0.351$), which were also longer in patients than in healthy subjects. The value obtained in each side of subjects was averaged to obtain 1 single value for each individual and after that, to obtain the mean value of each group. All data are expressed in milliseconds. Comparisons between both groups were done using 1-way ANOVA (significant $P$ values are shown in italics).

Table 1. Data related to the study of transcranial magnetic stimulation and somatosensory-evoked potentials done in healthy subjects and patients with multiple sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects, $n = 13$</th>
<th>Patients, $n = 20$</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td>TMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEP latency</td>
<td>22.2 (1.2)</td>
<td>24.9 (3.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>iSP latency</td>
<td>34.7 (2.1)</td>
<td>41.3 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SEP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N19 latency</td>
<td>19.5 (1.1)</td>
<td>20.6 (1.9)</td>
<td>0.028</td>
</tr>
<tr>
<td>P22 latency</td>
<td>22.4 (1.3)</td>
<td>23.3 (2.0)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

TMS, transcranial magnetic stimulation; MEP, motor-evoked potential; iSP, cortical ipsilateral silent period; IHCT, interhemispheric conduction time (see data reduction in METHODS); SEP, somatosensory-evoked potential. The value obtained in either side of subjects was averaged to obtain 1 single value for each individual and after that, to obtain the mean value of each group. All data are expressed in milliseconds. Comparisons between both groups were done using 1-way ANOVA (significant $P$ values are shown in italics).

Reaction Time

Data on mean and shortest reaction times are summarized in Table 2 for healthy subjects and patients, distributed according to stimulus-response congruence (uncrossed and crossed) and experimental condition (baseline-SRT and SAS-SRT). Figure 1 shows raw recordings from a healthy subject and a representative MS patient.

Baseline-SRT trials. Crossed SRT was significantly longer than uncrossed SRT for healthy subjects and patients (Table 2; $t$-test, $P < 0.001$ for both groups). There was no effect of group on baseline-SRT, neither for uncrossed nor for crossed SRT, although there was a tendency for patients to have longer values for mean ($F[1,31] = 3.994, P = 0.054$) and shortest crossed SRT ($F[1,31] = 3.873, P = 0.058$; ANOVA). A significant effect of group was, however, found for the IHRTd, which was significantly larger in patients (23 ± 12.7 ms) than in healthy subjects (13.8 ± 6.9 ms; $F[1,31] = 5.957, P = 0.021$). The total number of patients that exceeded the normal, upper-limit SRT values was seven, four of them for uncrossed SRT and six of them for crossed SRT (three patients shared both conditions).

SAS-SRT trials. In general terms, mean reaction time in SAS-SRT trials was shorter than in baseline-SRT trials in healthy subjects and patients (Fig. 1 and Table 2). The differences were significant in healthy subjects for uncrossed and crossed SAS-SRT (t-test; $P < 0.001$ for both comparisons) and for patients for uncrossed trials ($P < 0.001$) but not for crossed trials ($P = 0.08$). Similar to what occurred in baseline-SRT trials, both healthy subjects and patients had a significantly longer mean reaction time for crossed SAS-SRT trials than for uncrossed SAS-SRT trials (t-test, $P < 0.001$ for both groups). In patients, SAS-SRT were statistically, significantly longer than in healthy subjects for crossed (ANOVA; $F[1,31] = 10.22$).
Table 2. Data on uncrossed and crossed reaction times (the mean and the shortest values) in the 2 experimental conditions (baseline-SRT and SAS-SRT) together with the StartReact effect calculated in healthy subjects and MS patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Congruence</th>
<th>Healthy subjects, n = 13</th>
<th>Patients, n = 20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-SRT, ms</td>
<td>Uncrossed</td>
<td>127.5 (12.6)*</td>
<td>145.6 (39.3)*</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
<td>Crossed</td>
<td>140.9 (12.6)*</td>
<td>163.5 (39.4)*</td>
<td>0.054</td>
</tr>
<tr>
<td>SAS-SRT, ms</td>
<td>Uncrossed</td>
<td>91.8 (10.9)</td>
<td>117.6 (39.8)</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Crossed</td>
<td>102.0 (9.0)*</td>
<td>146.6 (65.3)*</td>
<td>0.022</td>
</tr>
<tr>
<td>StartReact effect, %</td>
<td>Uncrossed</td>
<td>27.7 (8.0)</td>
<td>20.0 (8.7)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Crossed</td>
<td>27.5 (6.2)</td>
<td>17.0 (11.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Shortest values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-SRT, ms</td>
<td>Uncrossed</td>
<td>116.9 (12.4)</td>
<td>126.3 (26.0)</td>
<td>0.235</td>
</tr>
<tr>
<td></td>
<td>Crossed</td>
<td>130.5 (15.4)*</td>
<td>149.4 (32.1)*</td>
<td>0.058</td>
</tr>
<tr>
<td>SAS-SRT, ms</td>
<td>Uncrossed</td>
<td>86.2 (12.0)</td>
<td>105.9 (31.3)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>Crossed</td>
<td>98.6 (9.0)*</td>
<td>138.6 (64.8)*</td>
<td>0.035</td>
</tr>
<tr>
<td>StartReact effect, %</td>
<td>Uncrossed</td>
<td>25.7 (10.7)</td>
<td>17.6 (7.9)</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Crossed</td>
<td>23.8 (8.1)</td>
<td>16.2 (10.4)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Baseline-SRT, simple reaction time in the baseline experimental condition; SAS-SRT, reaction time in the test condition, in which a startling auditory stimulus (SAS) was applied; StartReact, significant shortening of reaction time that takes place when an SAS is applied together with the imperative signal; MS, multiple sclerosis. See Methods for definition of stimulus-response congruence. *Significant within-group differences (t-test, P < 0.05) were found between crossed and uncrossed stimulus-response congruence in the experimental condition (baseline-SRT or SAS-SRT). P (in italics values) refers to comparison in reaction time between healthy subjects and patients for each specific trial in the same stimulus-response congruence using 1-way ANOVA.

5.178, P = 0.030) and uncrossed (F[1,31] = 5.842, P = 0.022) trials.

In healthy subjects, the StartReact effect was not different between uncrossed and crossed trials (t-test, P = 0.803) and was significantly higher than in patients for both uncrossed (ANOVA; F[1,31] = 6.614, P = 0.015) and crossed (F[1,31] = 8.984, P = 0.005) trials. In eight patients, the StartReact effect was reduced beyond the limits of the mean ± 2 SD, calculated in healthy subjects. These eight patients did not show significant differences with respect to the remaining 12 patients in their median EDSS and brain stem functional system score (P > 0.05 for both comparisons).

There were no differences in the mean latency value of the ASR between healthy subjects and patients (38.5 ± 3.1 ms in OOC and 60.2 ± 5.3 ms in SCM muscles for healthy subjects and 41.3 ± 6.0 ms in the OOC and 61.9 ± 5.9 ms in the SCM for patients; P > 0.05 for the two muscles). Interestingly, the eight patients with no StartReact effect showed ASRs in the OOC and SCM with latencies not significantly longer than patients with a normal StartReact effect (P > 0.05 for both comparisons).

Interaction between experimental conditions. Because significant between-group differences were found in regard to the stimulus-response congruence and the effect of an SAS on reaction time, we examined the possibility of interaction between the two conditions. A two-way ANOVA showed no interaction between factors (crossed/uncrossed and presence/absence of SAS) in healthy subjects (F[1,24] = 0.250, P = 0.619) or patients (F[1,38] = 0.271, P = 0.604).

Correlation Analyses

Figures 2 and 3 show all of the correlation analyses between reaction time and conduction time measures. In the analysis of transcallosal connections (Fig. 2), the IHCT was positively correlated with the IHRTd in patients, i.e., the longer the crossed SRT, the longer the conduction times between hemispheres (Pearson’s, r = 0.520, P = 0.019). This was not the case for healthy subjects (r = 0.055, P = 0.857).

In pooling together data from healthy subjects and patients, we found positive correlations for uncrossed SRT and MEP or SEP latencies and for SAS-SRT and ASR latencies (Pearson’s, r > 0.4, P < 0.05 for all of them). As shown in Fig. 3, these correlations were also statistically significant when only patients were considered (uncrossed SRT and MEPs, r = 0.374, P = 0.021; uncrossed SRT and SEPs, r = 0.327, P = 0.04; SAS-SRT and ASR, r = 0.565, P = 0.009). In fact, though, only four out of the 20 patients had values beyond the upper normal limits for both variables of the study in all three correlations. Figure 3 shows that some patients had delayed reaction times with normal MEPs, SEPs, and ASRs; others had normal reaction times with delayed MEPs, SEPs, and ASRs, whereas some others had within normal range values on reaction times and normal MEPs, SEPs, and ASRs. An analysis done after excluding these four patients showed still statistically significant between-group differences in reaction time and StartReact effect (data not shown; P < 0.05 for all comparisons).

DISCUSSION

The corpus callosum and the brain stem are sites of frequent involvement in MS, where lesions may affect many functions. In our study, we have gathered evidence of dysfunction in the sensorimotor pathways running through these sites in reaction time tasks, which characterizes a new expression of disordered motor control in MS. Our results indicated no interaction between the two disorders, pointing to the fact that the two circuits studied are likely independent. This brings up new information on motor physiology in reaction time tasks.

Disordered Motor Preparation in MS

Normal performance of unilateral SRT tasks to a somatosensory IS requires the combination of multiple factors. First, an attentional process is required, including sustained alertness, to trigger the same fast response along the test. Second, afferent and efferent conduction times along central and peripheral pathways should be within normal limits for appropriate synchronization of inputs at the integration centers and output to the muscle. Third, sensorimotor integration must take place at cortical and subcortical levels to engage the detection of the IS with the voluntary drive needed to trigger the reaction. Finally, the movement is executed when pre-excited subcortical motor structures are brought to discharge level by the voluntary drive, which implies the indemnity of corticospinal tracts.

In agreement with previous reports (Stoquart-Elsankari et al. 2010; Zeller et al. 2011), we have found that patients with MS have a lengthening in motor-task execution in the context of an SRT paradigm. Several authors argue that this finding is most likely due to impairment in cognitive processing and defective
alertness (Godfrey et al. 2002; Kail 1998; Kujala et al. 1995). However, our results bring up the likely contribution of defective preparation to the slowness in reaction of MS patients (Henderson and Dittrich 1998; Valls-Solé et al. 1999). It is known that an SAS activates the reticulospinal tract at the brain stem level (Davis et al. 1982; Liegeois-Chauvel et al. 1989). Therefore, the StartReact effect indicates that the motor structures influenced through reticulospinal tract activation are fully prepared, according to the motor program. An interesting debate has been generated recently on the location of the trigger for task execution in trials in which there is an SAS accompanying the IS. Whereas some authors hypothesize that the execution of the motor program is triggered by direct SAS activation of motor circuits at the brain stem, others favor the cortical origin after a fast route from the brain stem upwards (Alibiglou and MacKinnon 2012; Nonnekes et al. 2014). We think that our results favor the first hypothesis, since it would be unlikely not to have an interaction between the two experimental conditions if the two of them used a cortical route. In any case, the StartReact effect indicates that the required cortical and subcortical circuits for motor-program execution had indeed enhanced excitability (Brunia 1993; Valls-Solé et al. 1995). Absence of the effect could occur because of defective preparation or abnormalities in the execution channel, a situation that may occur with severe brain stem neuronal loss, as in patients with progressive supranuclear palsy (Valldeoriola et al. 1998; Vidailhet et al. 1992).

To our knowledge, this is the first report that demonstrates a reduced StartReact effect in MS patients, suggesting that the structures implied in the release of the motor program are not energized sufficiently. Therefore, our patients did not only have longer reaction times than healthy subjects, which could be attributed to a clinical or subclinical involvement of an afferent pathway or the corticospinal tracts (Stoquart-Elsankari et al. 2010), but they also had an abnormal effect of an SAS on execution of the motor program, which is attributable to

Fig. 1. Raw recordings on simple reaction time (SRT) tasks. The graphs show surface electromyographic recordings of wrist-extension in an SRT task in a healthy subject (HS) and in a representative multiple sclerosis (MS) patient. In each subject, graphs are presented separately by stimulus-response congruence, as uncrossed and crossed, and by experimental condition, as baseline (Bs)-SRT and startling auditory stimulus (SAS)-SRT. Note that the shortening of reaction time in SAS-SRT trials with respect to baseline-SRT trials is more marked in healthy subjects than in patients.

Fig. 2. Contribution of interhemispheric connections to motor execution in crossed-reaction time tasks. Correlation between the conduction through callosal pathways, estimated by calculating the interhemispheric conduction time (IHCT; mean value between both sides) and the interhemispheric reaction time difference (IHRTd; for details, see Data Reduction in METHODS). A significant, positive correlation was found in MS patients (marked with white squares; dashed line for correlation; Pearson’s, $r = 0.520, P = 0.019$) but not in healthy subjects (black triangles; continuous line for correlation; $r = 0.055, P = 0.857$).
defective preparation for motor execution. Although this points to an abnormal function in structures activated by the reticulospinal tract, our findings do not rule out the possible implication of cortical mechanisms in the execution of the motor program (Alibiglou and MacKinnon 2012; Nonnekes et al. 2014). Extensive microstructural abnormalities of cortical and subcortical regions are found in MRI studies since early stages of the disease (Llufriu et al. 2014). White-matter lesions and widespread demyelination, gliosis, and axonal loss are part of the pathological events related to the MRI findings and to the functional and cognitive impairment in MS (Filippi et al. 2012, 2013; Llufriu et al. 2014). Brain stem lesions are a hallmark of the disease (Pelletier et al. 2001) and may explain the impairment of the StartReact phenomenon found in our patients.

Interhemispheric Communication and Sensorimotor Integration

The corpus callosum is the major commisure of the brain, providing communication between both hemispheres (Bloom and Hynd 2005). The iSP reveals the inhibitory effect caused mainly by transcallosal fibers, which are originated in the hemisphere where the TMS pulse is applied over the voluntary EMG activity generated in the contralateral motor cortex (Meyer et al. 1995). As noticed before, an altered conduction in corticospinal pathways may be part of the random involvement of neural tracts that typically occurs in MS. In fact, this was also the case in our sample of patients, who despite being only mildly disabled, had abnormally long central MEP and SEP latencies, and their reaction time correlated significantly with latencies of both the MEP and the SEP. However, this fact cannot explain, by itself, a reduction in reaction time because of the different magnitude of the delay (only a few milliseconds in MEP or SEP latency but several tens of milliseconds in reaction time), although we cannot rule out that the abnormality in conduction times reflects a widespread dysfunction in circuits, more closely related to sensorimotor integration than the rather crude latency value obtained in SEP and MEP studies.

Interestingly, in a study using TMS, Zeller et al. (2011) reported that when performing a unilateral motor task, patients with MS showed increased facilitation of the ipsilateral motor area compared with healthy subjects. Moreover, with functional MRI, patients with MS showed lower deactivation of ipsilateral sensorimotor cortex during unilateral hand move-
mements (Manson et al. 2008). These findings suggest difficulties for MS patients in focusing brain activity and may be due, in part, to the frequent impairment of transcallosal inhibitory pathways. We have calculated the IHCT, which should represent the conduction time through transcallosal inhibitory pathways. Our patients had a longer reaction time for contralateral than for ipsilateral trials, i.e., larger IHRTd, which correlated positively with longer IHCT. These data suggest that in MS patients, a defective sensorimotor integration requiring callosal transfer of information may be a key factor in the slowness of motor-task execution in SRT paradigms, requiring activation of the contralateral hand to unilateral somatosensory IS. This is indeed an adequate method for the assessment of functionally relevant sensorimotor integration of interhemispheric transfer of information (Kennedy et al. 2013; Schieppati et al. 1984; Schulte et al. 2005).

Limitations of the Study

Our sample of patients is small and of certain characteristics, i.e., mildly affected by the disease, with preserved cognition. These aspects should be considered important factors influencing our results. For instance, we found no interaction between experimental condition and stimulus-response congruence. This is taken to indicate that both mechanisms contribute independently to the delay of reaction time. However, this should just be considered an interim conclusion, since other patients with MS might show different results, possibly according to the irregular distribution of their brain lesions. Theoretically, more affected patients might have more involvement of not only the circuits participating in sensorimotor integration but also the pathways conveying the input and output commands. Therefore, the correlation that we found between reaction time delay and SEPs, MEPs, and ASRs may be of more importance in patients with more advanced disease.

Conclusions

We identified abnormalities in sensorimotor integration in two circuits of patients with MS, leading to slowness of motor-task execution in a reaction time task experiment. A slowness in transcallosal conduction may explain lengthening of crossed motor-task execution, whereas a defective subcortical motor preparation may explain reduced responsiveness to the external activation of subcortical motor pathways by an SAS. Although these abnormalities correlate with slowness in sensory and motor central conduction times, the size and distribution of the abnormalities affecting specific conditions and the fact that abnormalities were still significant if the patients with a more pronounced delay were excluded from the analysis point out a disorder that is beyond mere conduction, i.e., sensorimotor integration, which implies deterioration in the specific SRT tasks examined in this study.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: C.C. analyzed data; C.C., J.C-M., A.S., and J.V-S. interpreted results of experiments; C.C. prepared figures; C.C. and J.V-S. drafted manuscript; C.C., S.L., J.C-M., A.S., and J.V-S. approved final version of manuscript; S.L., A.S., and J.V-S. conception and design of research; S.L., J.C-M., and J.V-S. performed experiments; S.L., J.C-M., A.S., and J.V-S. edited and revised manuscript.

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