

Movement-related phase locking in the delta–theta frequency band



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ABSTRACT

Movements result from a complex interplay of multiple brain regions. These regions are assembled into distinct functional networks depending on the specific properties of the action. However, the nature and details of the dynamics of this complex assembly process are unknown. In this study, we sought to identify key markers of the neural processes underlying the preparation and execution of motor actions that always occur irrespective of differences in movement initiation, hence the specific neural processes and functional networks involved. To this end, EEG activity was continuously recorded from 18 right-handed healthy participants while they performed a simple motor task consisting of button presses with the left or right index finger. The movement was performed either in response to a visual cue or at a self-chosen, i.e., non-cued point in time. Despite these substantial differences in movement initiation, dynamic properties of the EEG signals common to both conditions could be identified using time–frequency and phase locking analysis of the EEG data. In both conditions, a significant phase locking effect was observed that started prior to the movement onset in the δ – θ frequency band (2–7 Hz), and that was strongest at the electrodes nearest to the contralateral motor region (M1). This phase locking effect did not have a counterpart in the corresponding power spectra (i.e., amplitudes), or in the event-related potentials. Our finding suggests that phase locking in the δ – θ frequency band is a ubiquitous movement-related signal independent of how the actual movement has been initiated. We therefore suggest that phase-locked neural oscillations in the motor cortex are a prerequisite for the preparation and execution of motor actions.

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Introduction

Oscillatory activity in brain areas associated with movement preparation and execution has thoroughly been studied (e.g., Gerloff et al., 1998a,b; Pfurtscheller and da Silva, 1999; Luu and Tucker, 2001; Neuper et al., 2006).

In particular, Baker et al. (1997, 2001) demonstrated that in monkeys performing a motor task, the activity of neural assemblies in M1 is strongly modulated during the different phases of a precision grip task, suggesting a tight relationship between synchronization dynamics and behavior. Despite this evidence in favor of an important role of synchronization for movement initiation, earlier studies using electroencephalography (EEG) mainly focused on the properties of signals in the amplitude domain (e.g., Pfurtscheller and da Silva, 1999; Neuper et al., 2006). Oscillations are, however, characterized by

their *amplitude* and *phase*. While the former represents the size (strength) of the oscillation, the latter represents its timing with regard to a reference point in time. Event-related desynchronization (ERD) and event-related synchronization (ERS) are two well-described phenomena where there are substantial changes in the power (i.e., amplitude) spectra in the α (8–12 Hz) and β (13–30 Hz) bands at the onset and the termination of the movement (e.g., Gerloff et al., 1998a,b; Pfurtscheller and da Silva, 1999; Luu and Tucker, 2001; Neuper et al., 2006). Other groups (Bartolo et al., 2014; Bartolo and Merchant, 2015; Merchant et al., 2013) also found characteristic changes of the local field potential (LFP), mainly in the beta frequency band, when studying internally driven and sensory-cued rhythmic movements in behaving monkeys. Rubino et al. (2006) and Takahashi et al. (2011) observed propagating beta waves that appear to be carriers of information in the motor cortex.

By contrast, the role of oscillatory *phase* during preparation and execution of motor actions remains to be elucidated. In the present study, we therefore focused on the properties and changes of phase locking prior to and at the onset of a movement. Specifically, we sought to identify *invariant* properties of the phase-related neural dynamics of

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movement initiation. We did so both in voluntary tapping conditions and in externally triggered ones. A voluntary movement originates internally, whereas an externally triggered one occurs in response to external stimuli, i.e., sensory input. Multiple lines of evidence have established that voluntary and externally triggered movements draw upon distinct cortical pathways whose activity converges onto a common final efferent pathway, i.e., the primary motor cortex (M1) and the corticospinal tract (CST) (Jenkins et al., 2000; Waszak et al., 2005; Hughes et al., 2011; Kriegerhoff et al., 2011). Hence, the neural dynamics that are invariant with regard to movement initiation represent a key mechanism of preparation and execution of motor actions. We hypothesized that preparation and execution of motor actions, irrespective of whether the movement is initiated internally or by an external trigger, rely on phase locking in the motor cortex prior to the actual execution, i.e. during preparation, of a particular action. Our findings could shed new light on the underlying neural dynamics.

Material and methods

Participants

Twenty-one healthy participants were recruited from the subject database of the Research Center Jülich. Data from three participants had to be excluded from further analysis due to insufficient quality of the recordings (see EEG preprocessing section). Hence, data from 18 subjects were used for the final statistics (11 women and 7 men; age range 22–35 years). All participants had normal or corrected-to-normal vision and there was no history of neurological or psychiatric diseases. None of the subjects had taken any psycho-active or psychotropic substance. The experimental protocol was approved by the Ethics Committee of the Medical Faculty, University of Cologne. All participants provided informed, written consent before the experiment. According to the selection criteria, all participants were right handed as defined by the Edinburgh Handedness Inventory (Oldfield, 1971).

Task design

Subjects were asked to perform button presses with their left or right index finger. There were two motor conditions: (i) self-initiated movements and (ii) movements upon appearance of a visual cue. Furthermore, an identical visual stimulus but without motor responses

served as control for the latter condition in order to estimate EEG activity evoked by the visual stimuli in the absence of response-related activity.

In the first condition (self-initiated tapping), subjects were allowed to choose when and with which hand to perform the button press. Apart from the fixation point that was displayed for the entire duration of the block (Fig. 1), there were no additional visual stimuli to indicate when and with which hand the button press was to be performed. The following constraints applied: (i) button presses had to be performed with an inter-trial interval of approximately 4–8 s; (ii) subjects had to roughly balance the number of left and right hand responses, and (iii) subjects had to avoid regular sequences (e.g., alternating between left and right hand).

In the second condition (visually-cued tapping), a right- or left-pointing arrow (2° wide and 1.2° high, expressed as visual angles), was presented first for 200 ms on a presentation screen with inter-stimulus intervals (ISI) of varying length ≥ 4 s. This lower bound arises from the inter-response intervals in self-initiated tapping (for details, see text below). The participant had to press the button, as soon as possible after the visual stimulus had appeared, with either the left or the right index finger, depending on the direction of the arrow.

In the vision-only condition, the same visual stimulus (i.e., a left- or right-pointing arrow) was presented as in the visually-cued tapping condition but now the participants were instructed to pay attention to the arrow, only, without pressing the button. Thus, no motor action was performed in this condition.

Prior to the experiment, participants were given instructions on how to perform the task. In order to help subjects to remember the actual condition, we used unique geometric objects, as indicated in the panels 1–3 of Fig. 1, for each condition. All of these visual objects were created using the software 'Presentation' (version 11.0, Neurobehavioral Systems, Albany, CA).

The whole experiment lasted about 70 min and was divided into 4 runs, with each run (approximately 17 min long) containing four blocks. Each of the total 16 blocks contained all three different conditions once (Fig. 1, bottom panel). Each condition was presented for 60 s after which the participant was informed about his/her performance. After this visual feedback, a white fixation point was shown for 10 s during which the baseline between two subsequent conditions was obtained. All blocks started with the self-initiated tapping condition but the other two conditions appeared in random order. The recorded inter-response

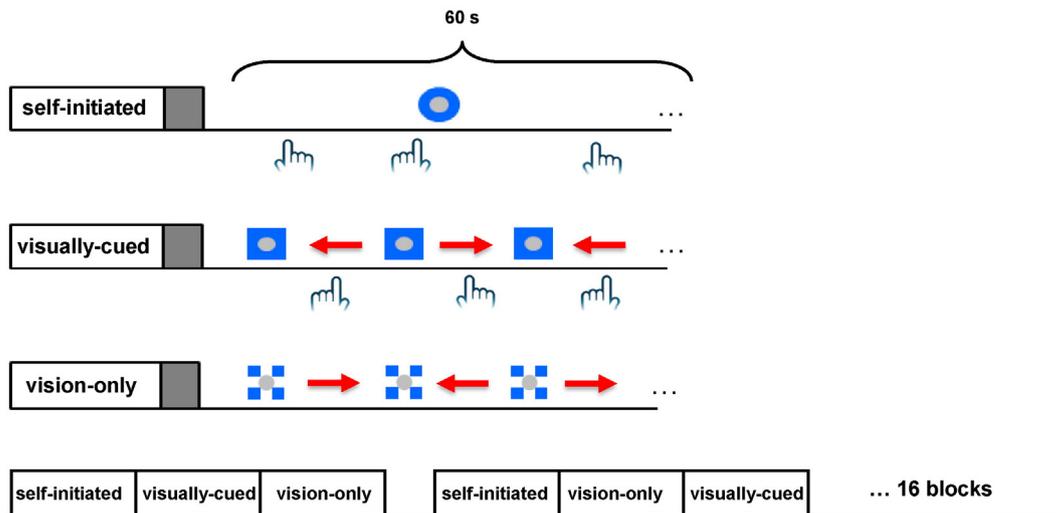


Fig. 1. Scheme of organization of the experiments. The first three lines show the experimental arrangements in the three conditions (self-initiated, visually-cued, and vision-only). Each condition is identified for the participant by a unique geometric sign (e.g., a circle in a square in the visually-cued tapping condition). The arrows in lines 2 and 3 indicate by their direction the hand (left or right) to be used. The bottom line is a schematic illustration of the temporal structure of the experiments. Each block consists of the three conditions, the first one always being the self-initiated tapping condition. The other two conditions appear in random order. See text for further details.

intervals of the self-initiated tapping condition were used as the inter-stimulus intervals in the vision-only and visually-cued tapping conditions, after randomizing their order. Intervals with a duration of <4 s were replaced with ones having random duration in the range from 4 to 8 s. This adaptive procedure limited the impact of poorly timed responses in the self-initiated tapping condition on the other conditions. Additionally, it ensured that the total number of responses, proportion of left/right responses, and the timing between responses were closely matched across conditions. Between blocks, the participants had 1 min resting time.

Procedure

The participants were seated in a comfortable chair in a sound-proof room, and their head was kept in a static position by a chin-rest. The distance of their eyes from the presentation screen was approximately 70 cm. During the EEG signal acquisition, the room lights were dimmed. We used an accelerometer to identify the onset of the finger movement and to measure the movement time, i.e., the time between movement onset and button press. Its sensors (Brain Products GmbH, Munich, Germany) were attached to the dorsal tip of both index fingers, and fixed by tape. Task performance was monitored online by the examiner via a video camera to ensure that the participants were alert and did not fall asleep. We also continuously monitored self-initiated tapping in order to prevent regularities in it. Moreover, the participants were asked to minimize the number of eye blinks during the recording. After the experiment, the participants were interviewed about their strategy to perform the task in the self-initiated tapping condition. The interviews were carried out in order to find out whether they had counted mentally the number of left- and right-hand tapings, or had tried to measure the time (e.g., by counting the seconds) between two button presses.

Recording of EEG and acceleration signals

EEG data were acquired using 64 active Ag/AgCl electrodes (Brain Products GmbH, Munich, Germany) placed according to the international 10–20 system in a spherical array. Bilateral horizontal and left vertical electro-oculograms (EOG) were recorded by three of the 64 scalp electrodes (FT9, FT10, TP10 in the 10–20 system) placed bilaterally at the outer canthi and under the left eye, respectively. The reference electrode was placed at the left earlobe. At the beginning and the end of the experiment, the impedance of each electrode was measured to ascertain that it was smaller than 15 k Ω . The EEG signals were amplified, band-pass filtered in the frequency band 0.87–500 Hz, and digitized at a sample rate of 2500 Hz.

All three components (X, Y, and Z) of the acceleration signal were recorded. Their first derivatives were computed, and the magnitude of the instantaneous acceleration change at each time point was calculated (Wyatt, 1998). The time-series were then smoothed, rescaled, and a threshold was set to identify the earliest point of time in a 125 ms window prior to each button press in which a monotonic increase in acceleration rate took place. All trials in which the movement onset could not be unambiguously detected were excluded from further analysis.

Preprocessing of the recorded data

For preprocessing and analysis of the EEG data, we used the EEGLAB toolbox (Delorme and Makeig, 2004) and scripts in Matlab R2014a (MathWorks Inc.). First, the data were band-pass filtered in the frequency band 0.5–48 Hz, and then down-sampled from 2500 to 200 Hz. Next, the raw EEG data were visually inspected for paroxysmal and muscular artifacts not related to eye blinks. Then, the noisy portions of the EEG signal were excluded from further analysis. The trials in the self-initiated tapping condition with inter-trial intervals shorter than 4 s were removed, as well as trials in the visually-cued tapping condition

in which the time between the stimulus and the onset of the movement (accelerometer signal) was longer than 1 s. This led to an exclusion of 10–20% of the data.

In the next step, the EEG records were epoched to single trials, i.e., they were subdivided into intervals of 4 s depending on the experimental condition. In the vision-only condition, the reference point (time zero) was assigned to the start of the visual stimulus. The intervals reached from 1500 ms before the stimulus to 2500 ms after it: [–1500, 2500] ms. In the self-initiated tapping condition, the onset of the finger movement as determined by the accelerometer signal was set to be the reference point (i.e., time zero). Here, the 4 s intervals started 2500 ms before the onset of the movement and lasted until 1500 ms after it ([–2500, 1500] ms). In the visually-cued tapping condition, two different subdivisions, hence intervals, were used. In one case, the reference point was assigned to the start of the visual stimulus, and we used the same interval [–1500, 2500] ms as in the vision-only condition. In the other case, the reference point (time zero) was set to the onset of the finger movement, and the interval reached from 2000 ms before the onset of the finger movement until 1500 ms after it ([–2000, 1500] ms), as illustrated in Fig. 1. Here, we used a shorter interval (3.5 s) because pilot experiments indicated that a 2 s long pre-stimulus interval was sufficient to compute the (actual) baseline.

In this way, the mutual comparability of all three conditions (visually-cued tapping, vision-only, and self-initiated) could be ensured. The length of the intervals before and after the reference point was chosen such as to avoid overlaps between subsequent trials, and to take the length (approx. 2 s) of the readiness potential (Bereitschaftspotential) in the self-initiated tapping condition into account (Shibasaki and Hallett, 2006).

After subdividing the data into single trials, they were further corrected for artifacts. All trials with an amplitude larger than 100 μ V in any of the recorded channels or showing a drift that exceeded 75 μ V over the whole interval (abnormal drift) were rejected (cf. Herz et al. (2012)). Trials with other artifacts (blinks, eye movements, muscle activity, and infrequent single-channel noise) were identified by means of a semi-automated procedure based on independent components analysis (ICA) (Jung et al., 2000a,b; Hyv'arinen et al., 2004; Langlois et al., 2010). ICA was used with the Info-Max ICA algorithm implemented in EEGLAB (Langlois et al., 2010). Signals containing blink/oculomotor artifacts or other artifacts that were clearly no brain signals were subtracted from the data by using the procedure ADJUST from EEGLAB (Mognon et al., 2011). Noisy channels were automatically detected by EEGLAB. The noisy signals were corrected by interpolation of adjacent noise-free channels using spherical splines (Perrin et al., 1989). After all these procedures, about 50–85 trials per condition and per subject could be used for data analysis (altogether 1149 for self-left, 1146 for self-right, 1202 for cued-left, and 1252 for cued-right).

Finally, the trials were baseline-corrected taking the first 1000 ms of each interval as baseline. In order to improve the spatial resolution and to eliminate the influence of distortions due to the reference electrode, we used the 'small Laplacian' (e.g., McFarland et al., 1997) for all EEG electrodes, except for the boundary ones.

Data analysis

There are various ways of time–frequency decomposition of EEG data. They mainly differ in the choice of the wavelet basis functions. We chose the complex Morlet wavelets as basis functions, which are often used for time–frequency decomposition of EEG/MEG data (Lachaux et al., 1999).

The Morlet transformation provided two (physical) quantities in each trial and at each electrode: the (instantaneous) phase $\varphi(t, f)$ and the (instantaneous) amplitude (power) $A(t, f)$, which depend on the time (t) and the oscillatory frequency (f). We computed the amplitude and the phase dynamics in each condition and derived properties that were common across trials. An important indicator of the phase

dynamics between trials is the phase locking index (PLI), also denoted as inter-trial phase locking or inter-trial coherence. PLI is defined as

$$PLI(t, f) = \left| \frac{1}{N} \sum_{k=1}^N \exp(i\varphi_k(t, f)) \right|$$

where N is the number of trials and φ_k is the phase of trial k at time t and at a given frequency f ; i is the imaginary unit: $i^2 = -1$. PLI is a measure of similarity of the phases of a signal over many repetitions. PLI ranges from 0 to 1. $PLI = 1$ means identical phase of the signal across trials. Low values of PLI suggest temporal heterogeneity of the phases between individual trials. Thus, PLI measures the degree of inter-trial variation in phase between the responses to stimuli and thereby quantifies phase locking of the oscillatory activity irrespective of its amplitude (Herrmann et al., 2005; Tass, 2007).

Amplitude and PLI were computed for all channels (electrodes) in the frequency range from 2 to 48 Hz using the numerical algorithms of the Statistical Parameter Mapping toolbox (SPM 12; Friston et al., 2006). The frequency range thus included all main frequency bands of the EEG: δ (1–3 Hz), θ (4–7 Hz), α (8–12 Hz), β (13–30 Hz), and low γ (30–48 Hz).

We selected the electrodes, which we considered to be the most appropriate ones with regard to the aims of our study for a detailed analysis as follows. First, we used normally distributed random numbers, with the same statistical properties as the baseline points, to produce 'reference' values at every sampled time point for each (discrete) frequency value in the given frequency band (between 2 and 48 Hz). This resulted in a reference plot for one electrode consisting of $n \times m$ points where n was 700 and 800 time points for self-initiated tapping and visually-cued tapping, respectively, and $m = 47$ was the number of discrete frequency values used. This procedure was carried out for all electrodes. We then performed, at each electrode, a paired t-test between the reference PLI and the one computed from the recorded EEG signal at each point (t, f) for a specific electrode using the data from the individual participants. The sample size of the t-tests was thus 18, since we had usable data from 18 subjects. We used False Discovery Rate (FDR) correction that took into account the number of experimental conditions, time points, frequency values, and electrodes (Benjamini and Hochberg, 1995). At (t, f) points at which the FDR-corrected significance level of 0.05 was attained, we considered the corresponding PLI of the EEG signal significant and kept the value it had at that particular (t, f) point. At all other points, the value of PLI was set to zero. We performed this procedure in four conditions: visually-cued tapping, self-initiated tapping with both the right and the left hand. Then we formed the (set theoretic) union of the electrodes where the PLI was significantly different (at some points (t, f)) from the reference one with right-hand and left-hand tapping in the same condition. We applied this operation to both (visually-cued and self-initiated) tapping conditions. Finally, we produced the (set theoretic) intersection of the two unions. PLIs of all electrodes that were contained in this intersection were selected for further detailed analysis. Note that this selection process ensured the automatic exclusion of the occipital electrodes (POx and Oy) that obviously were not directly related to preparation and execution of motor actions but had large signals in the visually-cued tapping condition.

As a result, the following electrodes were selected by the above procedure for further analysis: FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CP2, CP4 (14 out of 61 electrodes). In addition, adhering to common practice (e.g., Makeig et al., 2002), the EEG signal at the

electrode POz was used to monitor the effect of the visual stimulus, if present.

We calculated the average value of PLI over the frequency bands where significant PLIs occurred in both tapping conditions and for both hands. We then performed a pointwise t-test on each of the average PLI curves in both conditions (i.e., self-initiated and visually-cued tapping) for both hands. We compared the PLI obtained for each of these conditions with the corresponding averaged reference PLI at the significance level of $p < 0.05$ with FDR correction with regard to the number of conditions, time points, and electrodes (Benjamini and Hochberg, 1995). In self-initiated tapping, the baseline was computed in the interval $[-2300, -1500]$ ms, whereas in visually-cued tapping the interval $[-1800, -1000]$ ms was used. In both conditions, the baseline ended at least 1 s before the onset of the movement. It was thereby ensured that the baseline was not contaminated with movement- or stimulus-related activity (cf. epoching of data, in subsection 'Preprocessing of the recorded data'). The first 200 ms of the trial intervals were discarded in all cases in order to avoid edge effects of the wavelet transform.

To assess possible differences in EEG activity between the two hemispheres, we computed the lateralization index (LI) (Deiber et al., 2012). With regard to PLI, it represents the cumulative asymmetry between the PLI values in the right and left hemisphere. It is defined as follows:

$$LI = \frac{[PLI_{C2, \text{left}} - PLI_{C1, \text{left}}] + [PLI_{C1, \text{right}} - PLI_{C2, \text{right}}]}{2}$$

Here $PLI_{C2, \text{left}}$ is the value of PLI at the electrode C2 when the button presses were performed with the left index finger. The other $PLI_{C_{x,h}}$ ($x = 3, 4, h = \text{left or right}$) quantities are defined analogously.

Results

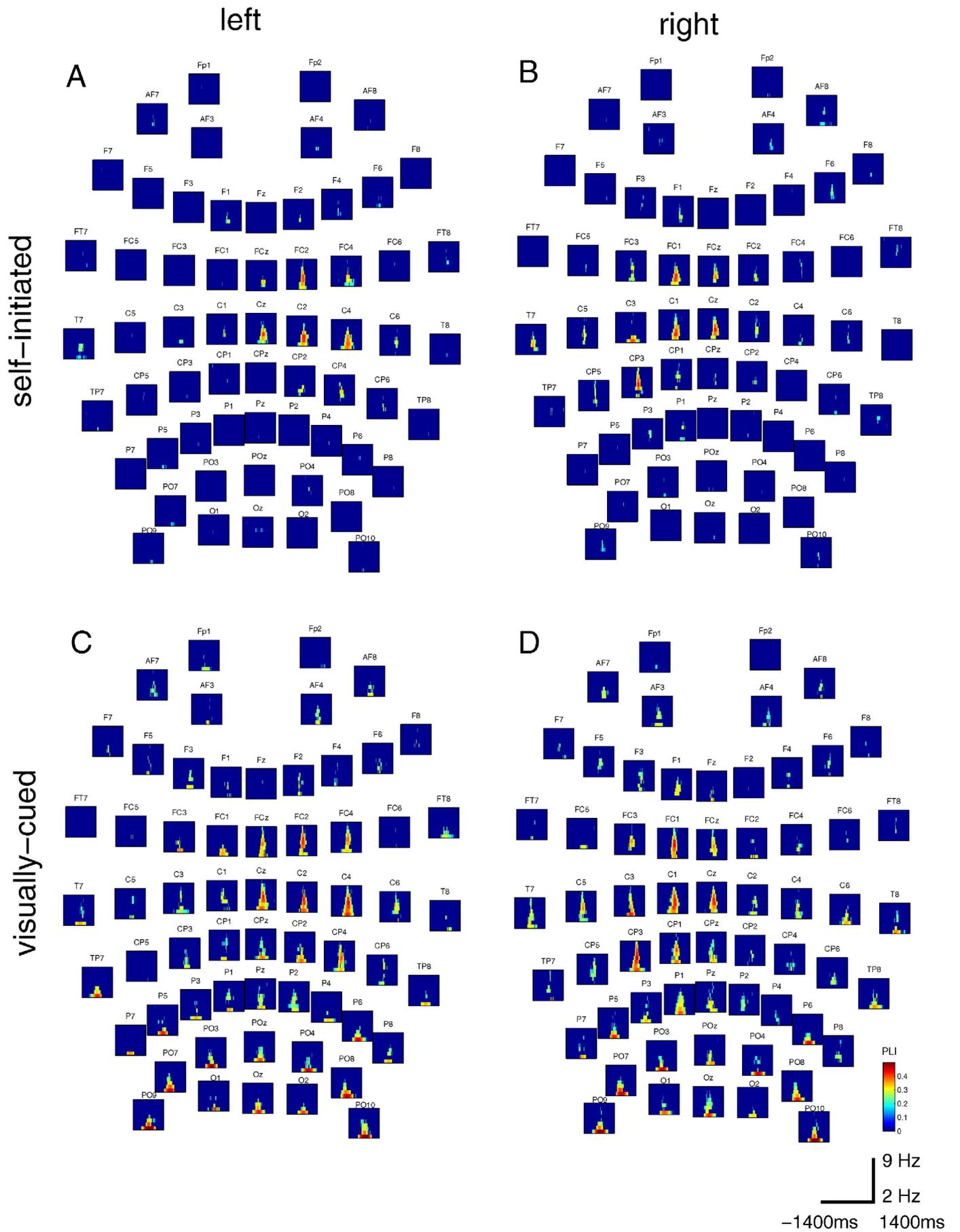
Amplitude dynamics

First, we investigated the amplitudes (power) of the wavelet transforms (cf. Material and methods) near the onset of the movement. Our results replicate the well-known event-related desynchronization (ERD) and event-related synchronization (ERS) at the onset and the termination of the movement in the α , β , and the lower frequency bands (e.g., Pfurtscheller and da Silva, 1999; Neuper et al., 2006). Hence, these findings provide evidence for the validity of our data.

Phase dynamics

In Fig. 2, the group average of the PLI over 18 participants for all 61 channels are displayed for the self-initiated (A,B) and visually-cued (C,D) tapping condition (A,C: left index finger, B,D: right index finger). Each small panel is placed according to the position of the corresponding EEG electrode. In each of them, PLI values were assigned according to the results of the statistical procedure described in Material and methods. Thus, non-significant values remain deep blue. In the panels, the horizontal axis is the time and the vertical axis is the frequency from 2 to 9 Hz. An increase of PLI can clearly be discerned in both conditions at the central electrodes that are located closest to the motor regions (Fig. 2A–D). In the visually-cued tapping condition, the increase also occurred at the electrodes lying above the occipital regions (Fig. 2C–D). Considering all experiments, we found significant PLI in the δ – θ frequency band, and in the lower α band, but no significant PLI occurred at frequency values >9 Hz.

Fig. 2. Phase locking index at all electrodes in self-initiated tapping with the left hand (A) or right hand (B); and in visually-cued tapping with the left hand (C) or right hand (D). The PLIs in the panels were constructed according to the statistical procedure described in Material and methods. In all panels, the horizontal axis is the time axis in the interval $[-1400, 1400]$ ms, and the vertical axis is the frequency axis in the band 2–9 Hz. The onset of the movement, as determined by the accelerometer, is set to $t = 0$. The color bar on the bottom right indicates the value scale of the PLI in the individual panels. Thus panels (electrodes) with no PLI remain completely dark blue. No significant phase locking occurred at frequencies >9 Hz. For further details, see Material and methods.

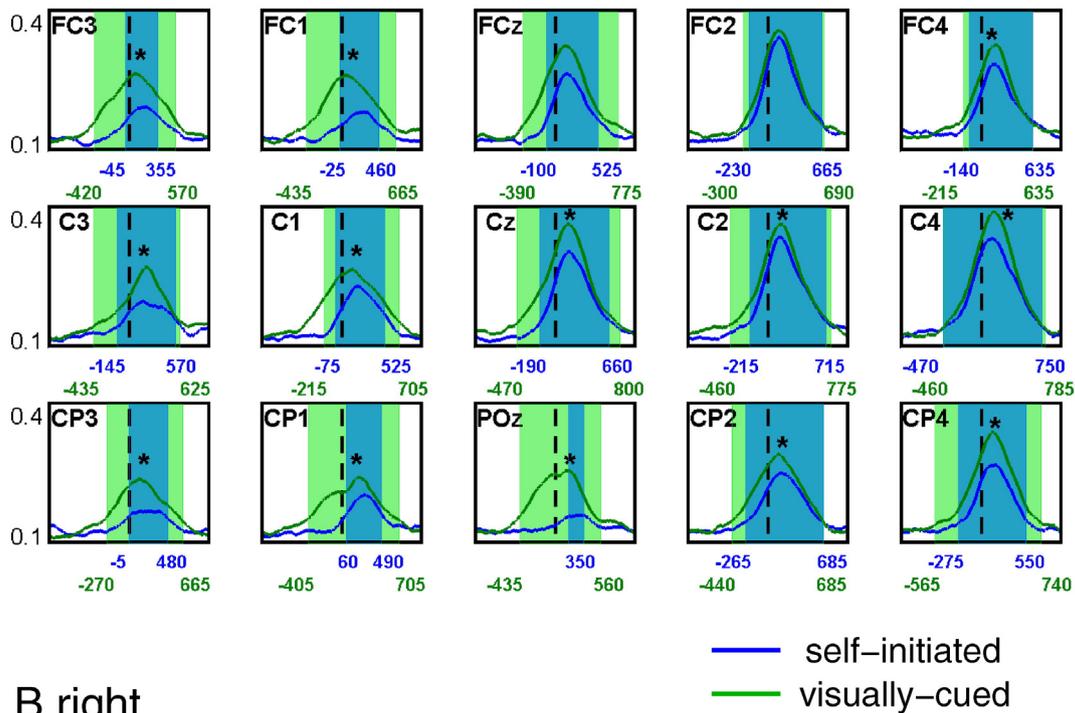


The electrodes C1–C4, FC1–FC4, CP1–CP4, FCz, and Cz were selected for detailed analysis by the procedure described in the [Material and methods](#) section. These electrodes happen to be near to the regions of the motor cortex.

For each of these electrodes, we first calculated the average value of PLI over the δ – θ frequency band (2–7 Hz) in both tapping conditions. The results are displayed in Fig. 3. The horizontal axis is the time axis, the vertical one that of the average values of PLI. Fig. 3A shows the

average PLIs as functions of time in self-initiated tapping in blue and those in visually-cued tapping in green when the left index finger pressed the button. Analogous results are displayed in Fig. 3B for the right index finger. In both sets of panels, the onset of the movement is at $t = 0$ (dashed vertical line). We then performed a pointwise t-test on each of the average PLI curves in both (self-initiated and visually-cued tapping) conditions, the sample size being the number of subjects. We compared the PLI obtained in each of these conditions with the

A left



B right

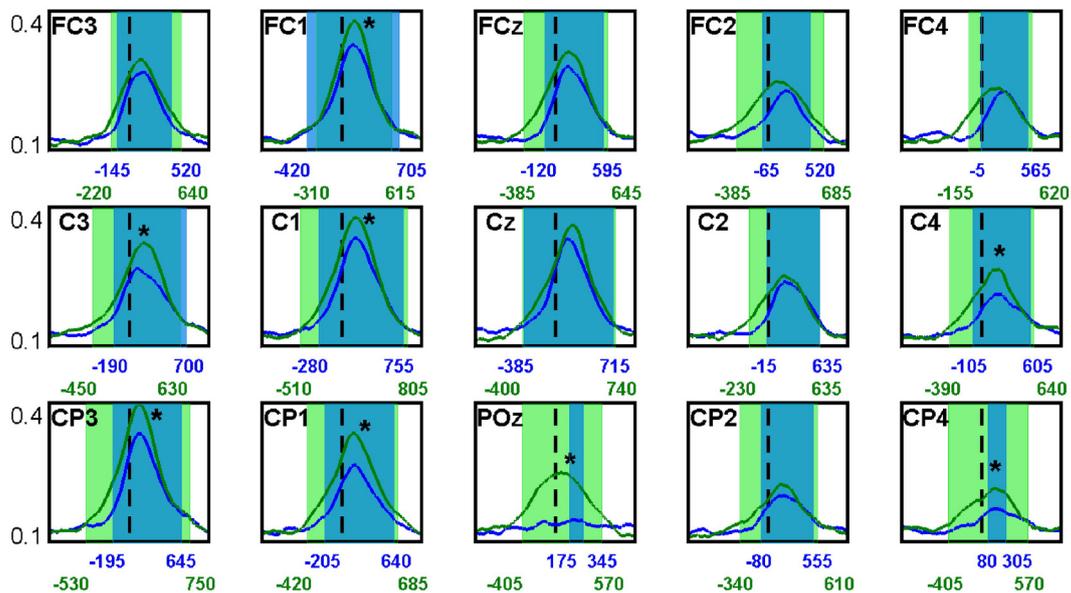
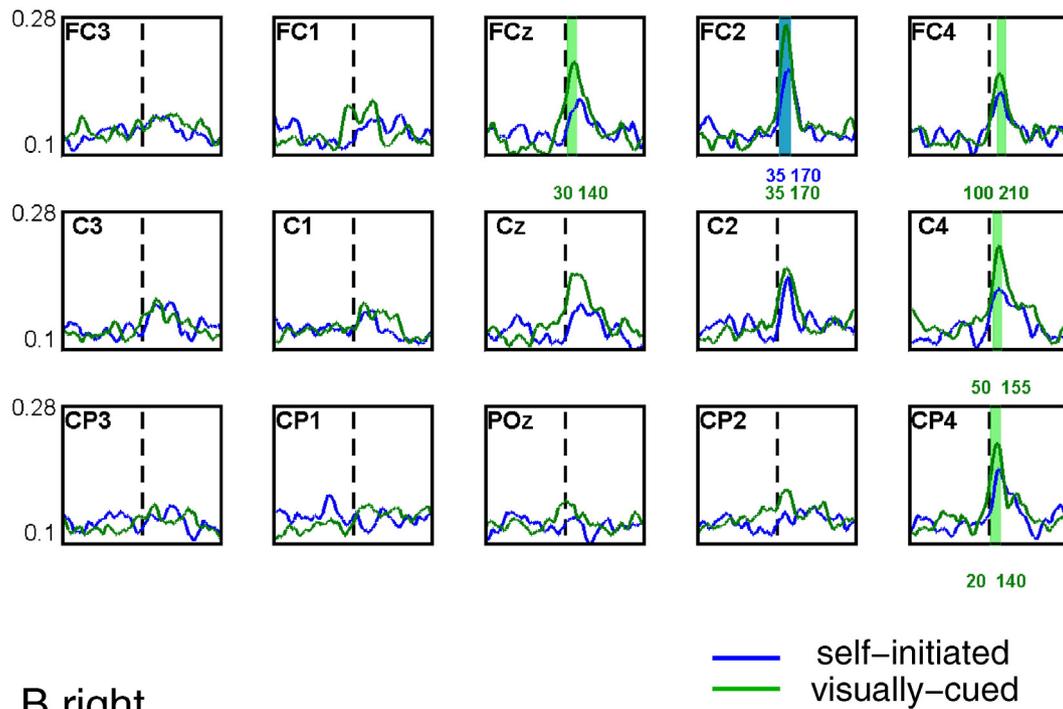


Fig. 3. Phase locking index (PLI) averaged over the 2–7 Hz frequency band in self-initiated (blue lines) and in visually-cued (green lines) tapping at the electrodes of interest that label the panels. The horizontal axis represents time in the interval the $[-1000, 1000]$ ms, the dashed vertical line marks the onset of the movement ($t = 0$). The vertical axis represents the PLI values. The time intervals in which the PLI is significantly different ($p < 0.05$, FDR corrected) from its reference value are shown in the same color (blue or green) as the PLI curves. In addition, the starting and end points of these intervals are displayed below each panel using the corresponding color. Stars in the panels denote a statistically significant ($p < 0.05$, FDR corrected) difference between the peak values of the PLI curves.

A left



B right

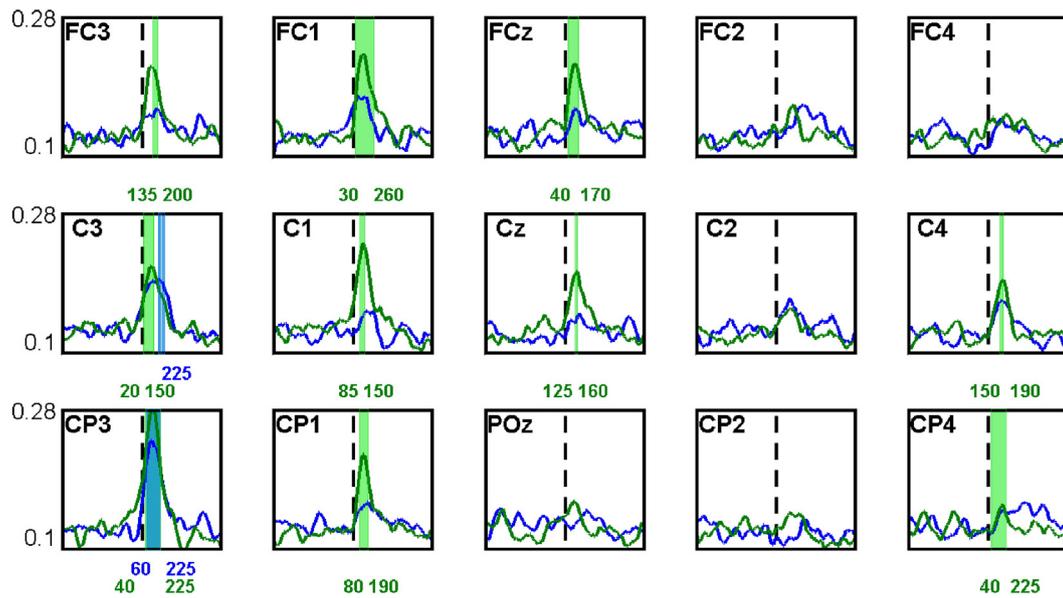


Fig. 4. The same illustration scheme as in Fig. 3 but for phase locking indices in the 8–12 Hz frequency band. The meanings of all axes and other notations are the same as in Fig. 3.

corresponding reference PLI at the significance level of $p < 0.05$, with FDR correction for multiple comparisons (for time points, channels, conditions, and hands). Intervals with significant differences to the reference PLI are marked in light blue for self-initiated and in green for visually-cued tapping. The results clearly reveal that the intervals in which PLI was significantly different from baseline were longer in the visually-cued tapping condition than in the self-initiated tapping condition at most of the electrodes. As illustrated, at almost all 15 electrodes (except for electrode FC1 in Fig. 3B), the interval of significant difference started at the same time or earlier in visually-cued tapping than in self-initiated tapping, and in most of them, it finished

later, too. Moreover, these intervals always started prior to the onset of the movement (vertical dashed line). We also tested, by paired t-test, the differences between the maxima of the two types of curves at each electrode. An asterisk indicates a significant difference between the maxima in the panels of Fig. 3. This significant difference occurred at all but 2 of the 15 electrodes for the left hand pressing but only at 8 out of the 15 electrodes for right hand pressing. This is a clear asymmetry, and might reflect hemispheric dominance effects in this sample of right-handed subjects.

For purposes of comparison, we carried out the same procedures and tests in the α frequency band (8–12 Hz). We performed them over the

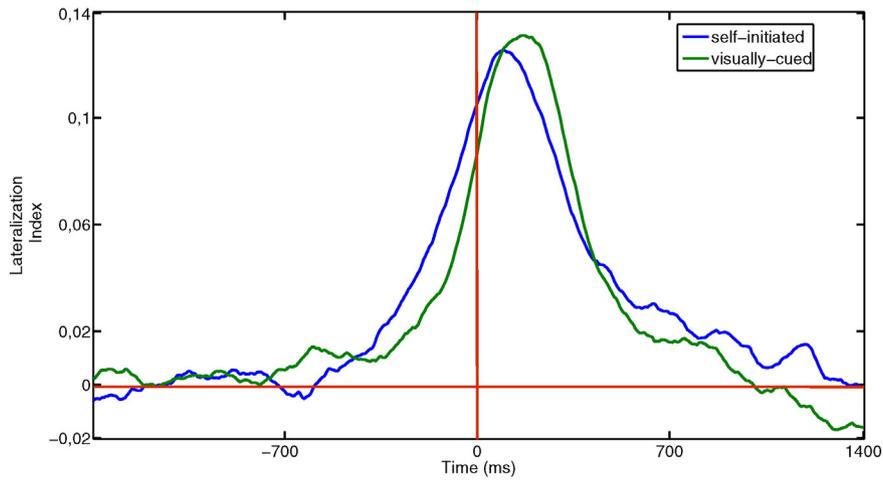


Fig. 5. The lateralization index related to the phase locking index in the self-initiated (blue curve), and in the visually-cued tapping (green curve) condition at the electrodes C1 and C2. Horizontal axis: time, vertical axis: value of the lateralization index. For further explanation, please see text.

whole α band for the sake of completeness, even though, as stated above, there was no significant PLI at frequencies >9 Hz. The results are displayed in Fig. 4 in the same format as those in Fig. 3. Compared with those in Fig. 3, the results show two striking differences: in about half of the panels the two PLI curves are not significantly different from their baseline. Even if an interval of significant difference occurred, it was very short and started after the onset of the movement (dashed

vertical line). Moreover, none of the maxima of the two types of PLI curves proved to be significantly different.

In summary, these results show that PLIs in the δ - θ frequency band were significantly different from their reference PLIs in a time interval around the onset of the movement at all electrodes of interest, in both conditions, and for both hands. By contrast, in the α frequency band, such intervals did not occur in half of the cases (at half of the

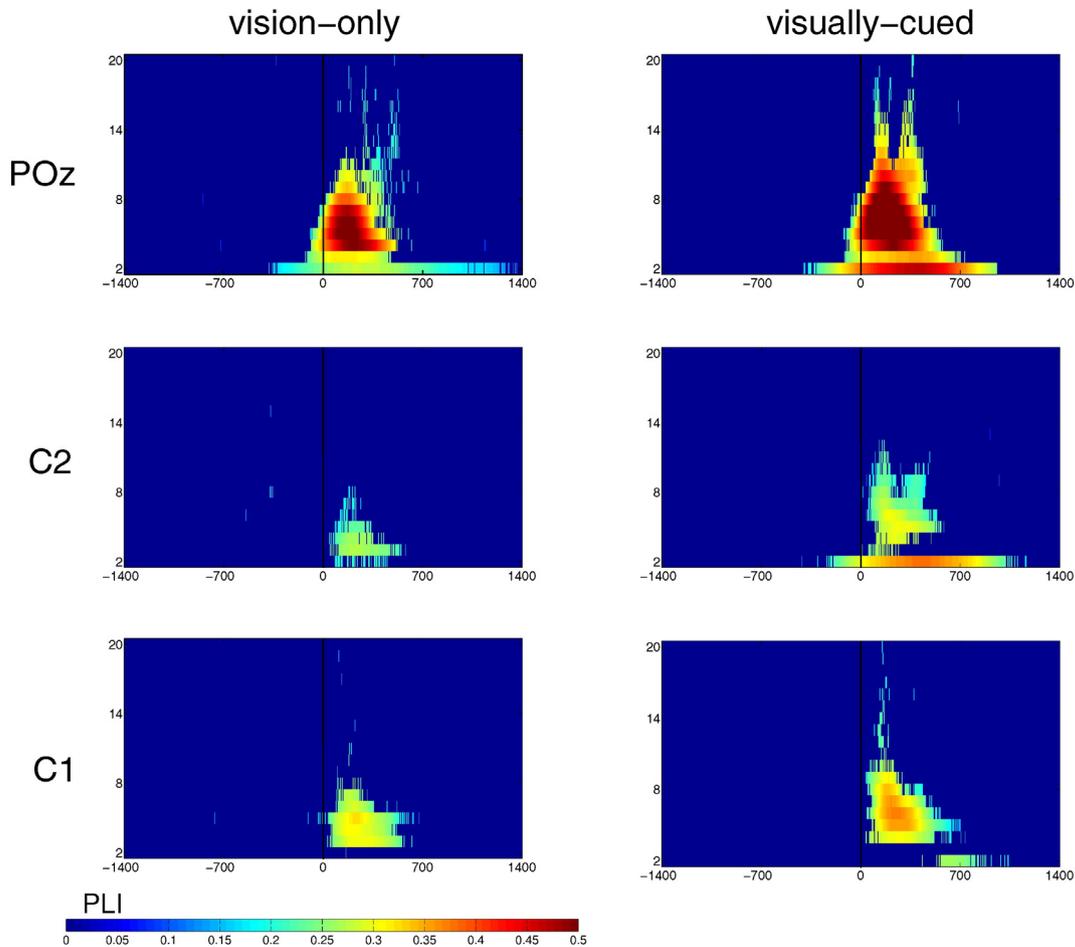


Fig. 6. Phase locking index around the onset of the visual stimulus ($t = 0$) at the electrodes POz, C1, and C2 in the vision-only condition with right-pointing arrow (left column), and in the visually-cued tapping condition with right hand tapping (right column). Comparing the signals at the electrodes C1 and C2 clearly shows that the size of PLI in the visually-cued tapping condition was not solely due to the visual stimulus. Time is shown on the horizontal axis and frequency (2–20 Hz) on the vertical axis.

electrodes), and even if they did, they were very short. These results stress the special role of phase locking in the δ – θ frequency band.

Hemispheric dependence of PLI in the δ – θ frequency band

Having confirmed that phase locking at the electrodes of interest (Fig. 3) was significantly enhanced already before movement onset in both conditions, we next investigated whether PLI exhibited hemispheric differences. To this end, we calculated the lateralization index (LI) (see Material and methods).

Fig. 5 illustrates the time course of LI in both tapping conditions in the interval 1400 ms before until 1400 ms after the start of the button press ($t = 0$) for the electrode pair C1–C2. The blue curve corresponds to self-initiated tapping, and the green one to visually-cued tapping. The figure shows that the cumulative asymmetry (LI) of the function of the hemispheres is large and about of the same size in the interval $[-600, 700]$ ms in both conditions. This means that phase locking was stronger at the electrode situated over motor regions, in particular M1, contralateral to the moving hand in a time interval around the motor action in both the self-initiated and the visually-cued tapping condition.

Furthermore, when the button presses were performed with the left index finger, phase locking was longest in both conditions at the electrodes FC2, C2, and C4 (cf. Fig. 3). An analogous result holds true when the button presses were performed with the right index finger. In this case, the longest phase locking in both conditions occurred at FC1, C1, and Cz (cf. Fig. 3). In both conditions and for both hands, these intervals started already approximately 300–500 ms before the onset of the movement at these electrodes. Moreover, these were also the PLI curves with the largest maxima.

Effect of the visual stimulus on PLI

In order to verify that phase locking found in the motor cortex in the visually-cued tapping condition was not solely due to visual stimulation, we compared PLIs in the visually-cued tapping condition with those in the vision-only condition in the time interval $[-2000, 1500]$ ms with respect to the onset of the visual stimulus ($t = 0$). By this, we could identify pure motor effects common to externally or internally triggered movements.

Fig. 6 displays the differences in the PLI values in the 2–20 Hz frequency band at the electrodes POz, C1, and C2 in the vision-only condition with right-pointing arrow (left column) and in the visually-cued tapping condition with the right index finger (right column). Phase locking appeared not only in the δ – θ frequency band, but also in the α and β frequency bands. It is evident from this figure that PLI was much larger at C1 and C2 (near the motor cortex) in the visually-cued

tapping condition than in the vision-only condition (t-test, $p < 0.05$ FDR corrected for time points, frequencies, and electrodes). The large signals at C1 and C2 cannot, therefore, result from effects of the visual stimulation alone.

The relation of PLI to behavior

We also tested whether the observed increase in phase locking in the set of electrodes of interest (i.e., the central and the occipital regions) could be linked to the behavioral performance of the individual subjects. To assess this performance, we defined processing time (PT) as the time that elapsed from the onset of the stimulus until the onset of the movement (as detected by the accelerometer), and movement time (MT) as the time from the onset of the movement to the button press. The sum of PT and MT corresponds to the reaction time (RT). The distributions of PT and MT are shown in Fig. 7. As it can be seen, all distributions are unimodal, but the distribution of PT appears to be asymmetric, having a long tail. In the visually-cued tapping condition, a significant correlation between the individual PTs of the 18 participants and the PLI maxima was found in the occipital region (POz) (Pearson, left $p = 0.0145$ and right $p = 0.0429$), providing evidence for the physiological validity of the data.

Furthermore, we found a significant correlation between the MTs of the 18 participants and the PLI maxima at the electrodes C1 and C2 for both left hand tapping (Pearson, $p = 0.0332$, $r = -0.50$) and right hand tapping (Pearson, $p = 0.0087$, $r = -0.60$), in the self-initiated tapping condition. Thus, the stronger the phase locking was at these electrodes during the preparatory phase of the movement, the faster was the movement carried out with the contralateral hand.

Discussion

In this study, we aimed at identifying and describing the neural dynamics common to neural processes underlying the preparation and execution of motor actions related to isolated finger movements irrespective of whether these are internally or externally triggered. We hypothesized that such markers of the neural dynamics of movement preparation and execution would be reflected in phase locking dynamics, and that they would most likely occur in motor cortex, prior to the actual execution of the motor action. To test this hypothesis, we obtained EEG recordings from 18 right-handed young healthy human subjects who performed internally or externally initiated isolated index finger movements. Even though this is a rather simple motor task, it has been shown that it is complex enough to engage the most important motor brain areas (e.g., Gerloff et al., 1998a,b; Witt et al., 2008; Michely et al., 2015). Furthermore, the task can be performed

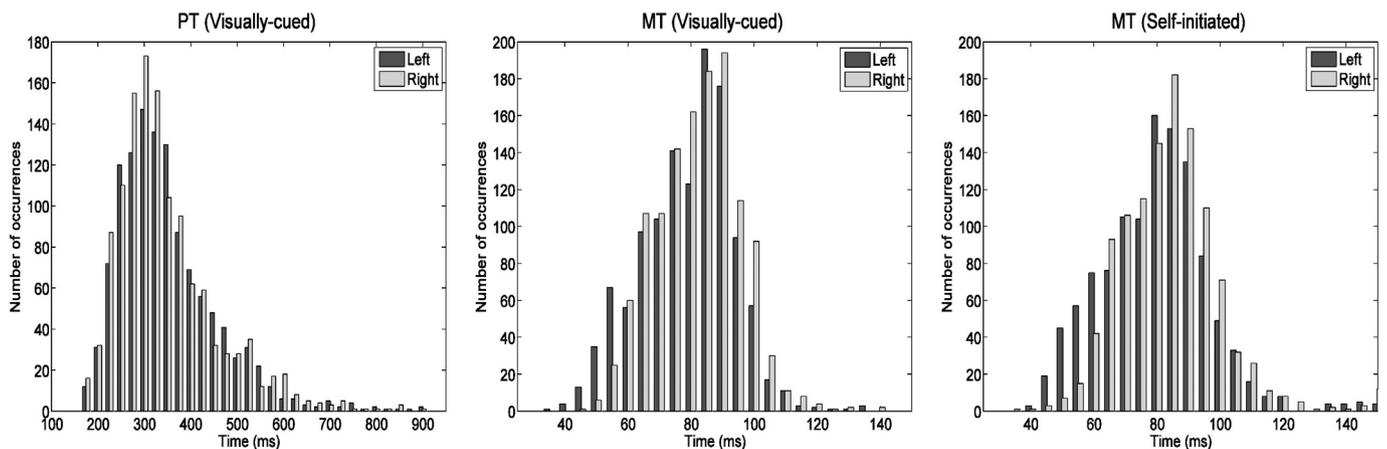


Fig. 7. Empirical distribution of the processing times (PT) and movement times (MT). On the left, the histograms of the processing time obtained in the visually-cued tapping condition (left and right hand) are displayed. In the middle, the histograms of the movement time are shown in the same condition. Finally, on the right, the histograms of the movement time obtained in the self-initiated tapping condition are illustrated. Note that all distributions are clearly unimodal but those of the processing times appear to have long tails.

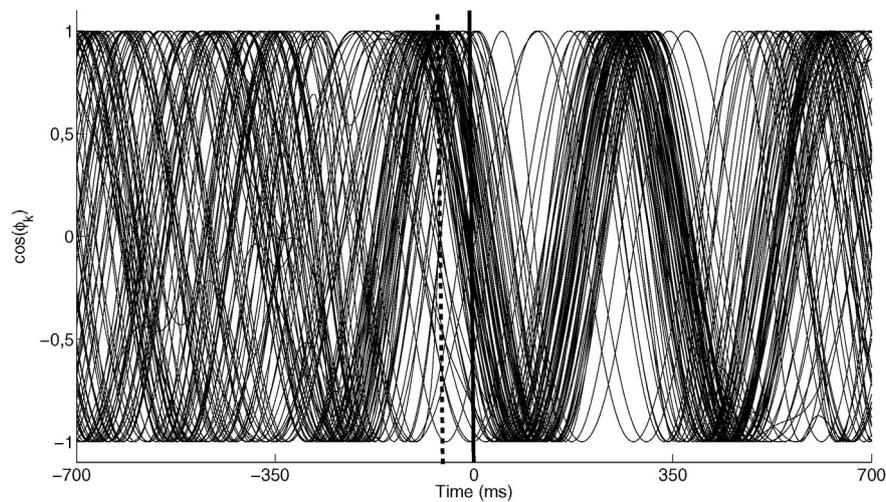


Fig. 8. The cosine of the phase φ derived from the individual trials k of the EEG data of a single participant at the frequency of 3 Hz at the electrode C4 in the self-initiated tapping condition with the left hand.

not only by healthy subjects but also by patients suffering from neurological disorders affecting the motor system (Michely et al., 2012). In the future, this might prove important to gain new insights into the pathophysiology of motor disorders.

We then calculated the power spectrum and the phase locking index (PLI) from the EEG records over the trials in each subject for every pair of sampled time and integer frequency value in the frequency band 2–48 Hz. In the δ – θ frequency band, we found significant PLI in a time interval starting already before the onset of the movement. This was true for all electrodes of interest (C1–C4, CP1–CP4, FC1–FC4, and FCz, Cz, and POz), and in both conditions and for both hands (except, of course, for POz in the self-initiated tapping condition, because of the lack of visual stimulus). Moreover, the lateralization index (LI) showed that the phase locking was stronger at the electrodes contralateral to the moving hand than at the ipsilateral ones. This held true in both the self-initiated and the visually-cued tapping condition.

The phase locking we uncovered cannot be attributed to the sensory feedback arising from the finger tapping, since PLI already became significant at the electrodes lying near to the primary motor regions (C1–C3 and C2–C4, respectively) 300–500 ms before the onset of the movement. Moreover, the relative high value of PLI in the visually-cued tapping condition was not due to the visual stimulus alone, since phase locking was (much) stronger at the electrodes C1 and C2 lying above the motor regions in the visually-cued than in the vision-only condition at the onset of the stimulus (Fig. 6).

At this point, we have to deal with the source identification problem. As a first step to tackle it, we selected the electrodes of interest using an objective selection process that is described in the **Material and methods** section. However, we did not perform source identification, since this usually is a laborious procedure, which nevertheless not always yields sufficiently reliable results. Instead, we used the small Laplacian in the preprocessing of the data, which has been shown to be closely related to local activity in motor EEG. Moreover, practical experience has shown that nearby placed (surface) electrodes pick up almost identical EEG signals showing very little phase difference (Brunner et al., 2006; Krusienski et al., 2012; Wang et al., 2006). The authors just cited did not use source identification, yet they obtained reliable results. We think that an explicit source identification procedure is not necessary in our case either, since the electrodes we use in the detailed data analysis are much closer to a specific cortical motor-related area than to other ones. Hence, we can relate the electrode position directly to the cortical source (e.g., M1, SMA).

In the light of this, we can say that in both conditions (i.e., externally and internally triggered movements), neural activity in the respective

areas of the motor cortex (i.e., PM, SMA, and M1) had already been phase locked before the motor action was executed. Furthermore, the presence of the visual stimulus in the visually-cued tapping condition increased the duration and size of phase locking in the motor cortex before and after the motor actions. We can therefore regard phase locking in the δ – θ frequency band as a specific indicator of the neural dynamics underlying motor actions, which can be observed irrespective of how they are initiated and which hand is used.

To date, the widely accepted neural signatures of movement preparation and execution are event-related desynchronization (ERD) and event-related synchronization (ERS) at the onset and the termination of a movement in the power spectra (amplitude domain) of the α and β as well as lower frequency bands (e.g., Gerloff et al., 1998a,b; Pfurtscheller and da Silva, 1999; Luu and Tucker, 2001; Neuper et al., 2006). While these results could be replicated from our EEG records (not illustrated), providing further evidence for the validity of our data, we focused on the phase locking properties of the EEG activity. This approach, that is the description and analysis of the phase locking properties during preparation and execution of motor tasks, is to the best of our knowledge novel in this field of research. Most importantly, PLI carries information that is independent of that in the power spectrum (amplitude). The latter expresses the intensity of the oscillatory activity of neuron populations in a brain area over a frequency range (α , β , etc.). The former, however, carries information on the temporal structure of the neural activity of the same neuron populations in the same condition. The information PLI provides is therefore complementary to that in the power spectrum (amplitude domain).

Previous studies investigating EEG activity during finger tapping tasks (Gerloff et al., 1998a,b; Zhao et al., 2014) did not report phase locking in EEG signals in the δ – θ band. Recently, Igarashi et al. (2013) showed, albeit in the rat, that θ oscillations play a part in the neuronal coordination during motor activity, in particular motor preparation and action. The authors demonstrated a close (functional) connection between θ oscillation and layer-dependent firing of cortical neurons (at high and low β frequencies). These data, at least indirectly, support our results concerning the role of δ – θ oscillations as indicators of human motor actions.

As far as the physiological significance of our key result, i.e., the strong phase locking just before the onset of the movement, is concerned, we suggest that the spike rate of the pre-motor neurons projecting from M1 to the spinal cord increases at a certain preferred phase angle of the δ – θ cycle. This concept is illustrated in Fig. 8. Here, the cosine of the phase of each trial k is shown for all trials of one subject

at the frequency of 3 Hz (at maximal PLI) in the visually-cued tapping condition. The vertical dashed line indicates the time at which this increase in the spike rate is expected to occur. This is the instant of time at which the command to move the finger is sent from M1 to the motor neurons in the spinal cord. This occurs approx. ≈ 50 ms before the onset of the movement.

This interpretation is in line with a study by Lee et al. (2005) who found that θ oscillations had a systematic effect on single neuron activity in the extrastriate visual cortex of monkeys, with neurons emitting more action potentials near to their preferred phase angle of each θ cycle. Lee and colleagues therefore suggested that θ oscillations provide a mechanism for structuring the interaction between neurons in different brain regions.

Finally, we suggest that phase locking in the δ - θ frequency band, most pronounced in M1 contralateral to the moving hand, signals a mechanism that ensures that distinct active cortical pathways, which initiate voluntary and stimulus-triggered movements, converge to the common motor output. This mechanism may thus guide the activation of the appropriate muscles, via the motor neurons, to perform the movement.

Conflict of interest

The authors declare no competing financial interests.

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References

- Baker, S., Olivier, E., Lemon, R., 1997. Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J. Physiol.* 501, 225–241.
- Baker, S., Spinks, R., Jackson, A., Lemon, R., 2001. Synchronization in monkey motor cortex during a precision grip task. I. Task-dependent modulation in single-unit synchrony. *J. Neurophysiol.* 85, 869–885.
- Bartolo, R., Merchant, H., 2015. Beta oscillations are linked to the initiation of sensory-cued movement sequences and the internal guidance of regular tapping in the monkey. *J. Neurosci.* 35, 4635–4640.
- Bartolo, R., Prado, L., Merchant, H., 2014. Information processing in the primate basal ganglia during sensory-guided and internally driven rhythmic tapping. *J. Neurosci.* 34, 3910–3923.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 57 (1), 289–300.
- Brunner, C., Scherer, R., Grainmann, B., Supp, G., Pfurtscheller, G., 2006. Online control of brain-computer interface using phase synchronization. *IEEE Trans. Biomed. Eng.* 53, 2501–2506.
- Deiber, M.P., Sallard, E., Ludwig, C., Ghezzi, C., Barral, J., Iban'ez, V., 2012. EEG alpha activity reflects motor preparation rather than the mode of action selection. *Front. Integr. Neurosci.* 6, 59.
- Delorme, A., Makeig, S., 2004. EEGLab: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21.
- Friston, K.J., Ashburner, J.T., Kiebel, S.J., Nichols, T.E., Penny, W.D., 2006. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. Elsevier, London.
- Gerloff, C., Richard, J., Hadley, J., Schulman, A.E., Honda, M., Hallett, M., 1998a. Functional coupling and regional activation of human cortical motor areas during simple, internally paced and externally paced finger movements. *Brain* 121, 1513–1531.
- Gerloff, C., Uenishi, N., Nagamine, T., Kumieda, T., Hallett, M., et al., 1998b. Cortical activation during fast repetitive finger movements in humans: steady-state movement-related magnetic fields and their cortical generators. *Electroencephalogr. Clin. Neurophysiol.* 109, 444–453.
- Herrmann, C., Busch, N., Grigutsch, M., 2005. EEG Oscillations and Wavelet Analysis. In: Handy, T.C. (Ed.), *Event-Related Potentials: A Methods Handbook*. MIT press, Cambridge, pp. 229–259.
- Herz, D.M., Christensen, M.S., Reck, C., Florin, E., Barbe, M.T., Stahlhut, C., Pauls, K.A.M., Tittgemeyer, M., Siebner, H.R., Timmermann, L., 2012. Task-specific modulation of effective connectivity during two simple uni-manual motor tasks: a 122-channel EEG study. *NeuroImage* 59, 3187–3193.
- Hughes, G., Schütz-Bosbach, S., Waszak, F., 2011. One action system or two? Evidence for common central preparatory mechanisms in voluntary and stimulus-driven actions. *J. Neurosci.* 31, 16692–16699.
- Hyv'arinen, A., Karhunen, J., Oja, E., 2004. *Independent Component Analysis*. vol. 46. Sons, John Wiley & Sons.
- Igarashi, J., Isomura, Y., Arai, K., Harukuni, R., Fukai, T., 2013. A θ - γ oscillation code for neuronal coordination during motor behavior. *J. Neurosci.* 33, 18515–18530.
- Jenkins, I.H., Jahanshahi, M., Jueptner, M., Passingham, R.E., Brooks, D.J., 2000. Self-initiated versus externally triggered movements. *Brain* 123, 1216–1228.
- Jung, T.P., Makeig, S., Humphries, C., Lee, T.W., Mckeown, M.J., Iragui, V., Sejnowski, T.J., 2000a. Removing electroencephalographic artifacts by blind source separation. *Psychophysiology* 37, 163–178.
- Jung, T.P., Makeig, S., Westerfield, M., Townsend, J., Courchesne, E., Sejnowski, T.J., 2000b. Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects. *Clin. Neurophysiol.* 111, 1745–1758.
- Krieghoff, V., Waszak, F., Prinz, W., Brass, M., 2011. Neural and behavioral correlates of intentional actions. *Neuropsychology* 49, 767–776.
- Krusienski, D.J., McFarland, D.J., Wolpaw, J.R., 2012. Value of amplitude, phase, and coherence features for a sensorimotor rhythm-based brain-computer interface. *Brain Res. Bull.* 87, 130–134.
- Lachaux, J.P., Rodriguez, E., Martinerie, J., Varela, F.J., et al., 1999. Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* 8, 194–208.
- Langlois, D., Chartier, S., Gosselin, D., 2010. An introduction to independent component analysis: Infomax and fastica algorithms. *Tutor. Quant. Methods Psychol.* 6, 31–38.
- Lee, H., Simpson, G.V., Logothetis, N.K., Rainer, G., 2005. Phase locking of single neuron activity to theta oscillations during working memory in monkey extrastriate visual cortex. *Neuron* 45, 147–156.
- Luu, P., Tucker, D.M., 2001. Regulating action: alternating activation of midline frontal and motor cortical networks. *Clin. Neurophysiol.* 112, 1295–1306.
- Makeig, S., Westerfield, M., Jung, T.-P., Enghoff, S., Townsend, J., Courchesne, E., Sejnowski, T.J., 2002. Dynamic brain sources of visual evoked responses. *Science* 295, 690–694.
- McFarland, D.J., McCane, L.M., David, S.V., Wolpaw, J.R., 1997. Spatial filter selection for EEG-based communication. *Electroencephalogr. Clin. Neurophysiol.* 103, 386–394.
- Merchant, P.O., Zarco, W., Ga'mez, J., 2013. Interval tuning in the primate medial premotor cortex as a general timing mechanism. *J. Neurosci.* 33, 9082–9096.
- Michely, J., Barbe, M.T., Hoffstaedter, F., Timmermann, L., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2012. Differential effects of dopaminergic medication on basic motor performance and executive functions in parkinson's disease. *Neuropsychology* 50, 2506–2514.
- Michely, J., Volz, L.J., Barbe, M.T., Hoffstaedter, F., Viswanathan, S., Timmermann, L., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2015. Dopaminergic modulation of motor network dynamics in parkinson's disease. *Brain* 138, 664–678.
- Mognon, A., Jovicich, J., Bruzzone, L., Buiatti, M., 2011. Adjust: an automatic EEG artifact detector based on the joint use of spatial and temporal features. *Psychophysiology* 48, 229–240.
- Neuper, C., Wörtz, M., Pfurtscheller, G., 2006. ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Event-Related Dynamics of Brain Oscillations* (Neuper C, Klimesch W, Eds), pp211–222, Vol. 159 of Progress in Brain Research. Elsevier.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychology* 9, 97–113.
- Perrin, F., Pernier, J., Bertrand, O., Echallier, J., 1989. Spherical splines for scalp potential and current density mapping. *Electroencephalogr. Clin. Neurophysiol.* 72, 184–187.
- Pfurtscheller, G., da Silva, F.L., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin. Neurophysiol.* 110, 1842–1857.
- Rubino, D.R., Kay, A., Hatsopoulos, N.G., 2006. Propagating waves mediate information transfer in the motor cortex. *Nat. Neurosci.* 9, 1549–1557.
- Shibasaki, H., Hallett, M., 2006. What is the Bereitschaftspotential? *Clin. Neurophysiol.* 117, 2341–2356.
- Takahashi, K., Saleh, M., Penn, R.D., Hatsopoulos, N.G., 2011. Propagating waves in human motor cortex. *Front. Hum. Neurosci.* 5, 40.
- Tass, P.A., 2007. *Phase Resetting in Medicine and Biology: Stochastic Modelling and Data Analysis*. vol. 172. Springer Science & Business Media.
- Wang, Y., Hong, B., Gao, X., Gao, S., 2006. Phase synchrony measurement in motor cortex for classifying single-trial EEG during motor imagery. *Engineering in Medicine and Biology Society. EMBS'06. 28th Annual International Conference of the IEEE. IEEE*, pp. 75–78.
- Waszak, F., Wascher, E., Keller, P., Koch, I., Aschersleben, G., Rosenbaum, D., Prinz, W., 2005. Intention-based and stimulus-based mechanisms in action selection. *Exp. Brain Res.* 162, 346–356.
- Witt, S.T., Laird, A.R., Meyerand, M.E., 2008. Functional neuroimaging correlates of finger-tapping task variations: an ALE meta-analysis. *NeuroImage* 42, 343–356.
- Wyatt, H.J., 1998. Detecting saccades with jerk. *Vis. Res.* 38, 2147–2153.
- Zhao, K., Gu, R., Wang, L., Xiao, P., Chen, Y.H., Liang, J., Hu, L., Fu, X., 2014. Voluntary pressing and releasing actions induce different senses of time: evidence from event-related brain responses. *Sci. Rep.* 4.