

Dissociation between Neuronal Activity in Sensorimotor Cortex and Hand Movement Revealed as a Function of Movement Rate

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It is often assumed that similar behavior is generated by the same brain activity. However, this does not take into account the brain state or recent behavioral history and movement initiation or continuation may not be similarly generated in the brain. To study whether similar movements are generated by the same brain activity, we measured neuronal population activity during repeated movements. Three human subjects performed a motor repetition task in which they moved their hand at four different rates (0.3, 0.5, 1, and 2 Hz). From high-resolution electrocorticography arrays implanted on motor and sensory cortex, high-frequency power (65–95 Hz) was extracted as a measure of neuronal population activity. During the two faster movement rates, high-frequency power was significantly suppressed, whereas movement parameters remained highly similar. This suppression was nonlinear: after the initial movement, neuronal population activity was reduced most strongly, and the data fit a model in which a fast decline rapidly converged to saturation. The amplitude of the beta-band suppression did not change with different rates. However, at the faster rates, beta power did not return to baseline between movements but remained suppressed. We take these findings to indicate that the extended beta suppression at the faster rates, which may suggest a release of inhibition in motor cortex, facilitates movement initiation. These results show that the relationship between behavior and neuronal activity is not consistent: recent movement influences the state of motor cortex and facilitates next movements by reducing the required level of neuronal activity.

Introduction

In daily life, we often make series of similar movements, such as knocking on a door, walking, and clapping our hands, but the exact same movements can also be made once. It is often assumed that one action results from a specific pattern of neuronal activity. In motor cortex, this would assume that similar, repeated movements are induced by the same amount and pattern of motor cortex activity. However, behavioral and functional imaging studies have discussed whether a single movement is generated in the same way when it is performed in a series of repetitions (Miall and Ivry, 2004; Schaal et al., 2004; Levy-Tzedek et al., 2011). Specific problems with movement initiation or perseveration in neurological disorders such as Parkinson's disease suggest that,

during repeated movements, not all movements are similarly generated (Ebersbach et al., 1994; Ridley, 1994; Praamstra et al., 1998; Redgrave et al., 2010). The assumption of a one-to-one correspondence between action and motor cortex activity can therefore be questioned.

The beta rhythm decreases during motor tasks (Jasper and Andrews, 1938; Pfurtscheller, 1981), and EEG research has shown that beta rhythm activity does not return to baseline between fast movements but remains suppressed (Toma et al., 2002). Increased amplitude of the sensorimotor beta rhythm is related to decreased corticospinal excitability and difficulty to induce hand movements by motor cortex stimulation (Hummel et al., 2002). Also, increased beta power is related to successfully stopping unwanted actions (Swann et al., 2009). This suggests that, during increased beta power, motor cortex is inhibited. These studies may thus indicate that, when beta power is suppressed during fast, repetitive action, the motor cortex is continuously released from inhibition. Movements have also been linked to transient increases in high-frequency power of >60 Hz (Crone et al., 1998; Miller et al., 2007) associated with local processing in motor cortex. Whether the release from inhibition during repeated movement is also linked to a different level of the actual local neuronal activity that is associated with a movement is yet unknown.

We recorded brain signals from high-resolution implanted electrode grids in epilepsy patients [electrocorticography (ECoG)] from motor and somatosensory cortex and

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Table 1. Behavioral results

Subject	Reaction times [mean \pm SD (ms)] One movement	Number of movements			
		0.3 Hz (3 cues)	0.5 Hz (4 cues)	1 Hz (7 cues)	2 Hz (13 cues)
1	404 \pm 77	3	4	7.9	13.5
2	577 \pm 73	2.9	3.9	4.8	11.2
3	445 \pm 77	3	4	7	9.2

Reaction times during the first task in which patients made one hand movement. For the repetition tasks, the average number of hand movements for each trial is shown. Note that patients started to miss cues or make too many movements (holding their own pace) with movement rates of 1 and 2 Hz.

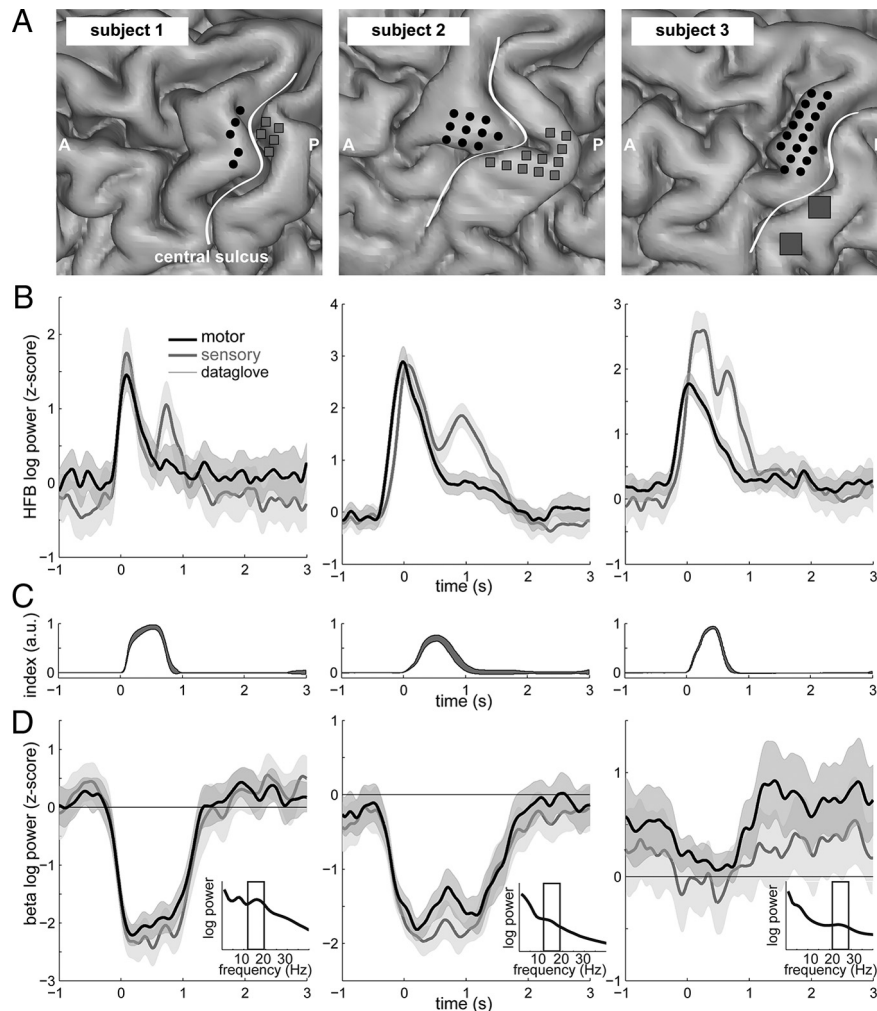


Figure 1. Responses in HFB and beta power on motor cortex and sensory cortex. **A**, The distribution of electrodes on motor and sensory cortex (A, anterior; P, posterior). Subject 3 did not have coverage of high-resolution electrodes on sensory cortex, and larger electrodes from the regular grid were selected. **B**, The HFB response during movement onset at 0 ms averaged for electrodes on motor cortex (black) and sensory cortex (gray); light gray areas indicate ± 3 SE. **C**, The index finger movement from the data glove. **D**, Beta response after movement onset. The small inset shows the power spectra during the task, which were used to define the indicated beta peak (12–18 Hz for subjects 1 and 2 and 22–28 Hz for subject 3). a.u., Arbitrary units.

calculated beta power (12–28 Hz) and high-frequency band activity (HFB; 65–95 Hz). Broadband high-frequency activity is associated with neuronal population firing rate (Manning et al., 2009; Miller et al., 2009a; Ray and Maunsell, 2011) and correlates well with the fMRI signal (Hermes et al., 2011). We hypothesize that, during fast, repeated movements, when the motor cortex is presumably in a continuously disinhibited state, the amount of high-frequency activity related to repeated movements will change. Three subjects made movements at four rates (0.3, 0.5, 1, and 2 Hz). During the fastest rates, beta power remained sup-

pressed between movements, and high-frequency power in motor cortex was suppressed after the initial movement. These data suggest that the correspondence between neuronal activity in sensorimotor cortex and hand movement changes with movement rate.

Materials and Methods

Subjects and procedure. Three right-handed patients (one female, two males; mean age, 27 years; range, 19–43 years) who were scheduled for the implantation of ECoG arrays for the clinical purpose of epilepsy monitoring gave informed consent to participate in this study. These patients had normal hand function, and the pathological region did not extend to sensorimotor cortex. The study was approved by the ethical committee of the University Medical Center Utrecht, in accordance with the Declaration of Helsinki 2008. On average, 125 electrodes were implanted, of which 32 in each subject were high-resolution mini-grids of 8×4 electrodes located on left sensorimotor cortex. Mini-grids had an inter-electrode spacing of 3.3 mm center to center and a spherical measurement surface of 1 mm diameter. To localize the electrodes with high accuracy, we used the method presented previously (Hermes et al., 2010), in which electrodes were localized from a high-resolution computed tomography scan (Philips Tomoscan SR7000) and projected to the cortical surface rendering generated from a preoperative MRI scan of each subject (Philips 3T Achieva).

Experimental paradigm. The experiment consisted of two parts, the first to map ECoG responses during a single movement (see Fig. 1) and the second to test repeated movement effects (see Fig. 2). The single-movement part started and ended with a 30 s rest period during which a red circle was presented on a computer screen and subjects relaxed with their right hand open, palm facing up. After the first 30 s rest, the circle turned green 54 times for 500 ms at intertrial intervals varying from 3 to 18 s, with an average of 8 s. When the circle turned green, the subjects closed and opened their right hand.

The repeated-movement part consisted of four movement repetition tasks in which subjects moved at four different rates (0.33, 0.5, 1, and 2 Hz; see Fig. 2A). In the first task, each trial consisted of three visual cues (the red circle turning green similar as in the first part, for 400 ms), presented at 3 s intercue interval, instructing the subject to close and open their hand, thus resulting in 0.33 Hz movement. In the second, third, and fourth tasks, respectively, 4, 7, or 13 cues were given with 2, 1, and 0.5 s intercue interval. Each trial was followed by a rest period until a total trial duration of 19 s was reached.

Each task consisted of 13–15 trials of 19 s.

Behavioral measurement and analysis. Finger movements were measured using a five degrees of freedom data glove (5DT Inc.). The data-glove data were recorded simultaneously with the ECoG data using a custom workspace extension in Presentation (Neurobehavioral Systems). The onset of each movement was visually detected; there were drifts in the data-glove data, and assigning a simple threshold to detect movement onsets was not sufficiently accurate. Therefore, movement onsets were visually detected as the first deviation from the pre-movement baseline for optimal accuracy. To extract a measure for whole-hand

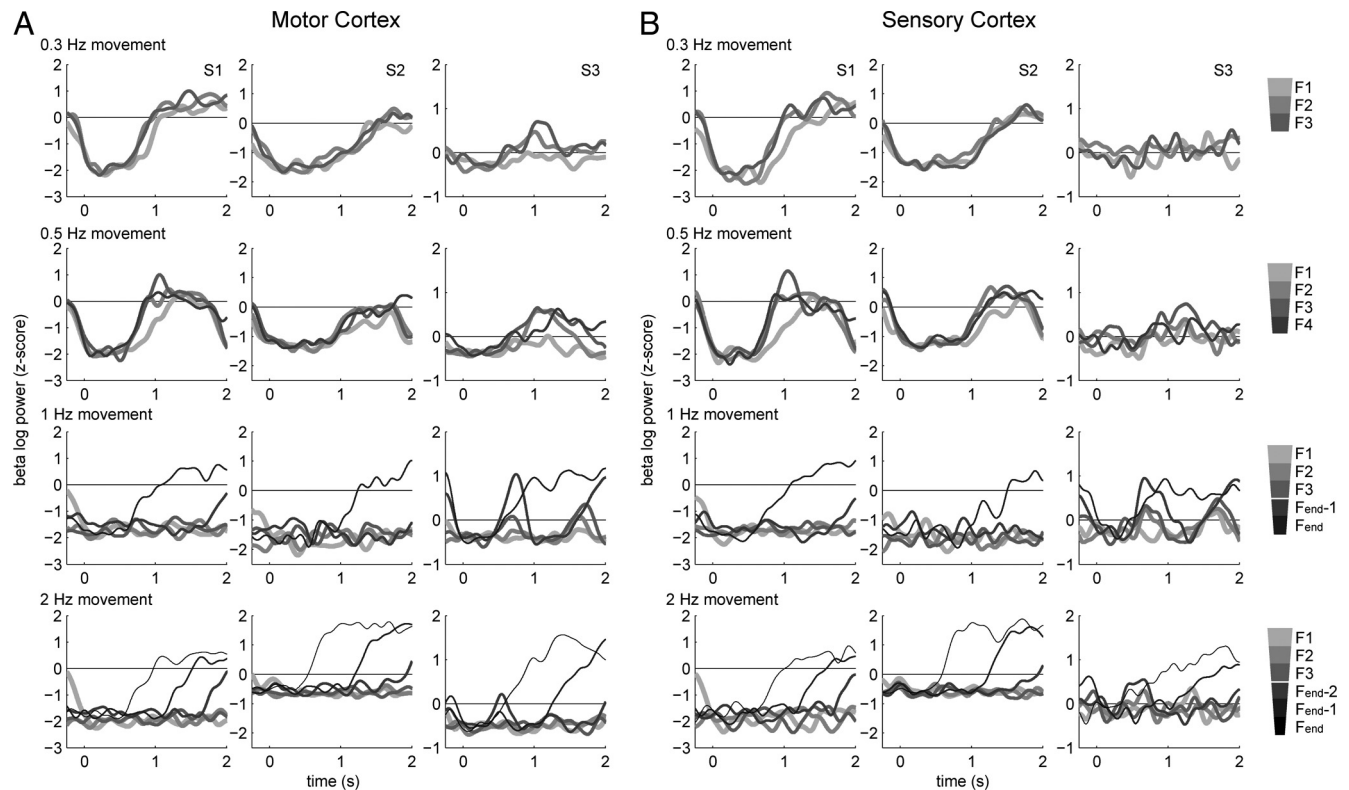


Figure 3. Beta responses on motor cortex and sensory cortex. **A**, Beta responses on motor cortex as a function of time after movement onset for subjects 1–3 (S1–S3) from left to right and during the different movement rates from top to bottom. Note that, at the faster rates with intercue interval of <2 s, the beta responses to the subsequent stimuli are also visible. The grayscale indicates the hand flexion number (F) as in Figure 2. **B**, Beta responses on sensory cortex for subjects 1–3 from left to right and during the different movement rates from top to bottom.

Behavioral data during movement repetition

Hand movement was measured with a data glove during the movement repetition task. Table 1 shows that, during 0.33 and 0.5 Hz movement, the subjects followed the cues, and when shown three or four cues, they made three and four movements on average, respectively. During the faster movements of 1 and 2 Hz, behavior changed: they sometimes moved before a cue or missed a cue. This indicates that they were moving more continuously at their own pace. As a result, when seven cues were given at 1 Hz, the three subjects made eight, five, or seven movements on average; when 13 cues were given at 2 Hz, they made 14, 11, and 9 movements. Using cues as onsets will thus blur the data, and we thus used movement onset, which is far more precise. Figure 2*A* demonstrates this effect in the data-glove responses for subject 3 during the four different tasks.

Next, we tested whether subsequent movements within a task differed in movement amplitude or speed (onset to maximum flexion). Figure 2*B* shows the average hand movement for the three subjects for flexion numbers 1, 2, and 3 from task 1 (0.3 Hz), flexion numbers 1, 2, 3, and 4 from task 2 (0.5 Hz), flexion numbers 1, 2, 3, and the last two flexions from task 3 (1 Hz), and flexion numbers 1, 2, 3, and the last three flexions from task 4 (2 Hz). Repeated movements look highly similar. To test for effects of repetition on movement size and speed within a task, a repeated-measures ANOVA was performed. No significant changes in movement amplitude or speed were noted that were consistent across the three subjects (Fig. 2*B* shows the results of the ANOVA for each individual subject).

Changes in the beta and HFB response with repeated movement

First, we studied the effect of movement rate on beta power. Figure 3 shows the average beta response during the movement repetition task in motor cortex and sensory cortex for all three subjects. It can be seen that, at the faster movement rates (1 and 2 Hz), the beta band activity remains continuously suppressed: power does not return to baseline after every individual movement but only after the last movement of a series.

To test whether there were any significant changes in beta amplitude with repeated movement within one task, the beta power was averaged from 0 to 300 ms after movement onset (time window chosen based on Fig. 1*D*). A repeated-measures ANOVA on beta amplitude for each task showed no significant effect of repetition on beta amplitude across the three subjects, indicating that the amplitude change was the same regardless of movement rate.

Second, we then studied the effect of movement rate on high-frequency power. High-frequency power was extracted from electrodes on motor and sensory cortex as a measure of local neuronal activity. Figure 4, *A* and *B*, shows the average HFB response in motor and sensory cortex during the different movement repetition tasks. It can be seen that, during the faster movements of 1 and 2 Hz, the first HFB response is larger than the subsequent responses. Note that this effect is most pronounced in motor cortex.

To test whether this change in HFB activity with repeated movements was significant, the HFB power was averaged from -100 to 300 ms around movement onset (time window chosen

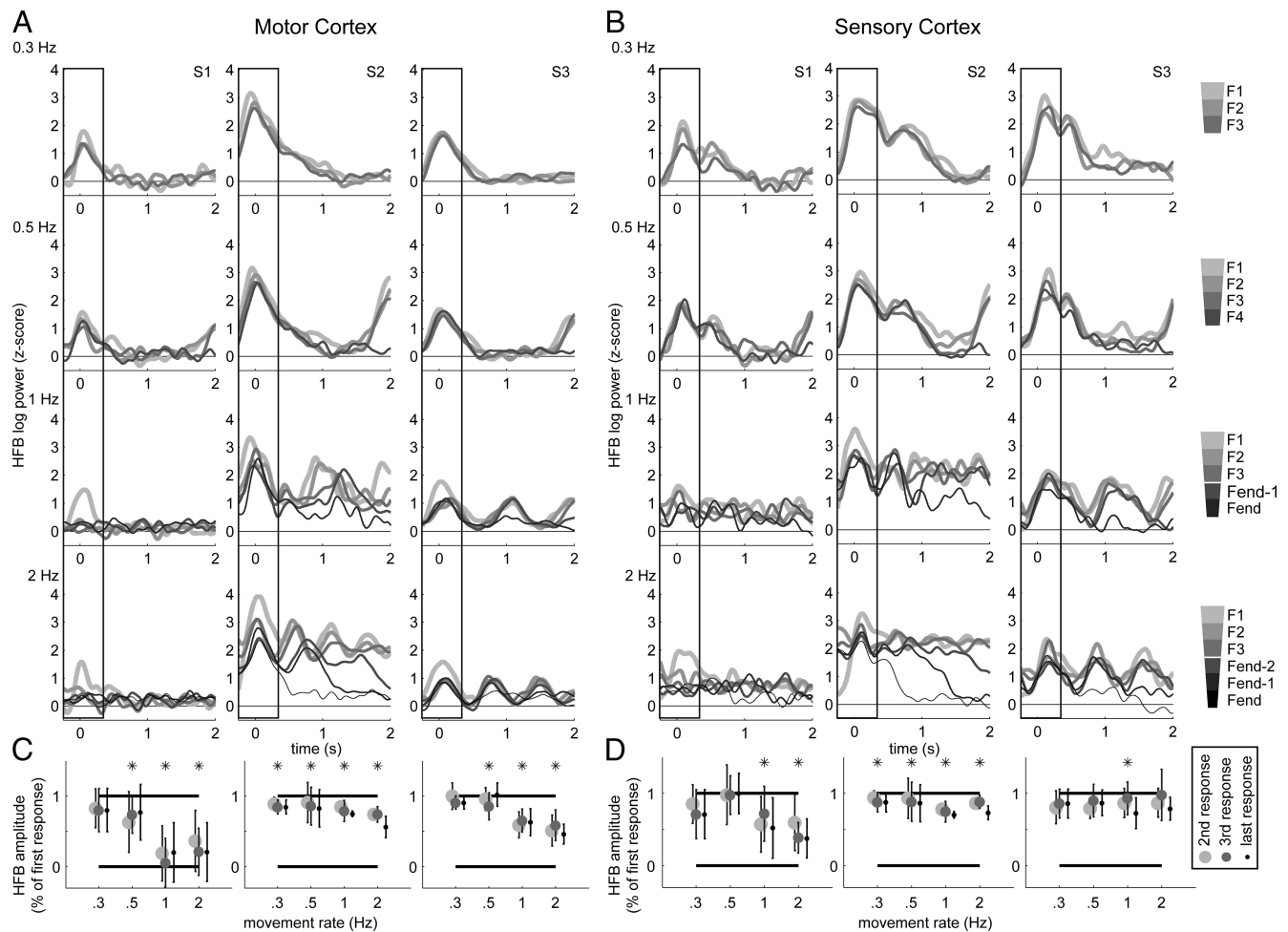


Figure 4. HFB responses on motor cortex and sensory cortex. **A**, HFB responses on motor cortex as a function of time after movement onset for subjects 1–3 (S1–S3) from left to right and during the different movement rates from top to bottom. The grayscale indicates the hand flexion number (F) as in Figure 2. The box accentuates the response related to onset of the current movement (at the faster rates with intercue interval of <2 s, the responses to the subsequent stimuli are also visible, but these are irrelevant for analysis). **B**, HFB responses on sensory cortex for subjects 1–3 from left to right and during the different movement rates from top to bottom. **C**, The relative change from the first response amplitude ~ 100 to 300 ms around movement onset during the second, third, and last responses in motor cortex during the four different repetition tasks (0.3, 0.5, 1, and 2 Hz). An * above the task denoted that flexion number had a significant effect on HFB amplitude ($p < 0.05$ by a repeated-measures ANOVA). **D**, The same results but in sensory cortex. Note that, during the faster repetition tasks, the second, third, and last responses are suppressed. Note also that this suppression is more pronounced on motor cortex compared with sensory cortex.

based on Fig. 1B). Figure 4, C and D, shows the change in HFB amplitude with respect to the size of the first response. Similarly as in Figure 3, A and B, a decrease in response size for subsequent movements can be noted, especially for the faster movement conditions of 1 and 2 Hz. As shown in Figure 4C, a repeated-measures ANOVA indicated that, in motor cortex, this decrease in HFB amplitude with subsequent movements was significant in one subject for the 0.3 Hz task and for all three subjects in the 0.5, 1, and 2 Hz tasks. In sensory cortex (Fig. 4D), a repeated-measures ANOVA indicated that the decrease in HFB amplitude with subsequent movements was significant in one subject for the 0.3 and 0.5 Hz tasks, for all three subjects in the 1 Hz task, and for two subjects in the 2 Hz task. With faster movement repetition rate, there is thus a clear decrease in HFB amplitude after the first response; in sensory cortex, this effect is similar but less pronounced.

To test whether HFB response amplitude might depend on the degree of beta suppression, we correlated the beta power -700 to -300 ms before movement onset with the HFB amplitude across trials. With the fast movement rates, there was a significant positive correlation between prestimulus beta and HFB amplitude

across all subjects in motor cortex, but this was not the case in sensory cortex. It is not surprising that there was only a significant positive correlation in the fast movement conditions, because premovement beta does not enter the suppressed regimen in the slow conditions. In general, in trials in which beta is suppressed before movement onset, there is less HFB activity related to the movement.

Is the change in the high-frequency response with repeated movement linear or nonlinear?

Next, we assessed the nature of the repetition effect by fitting a linear and a nonlinear model to the data. Figure 5 shows the HFB amplitude as a function of time. Two different models were fitted to the HFB response sizes as a function of time. The first linear model was of the form $Y_{\text{HFB}} = bt + c$, and the second nonlinear model was of the form $Y_{\text{HFB}} = a(1/t) + bt + c$, where t is the time of movement onset after the first cue, and Y is the HFB amplitude of each movement. Other nonlinear models could be fitted; this one was chosen because it converges to the linear function and has a sharp, nonlinear decrease in case a is positive, but except for its nonlinearity, we do not attempt to draw any conclusions about

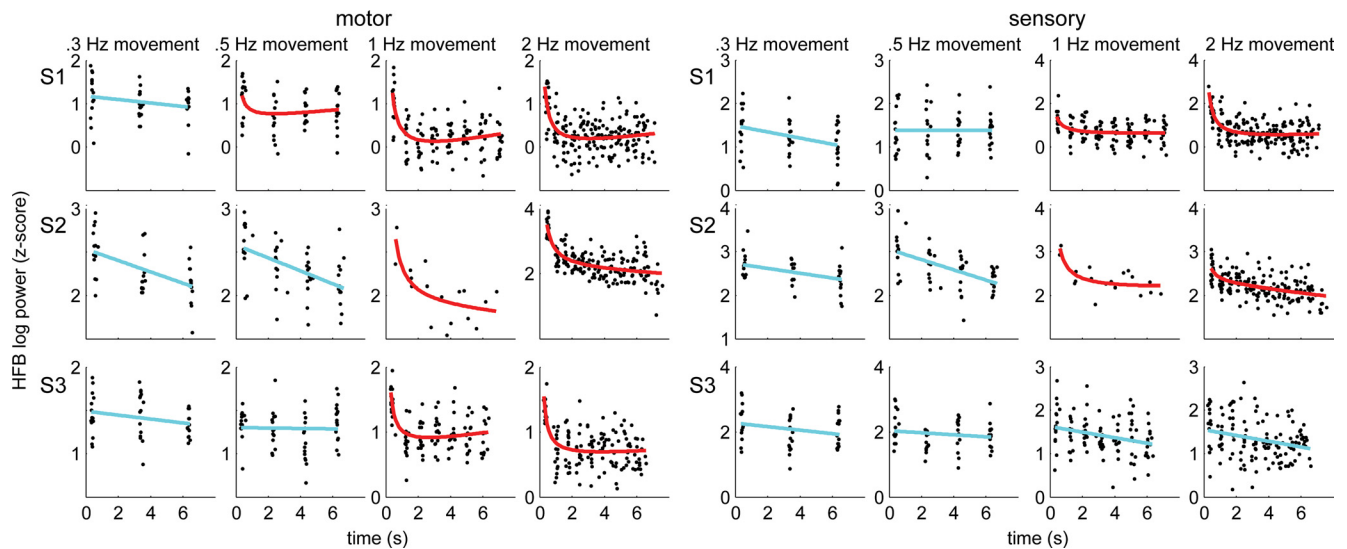


Figure 5. Fitting a linear or nonlinear model to the HFB change. The gray dots in every single plot display the HFB amplitude during one movement on the *y*-axis and the timing of that movement on the *x*-axis. Subjects (S1–S3) are shown in rows and the four different movement repetition tasks in columns; the average of the electrodes on motor cortex is shown on the left, the sensory cortex on the right. The linear model ($Y_{\text{HFB}} = bt + c$) fitted to the data is shown in the cyan line, but if the nonlinear model [$Y_{\text{HFB}} = a(1/t) + bt + c$] fitted significantly better ($p < 0.05$ by an *F* test), a red line shows the nonlinear model.

the actual shape of the nonlinear decrease. To test whether the nonlinear model explained the data better, an *F* test was performed on the difference in explained variance between the two models adjusted for the number of parameters ($\Delta R^2_{\text{adjusted}}$). In all subjects, in the faster 1 and 2 Hz movement tasks, the motor cortex HFB amplitude was better explained by a nonlinear model compared with a linear model ($p < 0.01$ for all subjects; Fig. 5). In sensory cortex, the nonlinear model explained the data during the faster 1 and 2 Hz movement tasks better than the linear model in the first two subjects ($p < 0.005$ for these two subjects). Only in one subject in motor cortex was the 0.5 Hz movement better explained by a nonlinear model ($p < 0.05$). This indicates that, in motor cortex, there is a significant, nonlinear suppression of high-frequency activity with repeated movements at higher rates that converges to a linear state.

It could potentially be argued that the more accurate fit of the linear model for the slow movements with ≤ 0.5 Hz frequency was attributable to the small number of movements (three or four) rather than the decreased repetition rate, and there were simply not enough time points recorded for saturation to occur and nonlinearity to emerge. To verify this issue, we included only the first three or four movements from the more rapid rates. Even if only the first three or four movements were used, the nonlinear model still fit the data better than the linear model for the fast movements. This emphasized that the main nonlinear effect in HFB amplitude for the rapid rates was the decrease after the first movement, and instead of using the model we chose, a step function could similarly be used.

Spatial distribution of nonlinear decrease during fast movement

The decrease in HFB response amplitude in the previous analysis was based on the averaged HFB response across electrodes on motor cortex and sensory cortex. We further explored whether this decrease was seen across a large number of individual electrodes on motor and sensory areas. The nonlinear regression model [$Y_{\text{HFB}} = a(1/t) + bt + c$] was fitted for each electrode individually, and spatial distribution of the nonlinear regression

coefficient, *a*, is shown in Figure 6. A positive regression coefficient, indicating that the HFB response shows a nonlinear decrease, can be noted for the faster tasks. Using the *F* test approach as explained above, a significant increase (Bonferroni's corrected for the number of electrodes) in the model fit was found for 0, 7, 47, and 70% of the electrodes in motor cortex after adding the nonlinear parameter for the 0.3, 0.5, 1, and 2 Hz tasks on average across the three subjects, respectively. For sensory cortex, the nonlinear model improved the fit in 0, 3, 26, and 33% of electrodes.

Discussion

In this study, neuronal population activity in sensorimotor cortex was assessed during hand movement (flexion–extension) at different rates to understand whether the link between neuronal activity and behavior is maintained with repetitive actions. We found that high-frequency (HFB) power exhibits a transient increase (response) in motor and somatosensory cortex during a movement and that this response, which reflects neuronal population activity, decreases after the initial movement at rates >1 Hz. This decrease was nonlinear: after activity related to the initial movement, activity dropped significantly for the subsequent repeated movement and then converges. In motor cortex, the nonlinear decrease in response size with faster movement rates was noted for a large percentage of electrodes and not in a small subset. Since broadband high-frequency power changes have been linked to population firing rate (Manning et al., 2009; Miller et al., 2009a; Ray and Maunsell, 2011), this suggests that, after movement initiation, fewer motor cortex neurons have to fire or firing rates decline when multiple similar movements are made at a fast rate.

Sensory cortex showed some suppression with repetition that was not as strong as in motor cortex. In sensory cortex, this suppression can potentially be explained by accumulation of presynaptic inhibition of afferent input (Seki et al., 2003), which occurs with active movements. The suppression in motor cortex activity, which we observe during fast repetitive movements, cannot however be explained by this phenomenon. During the

single-movement task, sensory responses differed from motor responses (Fig. 1). Although in motor cortex there was only one peak in the HFB response, sensory cortex showed two subsequent peaks. Cells on the postcentral gyrus are known to fire with two directions of movement (Fetz et al., 1980; Soso and Fetz, 1980), which may explain the two peaks in the sensory response. Surprisingly, our results showed that the first sensory response started before the onset of movement. Cells in sensory cortex can fire ~ 60 ms before movement onset, which is a similar time lag as shown in our results. Recent research has shown that sensory cortex may indeed be involved in motor control (Matyas et al., 2010), which may require some pre-movement activity. Whether the suppression we noted in sensory cortex can be fully explained by presynaptic inhibition or also partially by changes in the pre-movement motor control component has to be further investigated.

Although we found a significant decrease in high-frequency responses for subsequent movements at high repetition rates, we found no repetition effect for the beta-band response. However, beta-band suppression did not return to baseline at faster movement rates, in contrast with the slower movement rates. This agrees with a previous study with scalp EEG (Toma et al., 2002) and confirms that the phenomenon is present in primary sensorimotor cortex. Because previous studies reported decreased corticospinal excitability with high beta power (Hummel et al., 2002; Carroll et al., 2006), sustained suppression of beta-band activity may reflect a sustained release of inhibition. We indeed found a positive correlation between pre-movement beta and high-frequency amplitude. This correlation was apparent only during the fast movement tasks, which emphasizes that beta suppression may be a state in which inhibition is released rather than a continuum. It is possible that this release of inhibition may result in more efficient information processing, requiring less neuronal activity: ongoing beta oscillations only need to be suppressed during the first movement in the fast movement conditions, and initiation of the first movement may therefore require more activity than subsequent ones (Baker, 2007). This mechanism may explain why movements at slower rates are avoided (van der Wel et al., 2009) and fast movements are more efficiently processed.

Our results are important for the interpretation of fMRI and PET results during movement repetition. Previous fMRI and PET studies have found that increases in repetition rate are correlated with increased blood oxygen level-dependent (BOLD) activity and cerebral blood flow in motor areas, respectively, reaching a ceiling at fast repetition rates (Blinkenberg et al., 1996; Sadato et al., 1996, 1997; Turner et al., 1998; Wildgruber et al., 2001; Riecker et al., 2003). These studies generally assume that

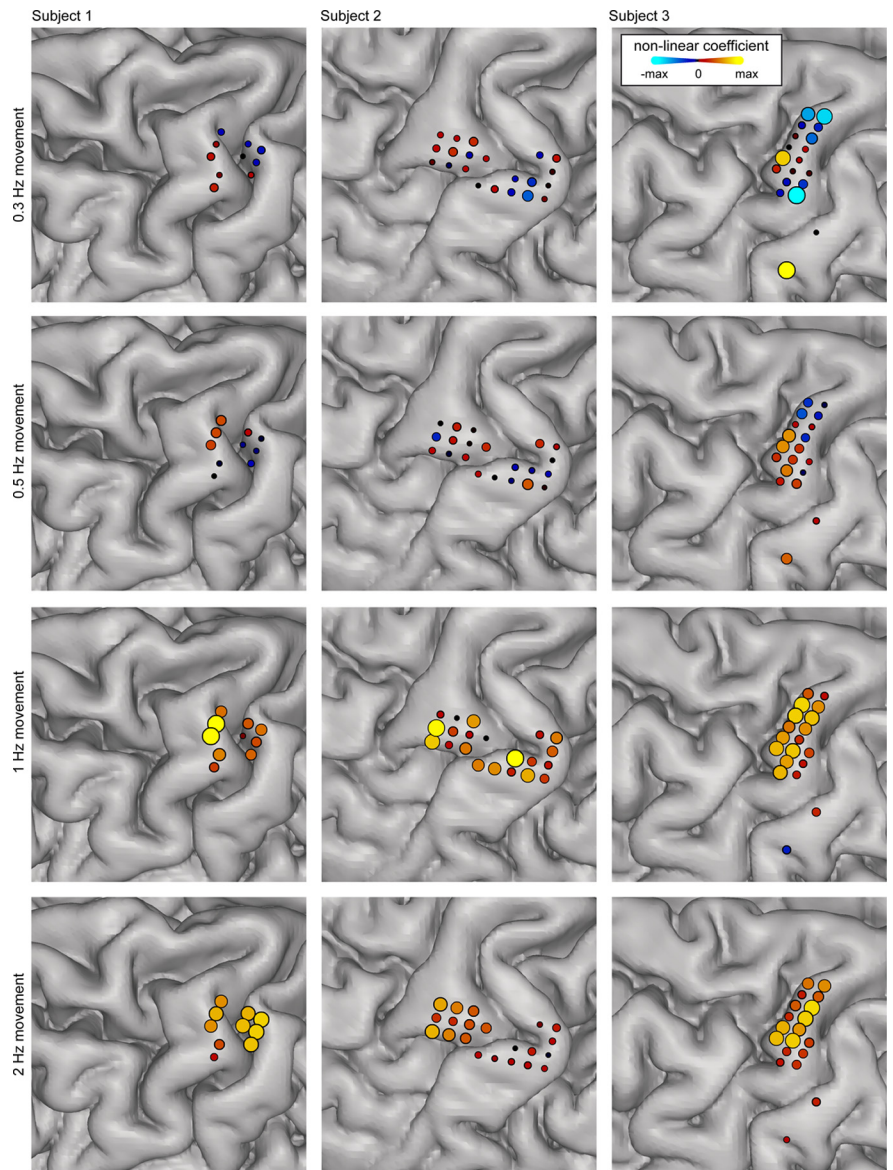


Figure 6. Spatial distribution of nonlinear coefficient. Spatial distribution of the amplitude of the nonlinear coefficient (a) from the model $V_{\text{HFB}} = a(1/t) + bt + c$. Subjects are shown in columns, and rows display different movement rates. Note that, at 1 and 2 Hz, there is an overall increase in the nonlinear parameter, indicating that responses became nonlinearly reduced across the grid.

underlying neuronal activity is the same for repeated movements and often attribute the ceiling effects to nonlinearity in the BOLD response. Similarly, the duration of movement repetition affects the fMRI signal, which has also been attributed to nonlinear effects in the BOLD response (Birn et al., 2001). The BOLD response correlates well with high-frequency activity (Logothetis et al., 2001; Niessing et al., 2005; Lachaux et al., 2007; Hermes et al., 2011). Considering our results of nonlinear effects in high-frequency activity with faster movements, it may well be that the reported nonlinearity in the BOLD signal is overestimated. Hence, the relationship between neuronal activity and the vascular response (“neurovascular coupling”) may be more linear than what has been reported.

It is important to understand the neurophysiology of repeated movements, because specific errors with movement initiation and perseveration are symptoms of several neurological disorders and in Parkinson’s disease in particular (Ebersbach et al., 1994; Ridley, 1994; Praamstra et al., 1998; Redgrave et al., 2010). We

showed that, for fast repeated movements, less primary motor cortex activity is generated after the initiation of the first movement. Also, after the first movement, there was a continuous power decrease of the beta rhythm, potentially indicating that the brain is in a different state. Interestingly, in subjects with Parkinson's disease, the suppression of the beta rhythm during movement is attenuated (Lim et al., 2006), and when deep brain stimulation alleviates the Parkinson's symptoms and normalizes the beta suppression, it is easier for these subjects to stop unwanted actions (Swann et al., 2011). Also, the onset of the beta decrease is delayed in these subjects (Magnani et al., 2002). Medication reduces this delay and also facilitates movement initiation. Parkinson's disease mainly affects subcortical structures, and beta rhythms have been related to subcortical–cortical interactions (Pfurtscheller and Lopes da Silva, 1999; Brown, 2003; Feige et al., 2005; Schnitzler et al., 2006; Jones et al., 2009). The combination of sustained beta desynchronization and a reduced high-frequency response after the initiation of repeated movements suggests a dynamic interplay between subcortical structures and motor cortex.

The suppression of high-frequency power effect could be associated with differences in hand movement. However, hand movement amplitude or speed did not show any significant differences with repetition. We were unable to obtain electromyographic measures, but because we did not notice significant differences in movement speed and subjects were not required to press against anything, it seems unlikely that force can explain this suppression effect. In addition, previous studies have not noticed any differences in electromyography between subsequent movements (Muthukumaraswamy, 2010) or movements made at different rates (Toma et al., 2002).

In conclusion, our data show that the relationship between motor actions and underlying neuronal activity is not consistent. The findings of repetition rate-dependent dynamics of neurophysiological parameters suggest that the amplitude of the HFB response in motor cortex may depend on the degree of synchronization of the beta rhythm. At slow rates, beta has time to return to baseline and a subsequent movement required a strong HFB response. At rates ≥ 1 Hz, beta power remains depressed, and subsequent movements require a smaller HFB response.

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