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RESEARCH ARTICLE

Sensory Processing

Reproducibility of Rolandic beta rhythm modulation in MEG and EEG

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Abstract

The Rolandic beta rhythm, at ~20 Hz, is generated in the somatosensory and motor cortices and is modulated by motor activity and sensory stimuli, causing a short lasting suppression that is followed by a rebound of the beta rhythm. The rebound reflects inhibitory changes in the primary sensorimotor (SMI) cortex, and thus it has been used as a biomarker to follow the recovery of patients with acute stroke. The longitudinal stability of beta rhythm modulation is a prerequisite for its use in long-term follow-ups. We quantified the reproducibility of beta rhythm modulation in healthy subjects in a 1-year-longitudinal study both for MEG and EEG at T_0, 1 month ($T_{1\text{-month}}$, n = 8) and 1 year ($T_{1\text{-year}}$, n = 19). The beta rhythm (13–25 Hz) was modulated by fixed tactile and proprioceptive stimulations of the index fingers. The relative peak strengths of beta suppression and rebound did not differ significantly between the sessions, and intersession reproducibility was good or excellent according to intraclass correlation-coefficient values (0.70–0.96) both in MEG and EEG. Our results indicate that the beta rhythm modulation to tactile and proprioceptive stimulation is well reproducible within 1 year. These results support the use of beta modulation as a biomarker in long-term follow-up studies, e.g., to quantify the functional state of the SMI cortex during rehabilitation and drug interventions in various neurological impairments.

NEW & NOTEWORTHY The present study demonstrates that beta rhythm modulation is highly reproducible in a group of healthy subjects within a year. Hence, it can be reliably used as a biomarker in longitudinal follow-up studies in different neurological patient groups to reflect changes in the functional state of the sensorimotor cortex.

cortical oscillation; cutaneous stimulus; event-related desynchronization; event-related synchronization; passive movement

INTRODUCTION

Oscillatory activity in the sensorimotor cortex at rest is dominated by the ~20-Hz beta rhythm, which attenuates as a result of the person's voluntary movement (1), evoked passive movement, or imagined movement (2–6). In addition, the ~20-Hz beta rhythm is modulated by somatosensory afferent stimuli, such as tactile or electrical stimulation (7–11). The beta rhythm is suppressed briefly after the onset of a stimulus or before self-paced movement. This so-called beta suppression (or event-related desynchronization; ERD) is thought to reflect the excitation of the sensorimotor cortex (12, 13). The suppression is followed by an increase of the beta rhythm above baseline level. This beta rebound (or event-related synchronization; ERS) is associated with neural deactivation or inhibition of the sensorimotor cortex (3, 14, 15). The generator area of the rebound is usually located more anterior than the suppression in the sensorimotor cortex (7, 16, 17). The rebound and suppression are regulated by distinct subunits of GABAergic interneurons (18–21).

Alterations in beta suppression and rebound have been reported in various neurological and psychiatric patient groups, such as stroke (22, 23), schizophrenia (24, 25), Parkinson's disease (26–28), and cerebral palsy (29–31). Longitudinal studies in patients with stroke have revealed that the strength of the sensorimotor cortex beta rebound correlates with recovery of motor function after acute stroke (11, 32, 33). Consequently, the beta rhythm modulation has been considered as a biomarker of the inhibitory state of the

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sensorimotor cortex, and it may thus be useful in the evaluation of changes in cortical inhibition during development, aging, and various interventions and the recovery process after brain injury, such as stroke. Espenhahn et al. (34) found the beta rhythm modulation to be well reproducible within a few weeks, but no previous study has investigated the reproducibility of beta suppression and rebound in longer-term measurements, to prove its feasibility for follow-up studies.

The primary aim of the present study was to examine the reproducibility of beta rhythm modulation to tactile and proprioceptive stimulation over a period of 1 year in healthy individuals separately for magnetoencephalography (MEG) and electroencephalography (EEG). In addition, reproducibility of baseline beta power was assessed, as it may affect the estimation of the relative suppression and rebound strengths. Based on previous experiments, indicating a high or excellent reproducibility of MEG and EEG measures related to somatosensory stimuli (35, 36), we hypothesized that the beta rhythm modulation is a reproducible measure when using both MEG and EEG. Stability of the beta modulation over a long period is necessary for its reliable use in clinical follow-up studies.

MATERIALS AND METHODS

Subjects

Twenty-one healthy subjects in total were recruited for the study. Nineteen of them (10 females, age 19–35, means ± SD: 23 ± 5 year) were able to complete the 1-year follow-up (13 ± 1.3 month). Additional 1-month follow-up recordings (31 ± 2 days) were performed for 8 (4 females, age 19–31, means ± SD: 25 ± 4 year) of the 21 subjects. All the subjects were right-handed (85 ± 12 on the scale from −100 to 100) according to Edinburgh Handedness Inventory score (37), and had no medication affecting their central nervous system (CNS).

The Aalto University Research Ethics Committee approved the study in accordance with the Declaration of Helsinki. The subjects were asked to sign written informed consent before all follow-up measurements.

Experimental Design

Reproducibility of the sensorimotor cortex beta rhythm suppression and rebound was assessed between baseline T_0 and 1-year $T_{1\text{-year}}$ follow-up (n = 19) and between baseline T_0 and a 1-month $T_{1\text{-month}}$ (n = 8) measurement sessions.

During the combined MEG/EEG measurement, the subject was fixating at a picture in front of them (size 12 × 15 cm, distance of 2.2 m), while the index fingers were stimulated with tactile and proprioceptive stimuli (Fig. 1) in two separate recordings, respectively. The order of the recordings was randomized. Stimulus-related potential auditory and visual contamination were prevented by using earplugs and visual barrier, respectively. The subject was asked not to pay attention to the stimuli. The total duration of measurement in the magnetically shielded room (MSR) was ~45 min, and the tactile and proprioceptive stimulus periods lasted ~9 min each.

Tactile stimulation.

Tactile stimuli were given alternately to the left and right hand index fingers every 3 s. The stimuli were produced with Aalto NeuroImaging in-house built pneumatic stimulator utilizing pneumatic diaphragms (4-D NeuroImaging Inc., San Diego, CA) driven by compressed air (4 bar) with a stimulus duration of 180 ms, peaking at 40 ms. The subject held their hands relaxed on a pillow during the stimulation.

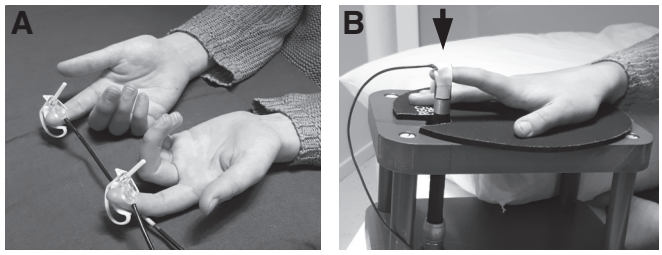

Figure 1. The experimental setup for magnetoencephalography (MEG) compatible tactile (*A*) and proprioceptive (*B*) stimulators.

Proprioceptive stimulation.

The proprioceptive stimuli were evoked to the left and right index finger in separate recordings. A mechanical movement actuator system (38), built at Aalto University, was used to evoke fast flexion-extension movement of the index finger every 5 s (duration 130 ms, mechanical delay from the trigger pulse 35 ms). The movement kinematics were recorded with an MEG-compatible three-axis accelerometer system, built at Aalto NeuroImaging based on an ADXL335 iMEMS Accelometer (Analog Devices Inc., Norwood, MA) attached on the index finger. Compressed air (4 bar) was applied to the actuator resulting in a movement range of ~5 mm. To minimize possible tactile sensation of the fingertip, the index finger was taped with surgical tape. To confirm the correct finger position during the measurement, the finger was lightly taped to the actuator and the stimulated hand was supported in a comfortable relaxed position with pillows.

Data Acquisition

The simultaneous MEG/EEG measurements were recorded at Aalto University (MEG Core, Aalto NeuroImaging), with a 306-channel (204 planar gradiometers, 102 magnetometers) whole scalp MEG system (Elekta Neuromag, Elekta Oy, Helsinki, Finland). A 60-channel MEG-compatible EEG cap (ANT Neuro waveguard original) with Ag-AgCl surface electrodes mounted according to the international 10-20 system, was used for EEG recordings. In addition, eye blink artifacts were detected with two vertical electro-oculogram electrodes (EOG). The MEG/EEG recordings were performed in a magnetically shielded room (MSR; Imedco AG, Hägendorf, Switzerland). Before the recordings, two indicator coils were attached above the ears and three onto the forehead of the EEG cap. The location of these five coils, three anatomical landmarks (left and right preauricular points and nasion) and additional 100–200 points from the surface of head, were determined with a three-dimensional (3-D) digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT). The head position was determined in the beginning of each measurement session and continuously during the measurement by sending a low current to the indicator coils and detecting the position of the coils with respect to the MEG sensor array.

A sampling frequency of 1000 Hz and bandpass filter 0.1–330 Hz was used in MEG, EEG, and accelerometer recordings. The impedances of the EEG electrodes were verified to be below 5–10 kΩ before the recording.

Data Processing and Analysis

Preprocessing.

A custom-made MATLAB script was used to transform the MEG raw signals from the different measurement sessions (T_0, $T_{1\text{-month}}$, $T_{1\text{-year}}$) to the same average head-coordinate system, separately to tactile and proprioceptive stimuli, for each subject. This improves the comparability of different measurement sessions when the obtained reference head positions are used for coordinate matching in the Maxfilter software (v2.2; Elekta Oy, Helsinki, Finland). MEG raw signals were filtered with the signal-space separation method with temporal extension (tSSS) and head movement compensation (threshold 25 mm) was obtained (39). The following parameters were used in the Maxfilter software: buffer length 16 s, subspace correlation limit 0.98, inside expansion order 8, and outside expansion 3.

Hereafter, the MEG and EEG data were analyzed with MNE Python (v. 0.17) (40). The EEG signals were re-referenced to the average reference over all good quality channels, individually for each subject. Eye blink artifacts (two magnetometer and two gradiometer components) were removed with principal component analysis (PCA; 41). Evoked responses related to stimulus onset, which can disturb the baseline detection of the beta modulation, were subtracted from each epoch from both MEG and EEG data (42).

Determination of beta rhythm modulation.

The temporal spectral evolution (TSE) method was used to quantify the strength of the stimulus-related beta rhythm modulation in the follow-up measurements (7). MEG and EEG data were first filtered to a 13- to 25-Hz frequency band (a symmetric linear-phase FIR filter with a transition band of 1 Hz at the low- and high cutoff frequency and Hamming window, filter length 3.3), which in a previous study has been found to show the strongest beta rhythm modulation for all subjects (43). The lower beta frequencies are needed specifically to detect the beta rebound (5, 29, 44). After bandpass filtering, a Hilbert transform was applied to obtain the envelope signal, after which the data were averaged from −500 to 3,000 ms with respect to the stimulus trial. Peak strengths and latencies of the beta rhythm suppression and rebound were determined from the individual TSE curves. MEG and EEG channels used for rebound/suppression determination were individually selected over the sensorimotor cortex areas and they remained the same (within one subject) in all sessions. Channels were selected based on the strongest response, noticing that in some subjects the suppression and rebound were more pronounced in different channels (one or two channels in one hemisphere). The baseline beta rhythm power was determined from these individually selected MEG and EEG channels from a time window of −500 to −100 ms, and the absolute suppression and rebound strengths were converted to relative values (in percentage) with respect to the prestimulus baseline from −500 to −100 ms to allow better comparability between different subjects and measurement sessions. The interstimulus intervals of the stimuli were chosen to allow a return of the beta rhythm to baseline level well before next stimulus onset, i.e., to keep the baseline stable during the measurement.

Beta rhythm modulation to tactile and proprioceptive stimuli was visualized with topographic TSE maps and time-frequency representations (TFRs; 45) averaged over all subjects in both MEG and EEG. TFRs, in the frequency range of 3–36 Hz and a time window of −700 to 3,200 ms with respect to stimulus onset, were calculated using Morlet wavelets by scaling the number of cycles by frequency ($f/2$).

Statistical Analysis

Statistical tests were performed with IBM SPSS Statistics (v. 27.0. Armonk, NY, IBM Corp). The Shapiro–Wilk test was used to test the normality of the data. The latencies and relative peak strengths of the beta rhythm suppression and rebound turned out to be not normally distributed, and therefore the nonparametric Wilcoxon test was used to test differences in the latency and strength of beta suppression and rebound between the follow-up measurements.

Correlations of beta suppression and rebound strengths between the follow-up measurements were determined with Spearman's correlation coefficient test. The reproducibility of suppression and rebound was in addition tested with the intraclass correlation coefficient (ICC) with two-way random effects and absolute agreement. In addition, coefficient of variation (CV) was defined to show interindividual variability of beta suppression and rebound at T_0, $T_{1\text{-month}}$, and $T_{1\text{-year}}$.

The effect of multiple tests was corrected with Bonferroni correction. A P value between 0.05 and 0.001 was used to assess significance.

RESULTS

A consistent number of trials (means ± SD) were collected for the TSE analysis between T_0 and $T_{1\text{-month}}$ follow-up measurements to tactile (105 ± 11 vs. 101 ± 6) and proprioceptive (108 ± 12 vs. 101 ± 10) stimulation. As can be seen from the results, the number of trials was higher at T_0 than at $T_{1\text{-year}}$ measurements to tactile (105 ± 11 vs. 92 ± 13, $P > 0.001$) and proprioceptive (108 ± 12 vs. 99 ± 7, $P > 0.001$) stimulation.

Spatiotemporal Characteristics of Beta Rhythm Modulation

Spatial distribution of beta suppression and rebound.

Figure 2*A* illustrates group averaged (n = 21) spatial distribution of beta rhythm suppression and rebound at T_0 both in MEG and EEG. Beta suppression and rebound were observed bilaterally over the sensorimotor cortex shortly after the onset of both tactile and proprioceptive stimuli, with stronger responses in the contralateral hemisphere (especially rebound) in relation to the stimulated hand. These contralateral responses were taken for further analysis.

Time-frequency representation.

Figure 2*B* shows contralateral beta rhythm modulations (group averaged over 21 subjects) to tactile and proprioceptive stimuli at T_0. The decrease of beta rhythm is most

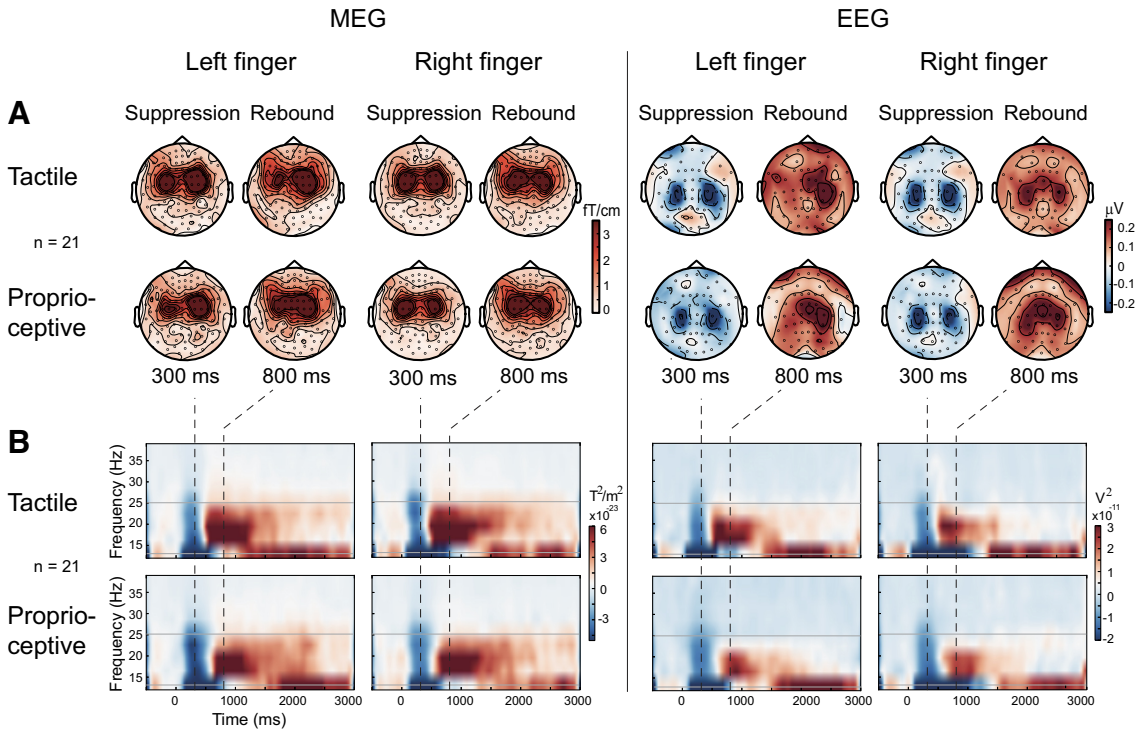

Figure 2. Grand averaged (n = 21 subjects) topographic distributions and time frequency representations (TFR) of the beta rhythm modulation to tactile and proprioceptive stimulation in the baseline T_0 measurement. *A*: topographic maps show magnetic field strengths (magnetoencephalography, MEG) and electrical scalp potentials (electroencephalography, EEG) of the beta suppression and rebound to left and right stimuli. Note that MEG topographies reflect the vector sum of the gradiometer pairs, and thus obtain only positive values. *B*: TFR images illustrates temporal evolution of the beta frequency power from one of the most representative gradiometer over the sensorimotor cortex contralateral to the stimulation with respect to trigger onset at 0 s. Black dashed lines indicate the time instants if the suppression and rebound illustrated in *A*. Gray lines indicate the beta frequency band used in temporal spectral evolution (TSE) analysis.

pronounced at 250–350 ms and subsequently increased at 700–850 ms after the onset of tactile and proprioceptive stimuli.

Reproducibility of Beta Suppression and Rebound

Reproducibility within 1 year.

Latencies. Mean latencies of beta suppression and rebound for both stimuli in MEG and EEG are shown in Table 1. No statistically significant differences ($P > 0.28$) in suppression or rebound latencies were observed between the different measurements (T_0, $T_{1\text{-month}}$, and $T_{1\text{-year}}$) and stimuli.

Strength of beta suppression and rebound. Figure 3*A* shows group averaged (n = 19) TSE curves to tactile and proprioceptive stimuli at T_0 and $T_{1\text{-year}}$. Beta rhythm suppression and rebound are well identifiable in all sessions both in MEG and EEG, and the suppression and rebound strengths appear similar between T_0 and $T_{1\text{-year}}$ sessions. Supplemental Fig. S1 (see https://doi.org/10.6084/m9.figshare.17032178.v1) shows the individual TSE curves for all subjects at three different measurement sessions.

Figure 4*A* illustrates the relative peak strengths (% to baseline) of beta suppression and rebound at T_0 and $T_{1\text{-year}}$ both in MEG and EEG to left and right finger stimulation. Beta suppression and rebound strengths did not differ significantly (MEG P = 1.0; EEG $P > 0.053$) between the 1-year follow-up measurements (T_0 vs. $T_{1\text{-year}}$, n = 19). Mean values and standard deviations of the relative peak strengths for beta suppression and rebound are shown in Table 1.

Intersession correlations. Figure 5*A* presents the relative peak strengths of beta suppression and rebound individually (n = 19) at T_0 and $T_{1\text{-year}}$. The suppression and rebound strengths are well reproducible both in MEG and EEG for most of the subjects. Intraclass correlation coefficient values indicated good to excellent intersession reproducibility for suppression 0.72–0.96 and rebound 0.70–0.95 strengths. However, the ICC values appeared to be stronger for the dominant compared with the nondominant hand. Figure 5*B* shows scatterplots respectively for suppression and rebound strengths between T_0 and $T_{1\text{-year}}$ measurements. The beta suppression and rebound strengths to tactile and proprioceptive stimuli correlated significantly between the measurements; the Spearman's correlation coefficients (r) for the suppression and rebound are 0.47–0.88 and 0.47–0.94, respectively. More detailed correlation values are shown in Table 2.

In summary, the strength of beta rhythm suppression and rebound to tactile and proprioceptive stimuli both in MEG and EEG were highly reproducible in the 1-year follow-up period.

Reproducibility within 1 month.

Strength of beta suppression and rebound. The additional 1-month follow-up recordings were performed for a subgroup of our participants to confirm that the reliability of beta rhythm modulation was similar for both the 1-month and 1-year follow up. Figure 3*B* shows group averaged (n = 8)

Table 1. *Relative peak strengths and latencies of the beta rhythm suppression and rebound in three follow-up MEG/EEG measurements*

	Tactile Stimulation				Proprioceptive Stimulation			
	MEG		EEG		MEG		EEG	
	LH	RH	LH	RH	LH	RH	LH	RH
Suppression								
T_0								
Relative amplitude, %	−29 ± 2	−25 ± 2	−19 ± 2	−19 ± 2	−31 ± 2	−23 ± 3	−20 ± 2	−20 ± 2
SD ±	10	10	9	10	11	12	9	8
CV, %	34	40	47	47	35	52	45	40
Peak latency, ms	260 ± 17	296 ± 17	247 ± 22	263 ± 17	320 ± 22	316 ± 20	304 ± 27	299 ± 17
$T_{1\text{-month}}$								
Relative amplitude, %	−28 ± 4	−23 ± 5	−21 ± 3	−15 ± 4	−30 ± 4	−23 ± 5	−23 ± 4	−22 ± 3
SD ±	12	14	9	10	12	14	12	10
CV, %	42	61	45	67	40	61	52	45
Peak latency, ms	213 ± 24	250 ± 38	224 ± 36	248 ± 39	232 ± 29	247 ± 29	339 ± 37	250 ± 26
$T_{1\text{-year}}$								
Relative amplitude, %	−30 ± 2	−27 ± 2	−20 ± 2	−23 ± 2	−33 ± 2	−21 ± 3	−22 ± 2	−20 ± 2
SD ±	9	10	9	7	10	13	7	8
CV, %	30	37	45	30	30	62	32	40
Peak latency, ms	255 ± 22	255 ± 15	291 ± 21	250 ± 21	341 ± 24	311 ± 19	361 ± 18	281 ± 22
Rebound								
T_0								
Relative amplitude, %	47 ± 8	37 ± 6	34 ± 4	30 ± 4	41 ± 7	36 ± 6	29 ± 4	27 ± 4
SD ±	35	29	20	19	31	28	17	17
CV, %	74	78	59	63	76	78	59	63
Peak latency, ms	729 ± 38	785 ± 57	703 ± 38	750 ± 47	893 ± 56	891 ± 58	845 ± 42	792 ± 37
$T_{1\text{-month}}$								
Relative amplitude, %	59 ± 16	50 ± 17	45 ± 9	46 ± 8	53 ± 10	53 ± 14	41 ± 7	35 ± 8
SD ±	45	48	24	22	30	39	19	23
CV, %	76	96	53	48	57	74	46	66
Peak latency, ms	765 ± 47	690 ± 85	724 ± 81	618 ± 66	866 ± 97	855 ± 91	813 ± 71	739 ± 60
$T_{1\text{-year}}$								
Relative amplitude, %	54 ± 8	40 ± 8	34 ± 5	33 ± 5	43 ± 7	37 ± 6	35 ± 4	30 ± 4
SD ±	35	34	20	24	32	27	17	18
CV, %	65	85	59	73	74	73	49	60
Peak latency, ms	711 ± 38	854 ± 82	722 ± 43	719 ± 57	889 ± 47	900 ± 68	897 ± 64	849 ± 46

Values (mean ± SE) are presented for contralateral responses to stimulated hand (LH, left hand; RH, right hand) for both tactile and proprioceptive stimulation. In addition, standard deviation (SD) and coefficient of variation (CV) are shown for the suppression and rebound strengths. The number of subjects is n (T_0) = 21, n ($T_{1\text{-month}}$) = 8, n ($T_{1\text{-year}}$) = 19. EEG, electroencephalography; MEG, magnetoencephalography; T_0, baseline; $T_{1\text{-month}}$, follow-up after 1 month; $T_{1\text{-year}}$, follow-up after 1 year.

TSEs in the T_0 and $T_{1\text{-month}}$ measurements. The relative peak strengths of suppression and rebound (seen in Table 1) did not differ significantly (P = 1.0) between the T_0 and $T_{1\text{-month}}$ measurements.

Intersession correlations. The beta suppression and rebound relative peak strengths between T_0 and $T_{1\text{-month}}$ measurements correlated strongly in MEG, but correlations were weaker in EEG. The ICC and Spearman's correlation coefficient values between T_0 and $T_{1\text{-month}}$ measurements are shown in Table 2.

Reproducibility of Baseline Beta Power

Baseline beta rhythm power, and Spearman's correlation and ICC coefficients for tactile and proprioceptive stimulation in MEG and EEG are shown in Table 3. Baseline beta power between T_0 and $T_{1\text{-month}}$ or T_0 and $T_{1\text{-year}}$ measurements did not show significant differences.

ICC coefficients were good or excellent between T_0 and $T_{1\text{-month}}$ (0.76–0.99) and T_0 and $T_{1\text{-year}}$ (0.72–0.95) measurements, and corresponding Spearman's correlations coefficients were 0.57–0.99 (T_0 vs. $T_{1\text{-month}}$) and 0.57–0.96 (T_0 vs. $T_{1\text{-year}}$).

Interindividual Variation of Beta Suppression and Rebound

Interindividual variation (coefficient of variation) for the relative strength of beta suppression was 30%–67% and for rebound was 46%–96% at T_0, $T_{1\text{-month}}$, and $T_{1\text{-year}}$. The coefficient of variation (in %) are shown in Table 1.

DISCUSSION

These novel results indicate that the beta rhythm modulation, i.e., suppression and rebound are highly reproducible over a long 1-year follow-up period. This information is essential for the usability of these biomarkers in longitudinal follow-up experiments. In addition, the absolute baseline beta power remained at stable level throughout the follow-up period. We used fixed and well repetitive tactile and proprioceptive stimuli to modulate the beta rhythm. Hence, the effects of instabilities, typical for active volitional movements, were eliminated and did not affect the assessment of reproducibility. Our study proves that the reproducibility of beta suppression and rebound within 1 year is good or

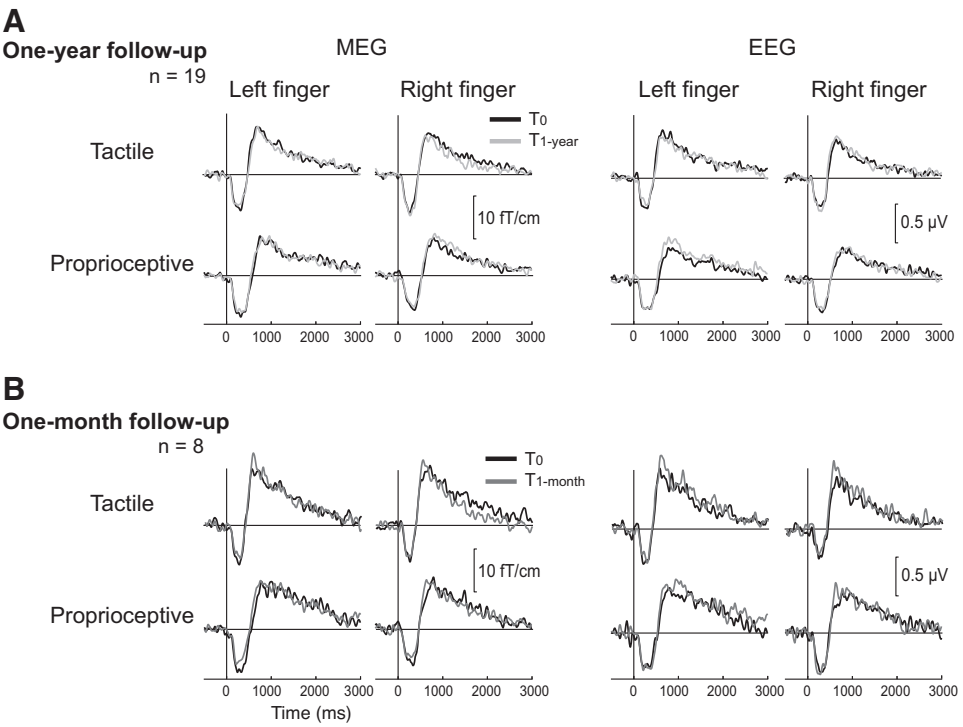

Figure 3. Grand averaged beta rhythm modulation to tactile and proprioceptive stimuli in the baseline and follow-up measurements. One-year ($T_{1\text{-year}}$, n = 19) (*A*) and 1-month ($T_{1\text{-month}}$, n = 8) (*B*) follow-up measurements are compared with the baseline (T_0) measurement, not showing significant differences between the measurements. Temporal spectral evolution (TSE) curves are showing the peak modulation of the most representative magnetoencephalography (MEG) and electroencephalography (EEG) channels over the sensorimotor cortex contralateral to the stimulated hand. Trigger onsets are shown as vertical lines at zero time; *n*, Number of subjects.

excellent both when using MEG or EEG, and therefore, the beta rebound can be reliably used as a biomarker to reflect the functional state of the sensorimotor cortex in follow-up studies.

Reproducibility of Beta Rhythm Modulation

In the current study, the reproducibility of beta suppression and rebound were verified to be good or excellent. Previous studies have reported that the beta rhythm modulation to active movement to be well reproducible within days or weeks in EEG (34, 46).

Beta suppression versus rebound.

The beta suppression is mainly thought to reflect the excitation of the SMI cortex to sensory input, whereas the rebound appears later, lasts longer, and is regulated by more complex inhibitory interneuron networks, and is thus more sensitive to alterations in the stimulus or environment. The beta suppression and rebound are generated in slightly different locations in the SMI cortex, with the rebound more anteriorly in the primary motor cortex (MI) (16, 47, 48). The rebound appears to be stronger in the contralateral hemisphere with respect to stimulus, whereas the suppression is similarly strong in both hemispheres (49). Due to these spatiotemporal differences in beta suppression and rebound, they are thought to reflect distinct functional roles in the sensorimotor cortical processing. Consequently, the beta rebound has been shown to be altered in different neurological conditions, such as stroke and schizophrenia, whereas the suppression has shown to remain relatively stable in these conditions and during follow-up (11, 32, 33). It may be that the suppression is more like all-or-nothing type of response, whereas the rebound is more prone to changes in the functional state of the sensorimotor cortex.

Active movement versus tactile and proprioceptive stimulation.

Although beta rhythm modulation has been reported to be reproducible for well-controlled active movement (34, 46), active movement-induced beta rebound is susceptible for various factors, such as speed and intensity of movement (48, 50, 51). Movement preparation has been seen to induce the beta rhythm suppression before movement onset (1, 52), and even motor imaging has been shown to cause beta rhythm modulation (4), which can hamper the evaluation of its reproducibility. In patient studies, in particular, slight changes in the performance of the active movement may affect the assessment of the reproducibility of beta modulation and thus interfere in the interpretation of changes in sensorimotor cortex function. Proprioceptive and tactile stimulation are easy to standardize and remain the same throughout the measurement, which is especially important in clinical studies that are otherwise more prone to subject-related disturbances. Taken together, especially in patient studies, tactile or proprioceptive stimulation should preferably be used to study longitudinal changes in sensorimotor cortex function, since it is advisable to keep the measurement settings as stable as possible.

1-month versus 1-year.

The reproducibility of beta modulation has earlier been studied within few weeks (34), and there is no certainty about its reproducibility in longer term. We examined the reproducibility of beta rhythm modulation within 1-year period, to ensure its feasibility for long-term follow-up studies. This is

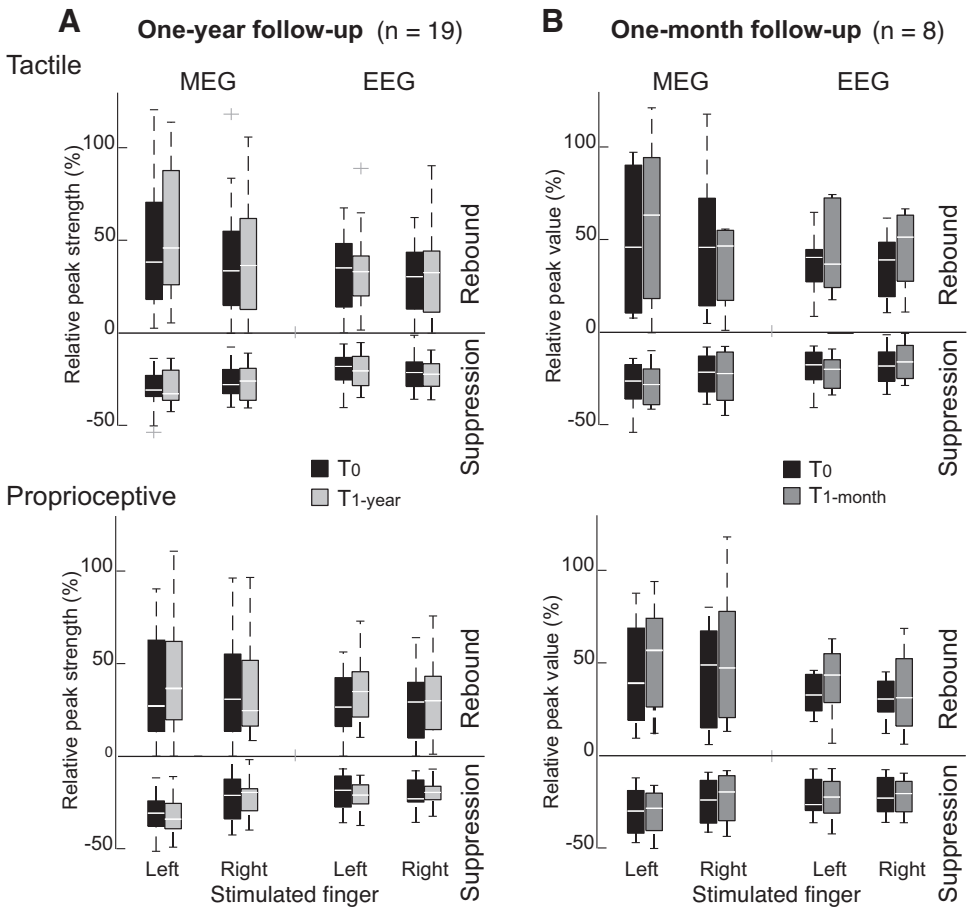

Figure 4. Peak strength of beta rhythm suppression and rebound to tactile and proprioceptive stimuli relative to baseline value for 1-year (*A*) and 1-month (*B*) follow-up measurement. Fifty percent of strength values are included in the box, horizontal lines indicate median value, and whiskers indicate variability outside the upper and lower quartiles. Outlier values are shown as crosses. EEG, electroencephalography; MEG, magnetoencephalography; *n*, number of subjects.

especially important, since the beta rhythm rebound has been proposed to be a biomarker reflecting functional recovery of the SMI cortex after acute stroke, whereas no clear association between suppression and motor recovery has been found (11, 32, 33). The beta power and the strength of beta modulation have been shown to increase in relation to aging (6, 47). However, such changes seem not to occur within a 1-year follow-up period, at least in relatively young adult participants. In older individuals, the aging effect may be more significant, and need to be clarified in future studies. Nevertheless, the present results encourage the use of beta rebound/modulation to evaluate the effectiveness of rehabilitation and drug interventions in short- or long-term follow-up studies. In addition, in well-recovering patients with stroke, the rebound in the affected hemisphere recovered to the level of the unaffected hemisphere within 1 year, although it was diminished in the acute phase and at 1 month (53).

Interindividual and intersession variations of beta suppression and rebound.

Beta rhythm suppression and rebound typically show high interindividual variation and are weak and even undetectable in some individuals. The higher interindividual variation likely arises from individual differences in the functional anatomy of the sensorimotor strip. For example, the sensorimotor rhythm generator may be located more on the gyral or fissural cortex affecting the depth and orientation of the strength of the source detected with MEG outside the skull (54). However, the beta suppression has proved to be more stable than the rebound, which is more sensitive to, for example, changes in stimulus properties, such as speed and intensity of movement. In addition, the state of the subject's alertness may also effect on the strength of beta rhythm modulation. For most of our participants, the beta modulation remained stable at individual level during the 1-year follow-up (on average suppression $< 9\%$ and rebound $< 26\%$ change), although some participants showed a greater intersession variability (suppression 0.1%–30% and rebound 0%–98%). It is noteworthy to mention that the interindividual variation of beta modulations were ~30%–62%, but the intersession variation was on average less than <26%. This further indicates that beta modulations are reproducible at group level, but in some individuals the variability can be substantial. Therefore, it is important to standardize the recording design as well as possible, e.g., to pay attention to the homogeneity of the stimuli and the state of the participants alertness during the MEG/EEG registration.

MEG versus EEG.

Our study showed high or excellent reproducibility both for MEG and EEG, but ICC values appeared to be higher for MEG than EEG. This is likely to be due to MEG's better sensitivity to detect beta rhythm modulation. However, the relative suppression and rebound strengths correlated well

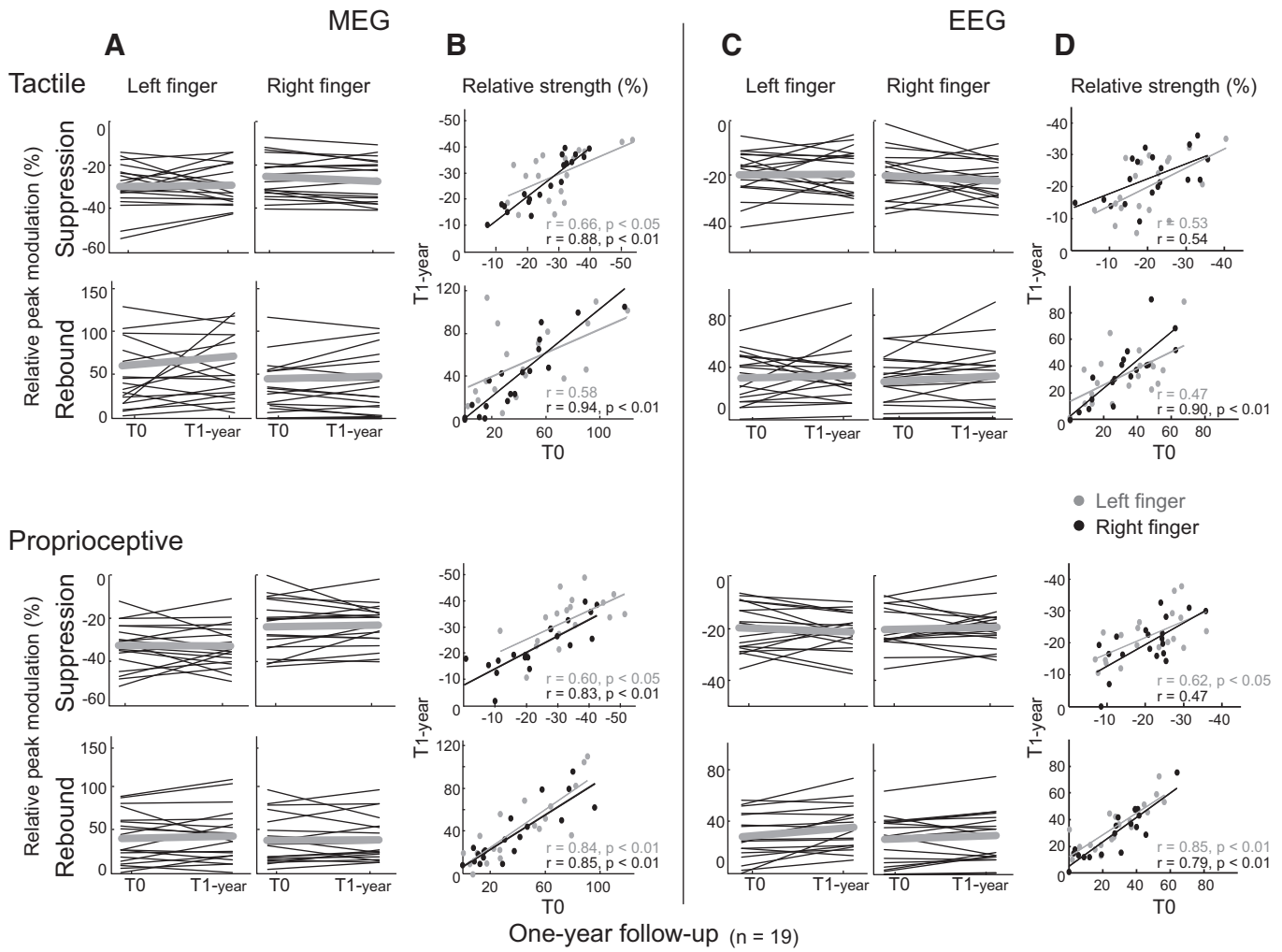

Figure 5. Individual subjects' beta suppression and rebound strengths in the baseline (T_0) and 1-year follow-up measurements (n = 19) to tactile and proprioceptive stimulations in magnetoencephalography (MEG) and electroencephalography (EEG). Relative peak modulations for each subject in the baseline (T_0) and 1-year follow-up ($T_{1\text{-year}}$) measurements for left and right hand stimuli for MEG (*A*) and EEG (*C*). Thin black lines represent direction of change for each subject separately, and gray lines the group-mean changes. Scatterplots and Spearman's correlation coefficients for the relative peak modulation strengths between the T_0 and $T_{1\text{-year}}$ measurements for MEG (*B*) and EEG (*D*). The gray color represents left and black color right hand stimulation.

between MEG and EEG measurements, and therefore both methods are valid for measuring beta modulation (5). Since mainly EEG has been adopted as a standard method in clinical trials, it is important that a neurophysiological biomarker can be reliably and reproducibly detected with it. The present study indicated the feasibility of both MEG- and EEG-based detection of the beta rhythm modulation and utilization in long-term follow-up studies.

Factors Affecting the Baseline or Induced Beta Power

In healthy individuals, the Rolandic beta power at rest has been shown to be highly reproducible both when assessed with MEG and EEG (34, 55, 56). Typically, the beta suppression and rebound are computed relative (in percentage) to the baseline beta power. For this reason, alterations in baseline beta power during a study may also affect induced beta suppression and rebound strengths (18, 57, 58). There are several factors (major ones are discussed in the following sections) that may alter the baseline level of the beta rhythm power, and hence should be taken into account when using baseline normalized modulation of beta suppression and rebound. However, previous studies have shown that baseline beta power remain the same during stroke recovery (59, 60), although the beta modulation amplitudes show prominent changes during the recovery period (11). In other words, the beta rhythm resting power and induced modulation strength appear to be distinct phenomena likely reflecting different aspects in cortical sensorimotor processing.

Age.

The beta rhythm has been shown to be age dependent. In children, the beta power has shown to be reduced than in adults (61). Concomitantly, several studies have shown that in elderly subjects the beta power at rest is increased than in younger subjects, leading to an increase of beta suppression (6, 47, 57, 62, 63), with the exception of Alzheimer's disease, where the resting-state beta power has been shown to

Table 2. *Intersession correlations of the beta rhythm suppression and rebound relative strengths for both tactile and proprioceptive stimulation in MEG and EEG*

	MEG				EEG			
	Left Hand		Right Hand		Left Hand		Right Hand	
	ICC	*r*	ICC	*r*	ICC	*r*	ICC	*r*
Tactile stimulus								
Suppression								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.75	0.66*	0.96	0.88**	0.73	0.53	0.72	0.54
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.84	0.74	0.96	0.91*	0.87	0.71	0.46	0.50
Rebound								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.70	0.58	0.95	0.94**	0.75	0.47	0.90	0.90**
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.91	0.74	0.95	0.91*	0.74	0.71	0.82	0.83
Proprioceptive stimulus								
Suppression								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.76	0.60*	0.88	0.83**	0.76	0.62*	0.80	0.47
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.88	0.79	0.96	0.86*	0.79	0.76	0.87	0.74
Rebound								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.92	0.84**	0.93	0.85**	0.87	0.85**	0.93	0.79**
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.90	0.81	0.93	0.95**	0.75	0.60	0.83	0.95**

Intraclass (ICC) and Spearman's (r) correlation coefficient values are presented for contralateral responses to stimulated hand. EEG, electroencephalography; MEG, magnetoencephalography; T_0, baseline; $T_{1\text{-month}}$, follow-up after 1 month; $T_{1\text{-year}}$, follow-up after 1 year. *$P < 0.05$; **$P < 0.01$.

decrease (64). The frequency of the beta rhythm has also been shown to be lower with increasing age (63).

Circadian rhythm.

The circadian rhythm is known to affect the level of the beta rhythm power, being lower in the morning and increasing toward the afternoon (46, 65). Also the strength of beta suppression has been shown to increase toward the afternoon, but no such effect has been observed for the beta rebound (46).

Drugs.

Drugs that affect the GABAergic neurotransmitter system have been observed to alter the intensity of the beta rhythm. Benzodiazepine, a nonselective $GABA_A$ agonist elevates the beta rhythm power and increases the strength of beta suppression (19, 21, 66, 67). In contrast, tiagabine (GABA reuptake transporter, which affects both $GABA_A$ and $GABA_B$ subunits) has been shown to increase the beta power and amplitude of beta suppression, but decrease the amplitude of beta rebound (18).

Alertness and attention.

Mental fatigue caused by long-lasting attentive task and overload has been shown to enhance the beta power (68), whereas reduced alertness, for example, due to sleepiness decreases the beta power and the amplitude of beta suppression and rebound (43). Enhanced vigilance and active

Table 3. *Baseline beta power (means ± SE) and intraclass (ICC) and Spearman's (r) correlation coefficient values on the sensorimotor cortex in three follow-up MEG/EEG measurements for contralateral responses to stimulated hand*

Tactile Stimulation					
MEG, fT/cm	**Left hand**	**Right hand**	**EEG, μV**	**Left hand**	**Right hand**
T_0	36.2 ± 3	42.0 ± 4		2.3 ± 0.2	2.4 ± 0.2
$T_{1\text{-month}}$	33.3 ± 3	41.8 ± 5		2.4 ± 0.4	2.3 ± 0.4
$T_{1\text{-year}}$	35.5 ± 4	43.2 ± 4		2.3 ± 0.2	2.3 ± 0.2
ICC					
T_0 vs. $T_{1\text{-year}}$	0.87	0.81		0.95	0.91
T_0 vs. $T_{1\text{-month}}$	0.84	0.86		0.95	0.96
Spearman's (r)					
T_0 vs. $T_{1\text{-year}}$	0.80**	0.75**		0.96**	0.88**
T_0 vs. $T_{1\text{-month}}$	0.81*	0.91**		0.98**	0.99**
Proprioceptive Stimulation					
MEG, fT/cm	**Left hand**	**Right hand**	**EEG, μV**	**Left hand**	**Right hand**
T_0	32.4 ± 3	39.1 ± 4		2.4 ± 0.2	2.3 ± 0.2
$T_{1\text{-month}}$	31.0 ± 4	37.6 ± 5		2.4 ± 0.5	2.6 ± 0.5
$T_{1\text{-year}}$	33.2 ± 4	41.1 ± 4		2.4 ± 0.2	2.3 ± 0.2
ICC					
T_0 vs. $T_{1\text{-year}}$	0.72	0.91		0.94	0.90
T_0 vs. $T_{1\text{-month}}$	0.76	0.92		0.99	0.95
Spearman's (r)					
T_0 vs. $T_{1\text{-year}}$	0.57*	0.85**		0.93**	0.87**
T_0 vs. $T_{1\text{-month}}$	0.57	0.79*		0.96**	0.83*

EEG, electroencephalography; MEG, magnetoencephalography. *$P < 0.05$; **$P < 0.01$.

attention to stimuli have also been shown to increase the beta power (69, 70), and either to increase (70, 71) or decrease (72) the intensity of beta suppression and rebound. In addition, cortical proprioceptive processing is altered when attention is directed to the proprioceptive stimuli, increasing the sustained-evoked field amplitude but reducing the beta power (73).

In the present study, all these confounding factors were strived to standardize as accurately as possible; measurements were taken at the same time of day, age distribution of the subjects was even, the subjects had no CNS medication, and they were instructed to keep good vigilance and not to pay attention to the stimuli during the recordings.

Conclusions

Our study demonstrates that the beta rhythm suppression and rebound to tactile and proprioceptive stimulation are reproducible both in MEG and EEG recordings within a 1-year period. This finding suggests that the beta modulation is a suitable tool for longitudinal studies to monitor changes in the level of sensorimotor cortex activation and inhibition. Such a need has arisen, for example, in evaluation of the effectiveness of rehabilitation and drug intervention in neurological patients. Our results encourage a wider use of beta rhythm modulation, especially the beta rebound, as a biomarker to study and follow-up the function of sensorimotor cortex.

SUPPLEMENTAL DATA

Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.17032178.v1.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

M.I., K.L., and H.P. conceived and designed research; M.I. performed experiments; M.I. analyzed data; M.I., H.P., and K.L. interpreted results of experiments; M.I. prepared figures; M.I. drafted manuscript; M.I., K.L., V.J., N.F., and H.P. edited and revised manuscript; M.I., K.L., V.J., N.F., and H.P. approved final version of manuscript.

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