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Effect of afferent input on motor cortex excitability during stroke recovery

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HIGHLIGHTS

- Motor cortex excitability, modulated by afferent input, is increased in the affected hemisphere in the acute phase after stroke and decreases subsequently during recovery.
- Motor cortex excitability correlates with strength of secondary somatosensory cortex (SII) activation, suggesting that modulatory afferent input may reach the motor cortex via SII.
- Afferent input modulated motor cortex excitability is associated with hand function, underlining the importance of parallel recovery of the sensory and motor systems for normal hand dexterity.

ABSTRACT

Objective: Afferent input is proposed to mediate its effect on motor functions by modulating the excitability of the motor cortex. We aimed to clarify – in a longitudinal study – how afferent input affects motor cortex excitability after stroke and how it is associated with recovery of hand function.
Methods: The motor cortex excitability was studied by measuring the reactivity of the motor cortex beta rhythm to somatosensory stimulation. We recorded the amplitude of the suppression and subsequent rebound of the beta oscillations during tactile finger stimulation with MEG in 23 first-ever stroke patients within one week and at 1 and 3 months after stroke, with concomitant evaluation of hand function.
Results: The strength of the beta rhythm rebound, suggested to reflect decreased motor cortex excitability, was weak in the affected hemisphere after stroke and it was subsequently increased during recovery. The rebound strength correlated with hand function tests in all recordings.
Conclusion: Motor cortex excitability is modulated by afferent input after stroke. The motor cortex excitability is increased in the AH acutely after stroke and decreases in parallel with recovery of hand function.
Significance: The results implicate the importance of parallel recovery of both sensory and motor systems in functional recovery after stroke.

1. Introduction

Motor impairment is a common consequence of an ischemic stroke. Intracortical recordings in animals (Nudo and Milliken, 1996; Nudo et al., 1996) and functional imaging studies in humans have indicated that motor recovery is associated with reorganization of the motor (Calautti et al., 2001; Ward et al., 2003a,b) and somatosensory cortices (Roiha et al., 2011; Rossini et al., 1998, 2001). However, regaining of normal motor function demands not only recovery of the motor or somatosensory systems, but also a fluent integration of somatosensory afferent input with motor programs (Bornschlegl and Asanuma, 1987).

Afferent somatosensory input has been proposed to mediate its effect on motor functions by modulating the excitability of the motor cortex (Asanuma and Arissian, 1984; Favorov et al., 1988; Liepert et al., 2004; Ridding and Rothwell, 1999; Tokimura et al., 2000). Accordingly, afferent somatosensory input has been shown to modulate the motor cortex beta rhythm (~20-Hz), leading to an initial suppression followed by a transient rebound of the rhythm

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(Neuper and Pfurtscheller, 1996; Salmelin et al., 1995; Salmelin and Hari, 1994). The increase of the rebound strength has been suggested to reflect decreased motor cortex excitability (Hari et al., 1998; Salenius et al., 1997; Salmelin and Hari, 1994), and the beta rebound has been used in several prior studies to monitor the functional state of the motor cortex (Juottonen et al., 2002; Silen et al., 2000; Visani et al., 2006).

To investigate how afferent somatosensory input modulates motor cortex excitability after stroke and how it is associated with recovery of hand function, we recorded beta oscillations and somatosensory evoked responses during tactile finger stimulation with a whole-scalp magnetoencephalography (MEG) in 23 first-ever stroke patients within one week, and at 1 and 3 months from stroke onset and in 10 healthy control subjects, with concomitant clinical evaluation of hand function.

2. Materials and methods

2.1. Patients and control subjects

We studied 23 patients with first-ever ischemic stroke in the middle cerebral artery territory affecting upper extremity motor function, and 10 healthy control subjects (5 females; mean age 61 ± 2 years; all right-handed). The patients were recruited within 3 days from stroke onset from the Department of Neurology, Helsinki University Central Hospital (HUCH). Exclusion criteria were earlier neurological diseases, neurosurgical operations or head traumas, severe psychiatric disorder, unstable cardiovascular condition, and poor general condition. Three patients were excluded from the study after the first measurement as magnetic resonance imaging (MRI) revealed prior silent strokes, and one patient because of a reinfarction after the first measurement. One patient's MEG data were excluded due to large artifacts preventing reliable analysis. Thus the follow-up data of 18 patients (9 females; age 44–84 years, mean 66 years ± 2 years; all right-handed) were used for further analyzes. One patient refused the third measurement because of claustrophobia, the rest participated successfully in all three measurements.

Local Ethics Committee approved the study protocol. All patients and control subjects gave written informed consent. Somatosensory evoked fields to tactile finger stimulation from the same patients have been reported in detail in our earlier studies (Forss et al., 2012; Roiha et al., 2011).

2.2. Clinical evaluation

The patients underwent clinical examination and MEG measurements within 1–7 (mean 3.5 ± 0.5) days (T_0) and after one (T_1) and three (T_2) months from stroke. Anatomical MRIs were performed with a 3 T scanner (Philips) at T_0 and T_1. Clinical examination included National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), and modified Rankin Scale (mRS) scoring. Tactile sensitivity of the affected hand (light and sharp touch) was categorized into two groups: normal or decreased (as compared with the healthy hand). To evaluate the hand dexterity, a physio- or ergotherapist performed the Nine Hole Pegboard test (Peg). In Peg, the amount of time needed to remove and replace nine pegs one at a time into nine holes is measured. The maximum time was defined as 120 s; this score was given if the task could not be performed faster.

2.3. Magnetoencephalographic (MEG) recordings

Rhythmic brain activity during rest and during tactile stimulation of the index fingers was recorded with a 306-channel helmet-shaped neuromagnetometer (Elekta Neuromag®, Helsinki, Finland) at T_0, T_1, and T_2. The recordings were performed in the BioMag Laboratory, HUCH, in a magnetically shielded room, and during the measurement the patients were, according to their clinical condition and their own wish, either in sitting or supine position with the head supported against the helmet-shaped sensor array. Tactile stimuli were alternately delivered to both index fingers with an interstimulus interval of 3005 ms with balloon diaphragms driven by compressed air, and raw-data during averaging of about 60–80 responses for each hand were recorded. Although tactile sensitivity was impaired in some patients, each subject was able to detect the stimuli as light touch. The stimulus intensity was kept constant across the subjects and measurement times, to allow direct comparison of the results during recovery. Eye movements were simultaneously recorded with a vertical electro-oculogram, and coinciding responses were automatically rejected. All subjects wore earplugs to avoid perception of any possible stimulus-related noise. The subjects were instructed to relax, not to move their head or fingers, and not to pay attention to the stimuli. In the second session spontaneous brain activity during rest was recorded for 6 min. A nurse inside the magnetically shielded room observed the patients for any possible movements.

To determine the exact head position with respect to the sensor array, four indicator coils were placed on the scalp, and magnetic signals produced by currents led into the coils were detected in the beginning of each measurement. To align the MEG and the anatomical MRI coordinate systems, a three-dimensional digitizer was used to determine the coil positions with respect to anatomical landmarks. The signals were filtered through 0.03–308 Hz and digitized at 941 Hz.

2.4. Data analysis

The MEG data were first processed with the temporal signal space separation (tSSS) method implanted in Maxfilter™ software (Taulu and Simola, 2006) to suppress the signals of interfering sources.

After preprocessing of the data, spectra of spontaneous brain activity (during rest, eyes open) were calculated in the frequency-range of 0–60 Hz to define the peak amplitudes and frequencies of spontaneous brain activity over the rolandic region. For each patient, amplitudes of the strongest spectral peaks (~10 Hz, ~15 Hz (beta 1), ~20 Hz (beta 2)) were quantified from 2–3 MEG channels over the left and the right sensorimotor region. Time–frequency representations (TFR; Tallon-Baudry et al., 1997) in the frequency-range of 10–30 Hz were calculated to define the frequency range of the strongest modulation of spontaneous brain activity to tactile stimulation. The TFR were calculated over all channels in each patient and each control subject. The channel showing the largest signal changes was used to determine the frequency-range for further analysis for each individual.

For each patient and control subject, a frequency band of 10 Hz width with an individual range between 12 and 26 Hz was chosen according to the observed spectral peaks of the beta rhythm and the TFR analysis. Earlier studies have shown that the beta rhythm is modulated by i.e. peripheral tactile stimulation, which leads to an initial suppression followed by a transient rebound of the rhythm (Salenius et al., 1997; Salmelin and Hari, 1994). The temporal spectral evolution method (TSE; Salmelin and Hari, 1994) was applied to analyze the temporal aspects and reactivity of the chosen frequency range in more detail. The averaged somatosensory evoked fields (SEFs) were first subtracted from the individual MEG signals. Thereafter the MEG signals were filtered through the individually chosen frequency-range between 12 and 26 Hz, rectified, and averaged time-locked to the stimuli. The analysis period was 3.5 s with a pre-stimulus baseline of 300 ms. The level of the

beta rhythm was quantified from signals of 2 to 4 MEG channels showing the strongest suppression/rebound of the rhythm, 1–2 channels over the contralateral and the others over the ipsilateral sensorimotor region. Onset/offset of the suppression and rebound were defined as the time point when the signal deviated ±2 SD from the baseline. The absolute suppression/rebound strength was calculated from the peak amplitude of the deflection. The absolute suppression/rebound values were converted into relative values by calculating the percentage of decrease/increase of the rhythm in relation to the reference baseline in the −300–0 ms pre-stimulus period (Pfurtscheller, 1992; Pfurtscheller et al., 1997). The relative values were used for further analysis. Detailed description of the analyzes of SEFs from the same patients are reported in our earlier study (Forss et al., 2012; Roiha et al., 2011).

2.5. Statistical analyzes

The results of the clinical tests and TSE analyzes were subjected to 3 (Time: T_0, T_1, T_2) × 2 (Hemisphere: affected, AH; unaffected, UH) fully within subjects ANOVAs. When a significant main effect was detected, pair-wise comparisons were performed between different time points or between hemispheres. Bonferroni correction was used to control for family-wise error rate in planned comparisons. Independent samples *t*-tests were used to compare the parameters between the patients and the control subjects. Spearman's correlation coefficients were used for correlation analysis. Statistical significance threshold was set at $p < 0.05$.

3. Results

3.1. Clinical outcome

Patients' clinical details are summarized in Table 1. The affected hand function was impaired at T_0 compared with the unaffected hand (Table 2), and it was significantly improved during follow-up, as shown in our earlier reports (Forss et al., 2012; Roiha et al., 2011). Pair-wise comparison showed that the Peg times for the affected hand were significantly longer at T_0 than at T_1 and T_2 ($p < 0.005$ for T_0 *vs.* T_1 and $p < 0.001$ for T_0 *vs.* T_2). Also the unaffected hand function was impaired at T_0: Peg times were significantly longer at T_0 than at T_2 (36 ± 4 s *vs.* 26 ± 1 s, $p < 0.01$). Although the performance of the affected hand was significantly improved, it did not reach the level of the unaffected hand in three months time (51 ± 9 *vs.* 26 ± 1, $p < 0.05$). NIHSS, mRS, and BI results were all significantly improved from T_0 to T_2 (Table 2).

3.2. Spectrum of spontaneous activity

In the control subjects, the spectra calculated from spontaneous brain activity during rest (eyes open) revealed strongest peaks at 9.4 ± 0.3 Hz, 14.7 ± 0.2 Hz (beta 1), and 18.6 ± 0.4 Hz (beta 2) over the right sensorimotor area and at 9.1 ± 0.4 Hz, 14.4 ± 0.2, and 18.3 ± 0.5 Hz over the left sensorimotor area. The strength of the beta 1 rhythm was 24 ± 2 fT/cm and 30 ± 4 fT/cm and of the beta 2 rhythm 22 ± 2 fT/cm and 23 ± 3 fT/cm in the right and left hemispheres, respectively. In the patients, strongest spectral peaks were observed at 8.9 ± 0.4 Hz, at 14.7 ± 0.4 Hz and at 20.2 ± 0.5 Hz in the affected hemisphere (AH), and at 9.1 ± 0.3 Hz, at 15.6 ± 0.5 Hz, and at 20.2 ± 0.4 Hz in the unaffected hemisphere (UH) at T_0. The strength of the beta 1 rhythm was 27 ± 3 fT/cm and 28 ± 3 fT/cm and of the beta 2 rhythm 19 ± 2 fT/cm and 22 ± 2 fT/cm in the AH and UH, respectively. No significant differences in the frequencies or in the strength of the rhythms between the hemispheres, between the different time points, or between patients and control subjects were found.

Table 2
Clinical scores of the patients (Peg, mean ± SEM; NIHSS, BI, mRs, median ± SEM).

	Peg (ah)	Peg (uh)	NIHSS	BI	mRS
T_0	84 ± 9	36 ± 4	4 ± 1	60 ± 7	3 ± 0
T_1	59 ± 10	28 ± 1	2 ± 0	90 ± 4	2 ± 0
T_2	51 ± 9	26 ± 1	1 ± 0	100 ± 3	2 ± 0

T_0, within 1–7 days; T_1, 1 month; T_2, 3 months from stroke onset. ah, affected hand; uh, unaffected hand; Peg, time (s); NIHSS, National Institutes of Health Stroke Scale (0–42); BI, Barthel Index (0–100); mRS, modified Rankin Scale (0–6).

3.3. Strength of the beta rebound

Fig. 1 illustrates the grand average TFR of brain oscillations in the 10–25 Hz frequency-range over the sensorimotor region in the affected and unaffected hemispheres to contralateral tactile index finger stimulation in the patients at T_0 and T_1. Individually analyzed TFR in the 10–30 Hz frequency-range indicated that the strongest modulation of rhythmic activity was detected in 15–25 Hz range in all patients and control subjects. Rhythmic activity was bilaterally modulated to unilateral stimulation both in the patients and in the control subjects. However, in line with earlier studies (Salenius et al., 1997; Salmelin and Hari, 1994), the reactivity of the hemisphere ipsilateral to the stimulated hand was weaker and less consistent than that in the contralateral hemisphere in both groups. Therefore, we compared the reactivity of the contralateral hemispheres to the stimulated hand between the groups and the time points. In other words, the affected hand was stimulated for evaluation of the AH, and the unaffected hand for the UH.

In line with an earlier study (Pfurtscheller et al., 1997), separate TSE calculations for the beta 1 and beta 2 bands showed that the reactivity in the beta 1 and beta 2 bands differ slightly from each other, with the lower beta band generating stronger rebound. However, the strongest reactivity was observed in a wider frequency band, which covered both rhythms. Moreover, in some

Table 1
Clinical details of the patients.

Pat.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sex	M	F	M	F	F	M	F	M	M	M	M	F	F	F	M	F	F	M
Age	60	72	74	84	55	68	72	44	62	57	67	67	68	74	78	72	48	61
AH	R	L	L	R	R	L	R	L	L	R	R	L	L	R	L	L	L	R
Site	C	C	C	C	CS	CS	CS	CS	CS	CS	S	S	S	S	S	S	S	S
Size	0.1	0.3	0.4	1	70	48	24	34	5	106	7	1	3	5	10	3	1	4
TS (T_0)	N	D	D	D	D	D	D	D	D	D	N	D	N	N	D	D	N	D
TS (T_1)	N	N	N	N	D	D	D	D	N	D	N	D	N	N	D	D	N	D
TS(T_2)	N	N		N	D	N	D	D	N	D	N	D	N	N	N	D	N	D

AH, affected hemisphere; C, cortical; CS, cortico-subcortical; S, subcortical; Size, lesion volume in cm^3; TS, tactile sensitivity. T_0, 1–7 days; T_1, 1 month, T_2, 3 months after stroke onset. N, normal; D, decreased.

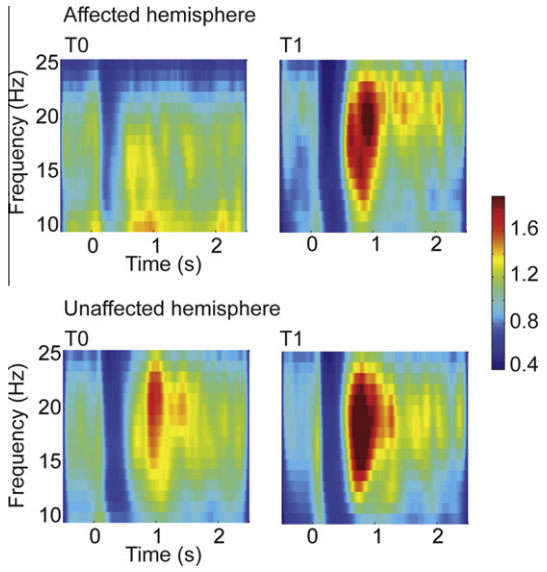

Fig. 1. Grand average of the time–frequency representation of the power (arbitrary scale) of brain oscillations at 10–25 Hz over the sensorimotor region in the affected (AH) and unaffected (UH) hemispheres to contralateral tactile index finger stimulation in the patients with detectable modulation of the beta rhythm at 1–7 days (T_0), and at 1 month (T_1) after stroke onset. Zero ms denotes the time point of tactile stimuli.

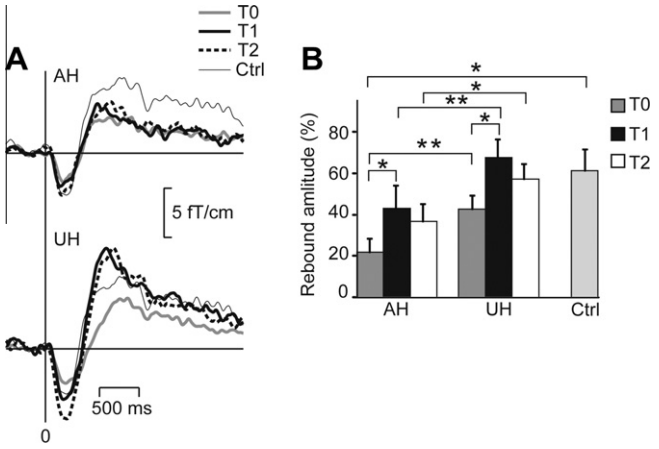

Fig. 2. (A) Mean strength of the beta rhythm over the sensorimotor region in the affected (AH) and unaffected (UH) hemispheres to contralateral tactile index finger stimulation at 1–7 days (T_0), 1 month (T_1), and 3 months (T_2) after stroke onset and in the control subjects (right and left hemispheres pooled). (B) Mean (+SEM) strength of the rebound of the beta rhythm over the sensorimotor region in the affected (AH) and unaffected (UH) hemispheres to contralateral tactile index finger stimulation in the patients and in the control subjects (right and left hemispheres pooled). Rebound strength is expressed as increase in percentage with respect to the reference baseline in the −300 to 0 ms pre-stimulus period ($^{*}p < 0.05$, $^{**}p < 0.005$).

control subjects and patients the separation between the higher and lower beta bands could not be reliably done. Therefore, we chose for each subject an individual frequency band with the width of 10 Hz, which covered both the lower and the higher beta peaks for further analysis.

Fig. 2 shows the mean strength of the beta rhythm over the sensorimotor region in the affected and unaffected hemispheres in the patients and in the control subjects. In agreement with earlier studies (Salenius et al., 1997; Salmelin and Hari, 1994) the beta rhythm of the control subjects starts to decrease 120 ± 15 ms after onset of the tactile stimulation and reaches its peak suppression at 250 ± 15 ms in both hemispheres. The subsequent increase starts at 550 ± 35 ms and maximal rebound is observed at 900 ± 85 ms. No significant difference was found in the strength of the suppression or rebound between the hemispheres of the control subjects.

At T_0, a rebound was not observed in the AH of 8 patients, and in 2 of them it was lacking in both UH and AH. At T_1 and T_2, the rebound was still absent in the AH in 5 patients, in the UH it was observed in all patients. Absence of the rebound was not systematically associated with site or size of the lesion or with decreased tactile sensitivity. Latencies of the beta suppression and rebound of the patients were comparable with the control subjects.

Repeated measures ANOVA showed a significant main effect for the factors time [$F(2,32) = 10.386$, $p < 0.001$, partial $\eta^2 = 0.39$] and hemisphere [$F(1,16) = 15.195$, $p < 0.001$, partial $\eta^2 = 0.49$] for the rebound in patients. The time × hemisphere interaction was not significant [$F(2,32) = 0.331$]. The strength of the rebound was significantly weaker at T_0 than at T_1 in both the AH and UH ($p < 0.05$). Pair-wise comparison showed that the rebound was significantly weaker in the AH than in the UH at all time points ($t(17) = 3.233$, $p < 0.005$ for T_0; $t(17) = 4.298$, $p < 0.001$ for T_1; and $t(16) = 2.404$, $p < 0.05$ for T_2; Fig. 2, Table 3). The rebound strength of the patients differed from that of the control subjects only in the AH at T_0 ($t(17) = 3.427$, $p < 0.05$). Repeated measures ANOVA showed a significant main effect for the factors time [$F(2,32) = 4.496$, $p < 0.05$, partial $\eta^2 = 0.22$] and hemisphere [$F(1,16) = 6.087$, $p < 0.05$, $\eta^2 = 0.28$] also for the suppression, but not for their interaction [$F(2,32) = 0.820$]. Pair-wise comparison showed that the suppression in the AH was weaker at T_0 than at T_2 ($t(16) = -2.722$, $p < 0.05$). No other differences in the suppression were observed between the hemispheres or the different time points. Neither did the strength of the suppression differ between the patients and the control subjects.

3.4. Correlation analysis

In patients, the beta rebound strength in the AH at T_0 correlated with the lesion size; the larger the lesion, the weaker the rebound ($r_S = -0.8$, $p < 0.001$). In contrast, no systematic relationship between the lesion site and beta rebound was found. The beta rebound strength in the AH correlated with results of the Peg tests in all three measurements ($r_s = -0.8$, $p < 0.001$ for T_0; $r_S = -0.5$, $p < 0.05$ for T_1; and $r_S = -0.6$, $p < 0.05$ for T_2); the stronger the rebound, the better the patient's performance in Peg (Fig. 3). Also in the UH the rebound strength correlated with results of the Peg test of the affected hand at T_0 ($r = -0.5$, $p < 0.05$); the stronger the rebound in the UH, the better the patient's hand dexterity.

Somatosensory evoked fields (SEFs) to tactile index finger stimulation were measured from the same patients in the same measurement sessions (Forss et al., 2012). SEFs were elicited in the contralateral primary (SI) and in the bilateral secondary somatosensory cortices (SII; Fig. 4). The amplitudes of the SI responses in the AH did not change significantly during follow-up. In contrast, the SII responses in the AH (contralateral to the stimulated affected hand) increased significantly from T_0 to T_1 ($p < 0.01$; Fig. 4, Table 3). The SEFs are described in more detail in our previous study (Forss et al., 2012). To evaluate further how alterations of motor cortical rhythms were modulated by changes in afferent input, the strength of the beta rebound was correlated with the strength of the SEFs. No correlations between the primary somatosensory cortex (SI) activation and the rebound were found. In contrast, the activation of the secondary somatosensory cortex (SII) correlated with the strength of the beta rebound at T_0 ($r_S = 0.5$, $p < 0.05$); the larger the SII amplitude, the stronger the rebound (Fig. 4). However, no correlation between the SII amplitude and the rebound were found at T_1 or T_2.

Table 3
SEF amplitudes and SII latencies (mean ± SEM) to index finger tactile stimulation of the affected hand (Forss et al., 2012), and beta rebound strength (increase of rhythm in relation to the reference baseline; mean ± SEM) in patients and in control subjects.

	SI amplitude, AH (nAm)	SII amplitude, AH (nAm)	SII latency, AH (ms)	Rebound, AH %	Rebound, UH %
T_0	17 ± 3	14 ± 4	109 ± 11	22 ± 7	43 ± 7
T_1	23 ± 3	25 ± 5	101 ± 5	43 ± 11	68 ± 9
T_2	23 ± 3	26 ± 4	101 ± 6	37 ± 9	57 ± 7
Ctrl.	25 ± 3	31 ± 3	112 ± 6	61 ± 11	61 ± 11

T_0, 1–7 days; T_1, 1 month; T_2, 3 months after stroke. Ctrl.; control subjects (left and right hands pooled); SI, primary somatosensory cortex; SII, secondary somatosensory cortex; AH; affected hemisphere; UH; unaffected hemisphere.

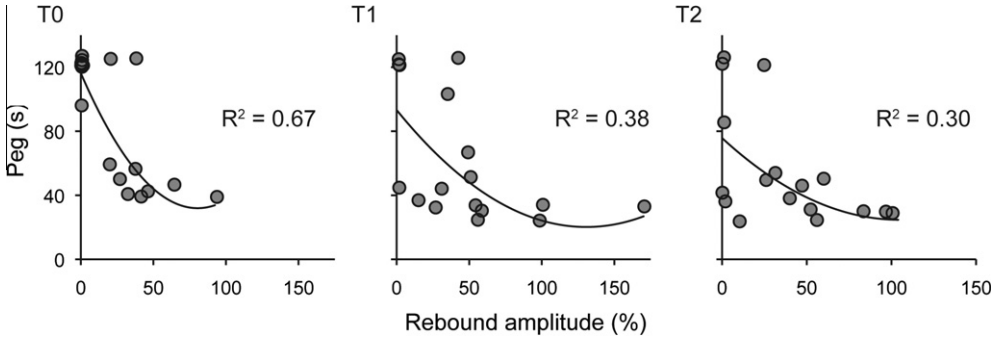

Fig. 3. Association between the beta rebound of the affected hemisphere and the Peg time of the affected hand (s) at 1–7 days (T_0), 1 month (T_1), and 3 months (T_2) after stroke onset. Nonlinear (x^2) regression line is shown in black.

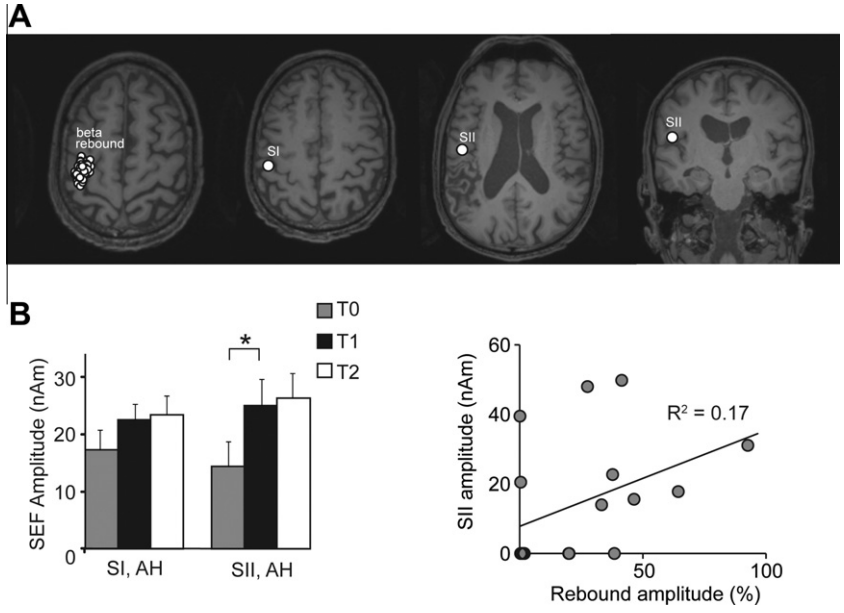

Fig. 4. (A) Source locations of the beta rebound and the SI and SII activation to tactile finger stimulation in the affected hemisphere of one illustrative patient at T_2. Sources are modeled with equivalent current dipoles. (B) *Left* Mean (+SEM) amplitudes of SI and SII sources to tactile finger stimulation in the affected hemisphere of the patients at 1–7 days (T_0), 1 month (T_1), and 3 months (T_2) after stroke onset ($^*p < 0.01$). *Right:* Association between the beta rebound and the SII response amplitude in the affected hemisphere at the acute phase (T_0). Regression line is shown in black.

4. Discussion

4.1. Beta rebound and motor cortex excitability

Several intracortical and scalp electroencephalography (EEG) as well as magnetoencephalography (MEG) studies have indicated that the sensory and motor cortical areas generate spontaneous beta oscillations in the frequency around 20-Hz (Jasper and Penfield, 1949; Pfurtscheller and Stancak, 1996; Salmelin and Hari, 1994). These oscillations are modulated by both motor (movement preparation or execution) and somatosensory (peripheral afferent stimulation) activation, which lead to an initial suppression followed by a transient rebound of the rhythm. In EEG studies this phenomenon is often denoted as event-related desynchronization (ERD) and event-related synchronization (ERS; Pfurtscheller, 1981; Pfurtscheller and Stancak, 1996).

Earlier studies have suggested that there are at least two distinct beta rhythms with different frequency bands and different functional roles. Further, it has been shown that the suppression/ERD and rebound/ERS may differ in their mechanism of generation

(Cassim et al., 2000; Feige et al., 1996; Hall et al., 2011; Jurkiewicz et al., 2006; Pfurtscheller et al., 1997). Therefore differentiation of the beta rhythms could be of importance. In the present study, the lower and higher beta bands behaved slightly differently to tactile stimulation with the lower beta band contributing more to the rebound. However, in general, the strongest rebound was observed when both beta components were lumped together in the TSE calculations. This is in line with an earlier study showing that the frequency band displaying the beta rebound is relatively broad, and the rebound may be found either in one single or in multiple frequency bands (Pfurtscheller et al., 1997). Therefore we chose for each subject an individual frequency band with the width of 10 Hz (ranging from 12–26 Hz), which covered both the lower and the higher beta components.

Although some earlier studies have indicated that the generator areas of the beta rhythm exceed the boundaries of the primary motor cortex (Crone et al., 1998; Parkes et al., 2006), several studies have shown, that the beta rebound, detected with MEG, has its main sources in the precentral gyrus harboring the primary motor cortex (Gaetz and Cheyne, 2006; Jurkiewicz et al., 2006; Salmelin et al., 1995). The rebound is attenuated during movement execution, observation or even motor imagery, and thus it has been suggested to reflect decreased motor cortex excitability (Hari et al., 1998; Salenius et al., 1997; Salmelin and Hari, 1994). In accordance, decreased cortical excitability was detected with transcranial magnetic stimulation (TMS) after electric median nerve or digit stimulation at latencies comparable with the beta rebound (Abbruzzese et al., 2001; Chen et al., 1999).

In the present study, no differences in the overall strength of spontaneous beta oscillations were observed between the hemispheres, between the different time points, or between patients and control subjects. In contrast, the strength of the beta rebound to tactile stimulation in the affected hemisphere (AH) was decreased in the acute phase. Therefore, we suggest that the decreased rebound of the beta rhythm observed in our stroke patients is independent from the overall level of beta oscillations, and that it reflects increased motor cortex excitability after acute stroke. This is in line with a recent transcranial magnetic stimulation (TMS) study, showing reduced short-latency afferent inhibition in the AH after acute stroke (Di Lazzaro et al., 2012). Further, we suggest that the gradual increase of the rebound reflects decreasing motor cortex excitability during stroke recovery.

Earlier studies have suggested that cortical excitability may be altered differently in cortical and subcortical strokes (Liepert et al., 2005a,b). In the present study, no systematic relationship between rebound strength and lesion site was found. In contrast, the rebound strength correlated with the size of the lesion. However, as the subgroups of patients were rather small, we cannot draw definitive conclusions whether the site of the lesion has an influence on the motor cortex excitability. Future studies are needed to address this issue.

4.2. Motor cortex excitability in the unaffected hemisphere

Earlier TMS studies in stroke patients have demonstrated increased excitability in the unaffected hemisphere (UH) at the acute phase after stroke (Liepert et al., 2000a; Manganotti et al., 2002). Hyperexcitability of the UH has been proposed to prohibit functional recovery (Manganotti et al., 2008; Murase et al., 2004) and it has been suggested that inhibition of the hyperexcitable UH with repetitive TMS (rTMS) may improve functional recovery (Mansur et al., 2005; Takeuchi et al., 2005).

In the present study, the beta rebound was significantly decreased also in the UH at T_0 as compared with T_1 and T_2, and the decrease correlated negatively with the dexterity of the impaired hand. These findings support the previously presented suggestions of the harmful effect of the hyperexcitated UH. The excitability in the UH may remain increased in patients with poor recovery (Manganotti et al., 2008). However, such long lasting changes were not observed in our data, as most of the patients recovered well.

4.3. Effect of afferent input on motor cortex excitability

The functional state of the motor cortex depends on the balance between several different excitatory and inhibitory influences, ranging from effects of local inhibitory circuits to influences of remote cortical areas. In addition to cortical excitatory and inhibitory circuits, also afferent input has been suggested to play an important role in the regulation of motor cortex excitability (Asanuma and Arissian, 1984; Favorov et al., 1988). For example, reduced afferent input i.e. due to a transient ischemic block of cutaneous afferents (Brasil-Neto et al., 1992) or transient immobilization (Todd et al., 2006) has been shown to cause motor cortex disinhibition.

Although some direct thalamocortical afferent connections to the motor cortex may exist (Asanuma et al., 1979), a major part of modulatory afferent input to the motor cortex is mediated through corticocortical connections from primary and secondary somatosensory cortices (Chen et al., 1999; Disbrow et al., 2000; Hinkley et al., 2007). Studies in animals have shown anatomical connections between areas 1 and 2 of the SI and the primary motor cortex area 4, whereas connections from the main cutaneous area 3b of the SI are only sparse (Jones et al., 1978). In addition to posterior parts of SI, area 4 has strong anatomical connections to area SII (Jones and Wise, 1977; Mori et al., 1989). In agreement with these anatomical studies, functional MRI and MEG studies in humans have shown that SII is an important region in integration of somatosensory information with motor functions, especially in tasks demanding hand dexterity (Disbrow et al., 2000; Hinkley et al., 2007).

The modulation of the beta rhythm by peripheral somatosensory stimulation suggests that afferent somatosensory input affects the motor cortex excitability (Cassim et al., 2000, 2001; Salenius et al., 1997; Salmelin and Hari, 1994). To study this further, we correlated the beta rebound strength during tactile finger stimulation with the strength of the simultaneously measured somatosensory evoked fields from SI and SII cortices. The SI amplitude did not correlate with the rebound strength at any time point. Instead, the strength of SII activation correlated with the strength of the beta rebound at T_0. Although the correlation was not strong, and the sample size was limited, these findings support the earlier studies suggesting that SII might be an important node in mediating the regulatory afferent input to the motor cortex. To our knowledge, this possible association between SII activation and motor cortex excitability has not yet been directly studied. However, deficient SII activation and changes in motor cortex excitability have both been reported in other disorders with motor deficits, such as Unverricht-Lundborg Type Epilepsy, Parkinson disease, and focal dystonia (Abbruzzese et al., 2001; Boecker et al., 1999; Butterworth et al., 2003; Forss et al., 2001; Sailer et al., 2003; Silen et al., 2000). Further studies would be needed to elucidate the possible association between SII activation and motor cortex excitability.

4.4. Motor cortex excitability and recovery

Changes of cortical excitability have been linked to plastic reorganization and thus suggested to be essential for functional recovery (Jacobs and Donoghue, 1991). Increased cortical excitability has been demonstrated in humans as enlarged motor task related activation patterns in functional MRI and positron emission tomography studies (Ward et al., 2003a; Weiller et al., 1993), and

more directly, in TMS studies using intracortical inhibition (ICI) and intracortical facilitation (ICF) paradigms (Liepert et al., 2000b; Manganotti et al., 2002, 2008). However, the exact relationship between cortical excitability changes and functional recovery has remained controversial. Several studies have suggested that although disinhibitory changes at the acute phase may be necessary for functional recovery (Butefisch et al., 2003; Liepert et al., 2000b), normalization of motor cortex excitability is associated with good recovery of the patients (Calautti et al., 2001; Swayne et al., 2008).

In the present study, the decreased rebound in the AH correlated with hand dexterity in the acute phase, suggesting that increased excitability of the motor cortex is associated with poor control of the affected hand. These results are in line with earlier studies that have shown attenuation of the beta rebound in association with impaired fine motor skills in patients suffering from Unverricht Lundborg Type Progressive Myoclonus Epilepsy or Complex Regional Pain Syndrome (Juottonen et al., 2002; Kirveskari et al., 2010; Silen et al., 2000; Visani et al., 2006).

During follow-up, the rebound in the AH increased from T_0 to T_1 and T_2, and correlated with hand dexterity both in the acute phase and during recovery, indicating that changes in cortical excitability are associated with recovery of hand function. This finding is in line with a recent TMS study, applying intracortical inhibition (ICI) and intracortical facilitation (ICF) paradigms, that showed a correlation between motor cortex excitability and hand function at 3 months after stroke (Swayne et al., 2008). Yet, changes in motor cortex excitability due to alterations in afferent input are apparently mediated by different circuits than those mediating ICI or ICF (Sailer et al., 2002). A recent TMS study, evaluating both SICI and short-latency afferent inhibition (SAI) in acute stroke patients, found a significant correlation between reduced SAI and long-term recovery, but not between SICI and recovery (Di Lazzaro et al., 2012). For our study, the most comparable TMS setup might be the long latency afferent inhibition (LAI) after conditioning somatosensory stimulus that has been detected at latencies comparable with the beta rebound in MEG (Chen et al., 1999; Sailer et al., 2002). However, to our knowledge no longitudinal TMS studies have investigated changes in LAI after stroke, but this could be an interesting target of future investigations.

As the motor cortex beta rhythm was modulated by afferent somatosensory input, one could argue that all the observed changes are due to recovery of somatosensory afferents with no alterations in the motor cortex excitability. However, in the light of earlier studies it is not likely that the motor cortex excitability would not be altered after stroke. Moreover, results of the present study do not support this possibility. Earlier studies have shown that the SI amplitudes increase linearly with increasing stimulus intensity (Jousmaki and Forss, 1998; Torquati et al., 2002). In the present study, the stimulus intensity was kept constant across the subjects and across the measurement times T_0, T_1, and T_2, and thus any enhanced afferent input due to recovery of tactile fibers would elicit increased SI amplitudes. However, in our patients, the SI amplitudes in the affected hemisphere did not significantly change during follow-up (Forss et al., 2012). Neither was there a systematic relationship between decreased tactile sensitivity and absent/diminished rebound. Moreover, the beta rebound was decreased at T_0 also in the UH to the stimulation of the unaffected hand with no impairment of tactile sensitivity. These results strongly suggest that recovery of the sensory system alone is not sufficient to explain the observed changes. Rather, the changes in the beta rebound result from recovery of both the modulatory sensory afferents and the motor system. In conclusion, the present results underline the importance of parallel recovery of the sensory and motor systems to allow fluent sensorimotor integration, which is required for normal hand dexterity.

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