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RESEARCH ARTICLE | *Neural Circuits*

Infraslow activity as a potential modulator of corticomotor excitability

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de Goede AA, van Putten MJAM. Infraslow activity as a potential modulator of corticomotor excitability. *J Neurophysiol* 122: 325–335, 2019. First published May 22, 2019; doi:10.1152/jn.00663.2018.—Fluctuations in cortical excitability are a candidate mechanism involved in the trial-to-trial variation of motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS). We explore whether infraslow EEG activity (<0.1 Hz) modulates corticomotor excitability by evaluating the presence of temporal and phase clustering of TMS-induced MEPs. In addition, we evaluate the dependence of MEP amplitude on the phase of the infraslow activity. Twenty-three subjects were stimulated at an intensity above the resting motor threshold (rMT) and ten at the rMT. We evaluated whether temporal and phase clustering of MEP size and MEP generation were present, using 1,000 surrogates with a similar amplitude or occurrence distribution. To evaluate the MEP amplitude dependence, we used the least-square method to approximate the linear circular data by fitting a sine function. We observed significant temporal clustering at a group level, in all individual subjects stimulated at rMT and in the majority of those stimulated above rMT, suggesting underlying determinism of corticomotor excitability instead of randomly generated fluctuations. The majority of subjects showed significant phase clustering for MEP size and for MEP occurrence, and significant phase clustering was found at the group level. Furthermore, in approximately one-quarter to one-half of the subjects we found a significant correlation and dependence of MEP amplitude on the phase of infraslow activity, respectively. Although other mechanisms very likely contribute as well, our findings seem to suggest that infraslow activity is involved in the variability of cortical excitability and TMS-induced responses.

NEW & NOTEWORTHY Cortical excitability measures are highly variable during transcranial magnetic stimulation. Although ongoing brain oscillations are assumed to modulate excitability, no consistent associations are found for the traditional frequency bands. We focus on the role of infraslow EEG activity, defined as rhythms with frequencies < 0.1 Hz. We provide experimental evidence suggesting that infraslow activity most likely modulates corticomotor excitability and that response variation could be reduced when stimulation is targeted at a specific infraslow phase.

cortical excitability; infraslow activity; motor evoked potential; phase dependence; transcranial magnetic stimulation

INTRODUCTION

Cortical excitability, defined as the strength of a particular cortical output in response to an external stimulus, can be assessed noninvasively by transcranial magnetic stimulation (TMS). Single-pulse TMS at the motor cortex can induce a motor evoked potential (MEP), of which the peak-to-peak amplitude is a measure of corticomotor excitability (Barker et al. 1985). This amplitude is not constant when stimulating multiple times at the same intensity (Goldsworthy et al. 2016; Hess et al. 1987; Kiers et al. 1993; Roy Choudhury et al. 2011). Although this may result from variations in experimental design, such as minor changes in coil position or experimental noise, biological variations are likely to be involved as well (Schmidt et al. 2015). A candidate mechanism responsible for these trial-to-trial variations is fluctuations in cortical excitability (Amassian et al. 1989; Ferreri et al. 2014; Kiers et al. 1993).

Several studies suggest that ongoing brain oscillations are an important modulator of cortical excitability (Berger et al. 2014; Ferreri et al. 2014; Iscan et al. 2016; Kundu et al. 2014; Mäki and Ilmoniemi 2010; Sauseng et al. 2009; Schulz et al. 2014; Zarkowski et al. 2006; Zrenner et al. 2018). Whereas some report a correlation between the MEP amplitude and the prestimulus power in the alpha (Sauseng et al. 2009; Zarkowski et al. 2006), beta (Mäki and Ilmoniemi 2010; Schulz et al. 2014), or gamma (Zarkowski et al. 2006) band, others fail to find significant correlations for the various frequency bands (Berger et al. 2014; Iscan et al. 2016; Zrenner et al. 2018). Instead of prestimulus power, a recent study suggests that the high-alpha power variability might be a better predictor of variations in MEP amplitude (Iscan et al. 2016). Other studies found a significant association between MEP amplitude and the instantaneous phase of mu oscillations in the alpha band (Zrenner et al. 2018) or of oscillations in the midrange beta band (Mäki and Ilmoniemi 2010) or in the alpha, fast beta, and gamma bands (Berger et al. 2014).

Although brain oscillations are assumed to modulate cortical excitability, no consistent associations are found for the traditional frequency bands, ranging from delta to gamma (Berger et al. 2014; Iscan et al. 2016; Mäki and Ilmoniemi 2010; Sauseng et al. 2009; Schulz et al. 2014; Zarkowski et al. 2006; Zrenner et al. 2018). However, the brain also generates activity below 0.1 Hz and far above 70 Hz (Aladjalova 1964; Bragin et al. 1999; Vanhatalo et al. 2004). Brain rhythms with frequencies below 0.1 Hz are termed infraslow activity, or infraslow oscillations if they have a (nearly) periodic character (Aladjalova 1957, 1964; Hughes et al. 2011). Infraslow activity was measured for the first time in rabbits by Aladjalova in 1957. She observed faster oscillations that were phase-locked to the rising phase of the infraslow oscillation,

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suggesting that infraslow activity modulates cortical excitability (Aladjalova 1957). This was supported by her finding that cortical responses to afferent stimulation were primarily evoked when cortical excitability was increased and not when it was decreased.

More recently, Vanhatalo et al. (2004) showed that during sleep the phase of infraslow oscillations clearly correlates with both the amplitude of higher frequencies (1–100 Hz) and the occurrence of K-complexes and interictal epileptiform discharges (Vanhatalo et al. 2004). Also, in awake subjects the amplitude of faster oscillations (1–40 Hz) is strongly related to the infraslow fluctuation phase. In addition, the ability to detect a sensory stimulus significantly depends on the phase of infraslow fluctuations but not on the amplitude (Monto et al. 2008). Infraslow oscillations are even observed in postanoxic encephalopathy, and in those patients with a burst-suppression pattern bursts are phase-locked to the phase of the infraslow activity (van Putten et al. 2015). These observations further support the notion that infraslow activity appears to be a modulator of cortical excitability and of importance for physiological and pathological brain function (Hughes et al. 2011; Vanhatalo et al. 2004; van Putten et al. 2015).

The only TMS study examining the association between infraslow oscillations and variations in MEP amplitude was performed during non-rapid eye movement (NREM) sleep. More suprathreshold MEPs (amplitude > 50 μV) were evoked during the rising state of the infraslow oscillation than during the falling state. In addition, MEP amplitudes were ~20% larger when evoked during the rising state. The more positive the rising state, or the less negative the falling state, the larger the MEP amplitude (Bergmann et al. 2012). Obtaining similar findings in awake subjects might provide possibilities to reduce the large variation in MEP amplitude, as stimulation can be targeted at a specific oscillatory phase.

We use TMS-evoked potentials to study whether oscillations in infraslow activity modulate corticomotor excitability. We focus on the relation between infraslow activity and *1*) the MEP amplitude, by stimulating above the resting motor threshold (rMT), and *2*) the occurrence of a MEP, by stimulating at the rMT.

METHODS

We used single-pulse TMS data that were collected as part of two larger trials (trial IDs: NL36317.044.11 and NL49854.044.14). Both study protocols were approved by the medical ethics committee of Medisch Spectrum Twente and were in accordance with the Declaration of Helsinki. In addition, we followed the guidelines for the use of TMS in clinical practice and research (Rossi et al. 2009). Part of the data set was previously used in another context by ter Braack et al. (2013, 2016) and by de Goede and van Putten (2017).

Subjects

Healthy adults (18 yr or older) were included after they gave written informed consent. Subjects with contraindications as mentioned in the TMS screening questionnaire of Rossi et al. (2011) were excluded. Subjects participated either in the study evaluating the relation between infraslow activity and MEP amplitude or in the study focusing on the relation between infraslow activity and MEP occurrence.

TMS Protocol

During stimulation, subjects were instructed to keep their eyes open and to hold their dominant hand pronated in a relaxed position. Handedness was determined with the Dutch Handedness Questionnaire (van Strien 1992, 2003).

In all subjects, we manually located the motor hot spot of the abductor digiti minimi (ADM) muscle in the dominant hemisphere (left hemisphere for right-handedness). A figure-of-eight air-cooled 70-mm coil (Magstim, Whitland, UK) was placed tangentially at the ADM hot spot, with the handle pointing backward and laterally at an angle of 45° from the midline. Single biphasic TMS pulses, with a pulse duration of 400 μs, were given with a Magstim Rapid^2 Stimulator (Magstim). The stimulation intensity depended on the rMT, which was defined as the minimum intensity needed to evoke at least 5 MEPs with an amplitude > 50 μV out of 10 consecutive pulses (Groppa et al. 2012; Rossini et al. 2015).

Relation between infraslow activity and MEP amplitude. Some subjects were stimulated with 50 single pulses at an intensity of 120% rMT, with a random interpulse interval between 3.5 and 4.5 s. In others, 75 single pulses were given at an intensity of 110% rMT, with a random interpulse interval between 3 and 4 s.

Relation between infraslow activity and MEP occurrence. Subjects were stimulated with 200 single pulses at the rMT, to provoke that MEPs were only evoked 50% of the time. Pulses were divided into four blocks of 50 pulses, so that the stimulation intensity could be slightly adjusted if the rMT showed drift between blocks. A random interval ranging from 9.5 to 10.5 s was kept between consecutive single pulses.

Electroencephalogram Recording and Analysis

Full-band electroencephalogram (EEG) was continuously recorded during single-pulse TMS with either NeuroCenter EEG or ASA software (Clinical Science Systems, Leiden, The Netherlands and ANT Neuro, Enschede, The Netherlands, respectively), a DC-coupled EEG amplifier (TMSi, Oldenzaal, The Netherlands), and a TMS-compatible EEG cap (ANT Neuro). The EEG was sampled at either 4,000 or 2,048 Hz, with the ground electrode located between electrodes Fz and Fpz. The sample frequency of 2,048 Hz was only used when stimulating at 110% rMT.

For analysis we selected the electrode closest to the stimulation location (electrodes C3 and C4 for the left and right hemispheres, respectively), referenced to electrode Cz. The TMS artifact was removed by linear interpolation over a period of 25 ms around the TMS pulse. Thereafter, the EEG data were filtered with a first-order Butterworth band-pass filter between 0.01 and 0.1 Hz, to evaluate infraslow activity. We extracted the phase of the infraslow activity at the moment of stimulation with the Hilbert transform in MATLAB (version R2015a; The MathWorks, Natick, MA).

Electromyogram Recording and Analysis

Two surface Ag/AgCl electrodes placed in a belly-tendon montage were used to measure ADM muscle activity. For recording we used either the bipolar inputs on the EEG amplifier or an additional amplifier coupled to the EEG amplifier (both from TMSi). In the first case the electromyogram (EMG) was sampled at 4,000 Hz and the EEG ground electrode was used, whereas in the second case the sample frequency was 2,048 Hz and an external ground electrode was placed on the dorsal side of the nondominant hand.

Even though subjects were asked to fully relax their ADM muscle, recordings were checked afterward for muscle preactivation. Trials containing EMG activity > 50 μV in the 50 ms preceding the pulse

were excluded. Thereafter, we calculated the peak-to-peak amplitude of the MEP.

Statistical Analysis

To evaluate temporal clustering beyond chance, we investigated whether a nonrandom pattern was visible over time in MEP size or MEP occurrence. For stimulation above the rMT, MEPs were divided into those having a "large" or "small" amplitude using the 50th percentile per subject. For stimulation at the rMT, responses were divided based on whether a MEP was "present" or "absent" using an amplitude threshold of 50 μV. The pattern formed by time periods of consecutive equal responses (TP-ER) was compared to the patterns obtained by Monte Carlo simulation. For each subject, we created 1,000 surrogates based on the recorded data. The measured responses were shuffled with random permutation without replacement, resulting in patterns with a similar large/small or present/absent distribution. To evaluate temporal clustering at the subject level, we calculated per subject the probability of TP-ER as a function of their length for the recorded data as well as for the 1,000 surrogates. To evaluate temporal clustering at the group level, we calculated per stimulation intensity (120%, 110%, and 100% rMT) the probability of TP-ER as a function of their length for the combined recorded and surrogate data of all subjects. Both at the subject and group level, significant temporal clustering was assumed if the probability curve fell outside the 5–95th percentile range of the surrogate data, i.e., 5th percentile of surrogates $>$ probability $>$ 95th percentile of surrogates. In addition, we defined for each stimulation intensity the mean length and number of TP-ER over all subjects, as well as over the combined surrogate data of all subjects. A significant difference in mean length and number of TP-ER between subjects and surrogates was assumed if the recorded values fell outside the 5–95th percentile range of the surrogate data.

Complementary to temporal clustering, we investigated the pattern in MEP size (large or small) and MEP occurrence (present or absent) as a function of the phase of the infraslow activity, to evaluate the presence of significant phase clustering. The pattern formed by phase periods of consecutive equal responses (PP-ER) was compared to the patterns obtained by Monte Carlo simulation with 1,000 surrogates. Again, surrogates were created with random permutation without replacement. Because of the periodic nature of the phase, PP-ER could be formed by equal responses at the beginning and end of the phase period $-\pi$ to π. At the subject level, we calculated for each subject the probability of PP-ER as a function of their length for the recorded data as well as for the 1,000 surrogates, whereas at the group level the combined recorded and surrogate data of all subjects were used to calculate the probability curve. Significant phase clustering was assumed if the PP-ER probability curve fell outside the 5–95th percentile range of the surrogates. Furthermore, we tested whether there was a difference in mean length and number of PP-ER between subjects and surrogates, by assuming significance if the recorded values fell outside the 5–95th percentile range of the surrogate data.

In addition to the binary approach of MEP amplitude (large or small), we investigated the relation between the size of the MEP amplitude and phase of the infraslow activity. We assumed that the relation between the linear (MEP amplitude) and circular (phase of infraslow activity) data can be described by the function

$$\text{MEP amplitude} = a + b \times \sin(\theta - c).$$

The larger the value of parameter b, the stronger MEP amplitude depends on the phase. The least-square method was used for curve fitting and to determine the correlation. Again, we used a Monte Carlo simulation (random permutation without replacement) with 1,000 surrogates to determine the significance of parameter b and correlation coefficient R^2. We assumed significant phase dependence if parameter b fell outside the 5–95th percentile range of surrogates and significant correlation if $R^2 >$ 95th percentile of surrogates.

RESULTS

Previously collected single-pulse data of 38 subjects were considered suitable for this study. Nevertheless, five subjects were excluded from analysis: three subjects showed a lot of muscle preactivation, and in two subjects MEPs were often not evoked at an intensity of 110% rMT. We included 13 subjects (2 men, 11 women; mean age 28 ± 9.0 yr, range 20–49 yr; 12 right-handed) who were stimulated at an intensity of 120% rMT, 10 subjects (8 men, 2 women; mean age 29 ± 10.4 yr, range 21–54 yr; all right-handed) stimulated at 110% rMT, and 10 subjects (6 men, 4 women; mean age 29 ± 9.2 yr, range 23–54 yr; 7 right-handed) stimulated

Table 1. *Estimated rMT values and applied stimulation intensities for subjects stimulated at 120% rMT, 110% rMT, and 100% rMT*

	Stimulation intensity 120% rMT												
Subject no.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
rMT, %	62	59	59	70	68	70	58	79	76	64	68	75	61
intensity, %	74	71	71	84	82	84	70	95	91	77	82	90	73
	Stimulation intensity 110% rMT												
Subject no.	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*			
rMT, %	87	80	70	86	80	88	74	77	84	74			
Intensity, %	96	88	77	95	88	97	82	85	93	82			
	Stimulation intensity 100% rMT												
Subject no.	*24*	*25*	*26*	*27*	*28*	*29*	*30*	*31*	*32*	*33*			
rMT, %													
block 1	62	51	58	56	57	40	58	63	64	60			
block 2	56	48	61	59	60	40	57	63	55	65			
block 3	60	52	60	53	56	41	58	61	58	65			
block 4	61	55	59	56	53	41	57	61	59	64			

Both resting motor threshold (rMT) and transcranial magnetic stimulation intensity are expressed as % of maximum stimulator output (0.8 T).

at the rMT. For an overview of the estimated rMT values and applied stimulation intensities, see Table 1. All participants tolerated the single-pulse protocol well, and there were no adverse events.

All subjects showed infraslow activity in the 0.01–0.1 Hz range, with peak amplitudes > 5 μV. Four examples are presented in Fig. 1, including the phase of the infraslow activity and MEPs.

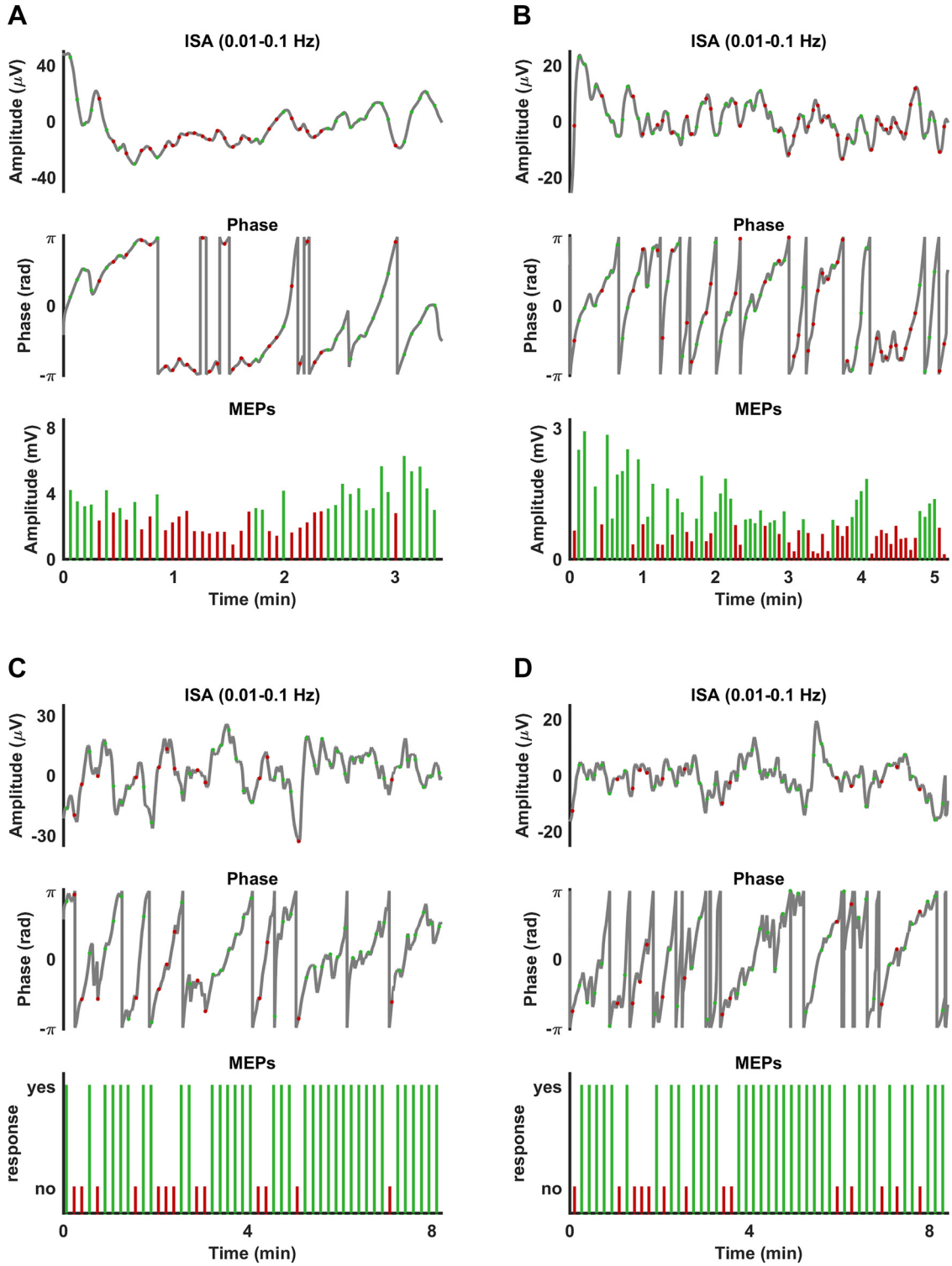

Fig. 1. Four examples of infraslow activity (ISA; *top*), the corresponding phase (*middle*), and motor evoked potentials (MEPs, *bottom*) in subjects stimulated at 3 intensities: 120% resting motor threshold (rMT) (*subject 8*; *A*), 110% rMT (*subject 19*; *B*), and 100% rMT (*subjects 30* and *27*; *C* and *D*). The moments of stimulation are represented by green and red dots (*top* and *middle*) or bars (*bottom*). Green, "large" and "present" MEPs; red, "small" and "absent" MEPs. In all subjects infraslow activity is present, with peak amplitudes > 5 μV.

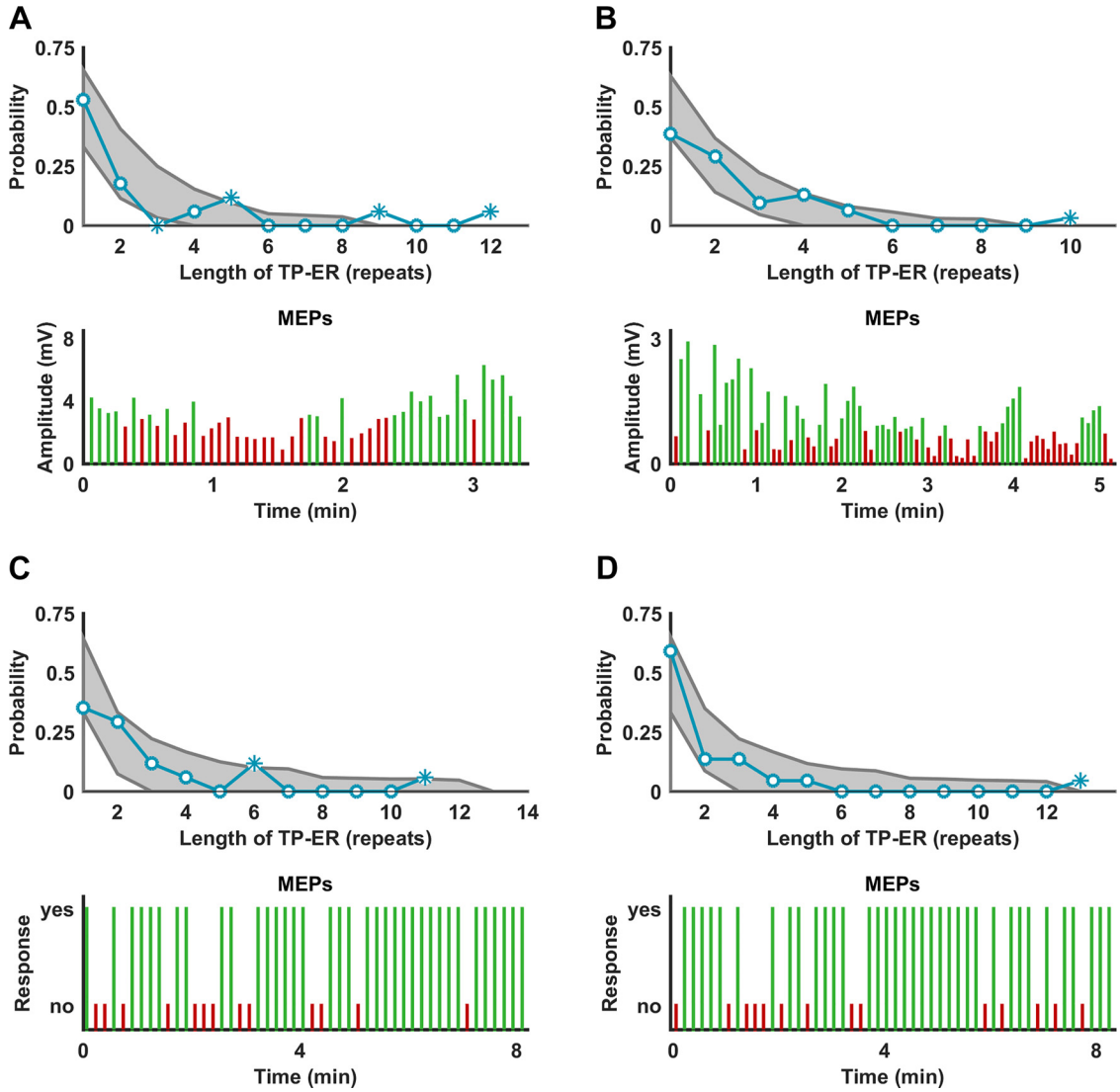

Fig. 2. Four examples of significant temporal clustering in subjects stimulated at 3 intensities: 120% resting motor threshold rMT (*subject 8*; *A*), 110% rMT (*subject 19*; *B*), and 100% rMT (*subjects 30* and *27*; *C* and *D*). *Top*: the probability curve of time periods of consecutive equal responses (TP-ER) as a function of their length (blue), including the 5–95th percentile range of the surrogate data (gray). *Significant probability values that fall outside the 5–95th percentile range of surrogates. *Bottom*: the pattern in motor evoked potential (MEP) size (*A* and *B*) or occurrence (*C* and *D*) over time. Green, "large" and "present" MEPs; red, "small" and "absent" MEPs.

Relation Between Infraslow Activity and MEP Amplitude: Stimulation Intensity 120% rMT

Figure 2*A*, *bottom*, shows the pattern in MEP size over time for *subject 8*: periods of consecutive large MEPs are alternated with periods of small amplitudes. Figure 2*A*, *top*, shows the probability of TP-ER as a function of their length. Even though a length of 1 has the highest probability, periods of 5, 9, or 12 consecutive repeats are also seen. As the probabilities of these longer TP-ER fall outside the 5–95th percentile range of surrogates, temporal clustering is present in this subject. Of all subjects, 69% showed significant temporal clustering. We also found significant temporal clustering at the group level when the recorded and surrogate data of all 13 subjects were combined (see Fig. 3*A*). Overall, the mean length of TP-ER was significantly longer in subjects than in surrogates (2.18; 5–95th percentile range of surrogates: 1.81–2.04) and the number of TP-ER was significantly lower (295; 5–95th percentile range of surrogates: 314–354).

In a similar way, Fig. 4*A* shows the pattern in MEP size over phase for the same subject, as well as the probability of PP-ER as a function of their length. Of all subjects, 69% showed significant phase clustering. At the group level, we found significant phase clustering (see Fig. 3*B*). Furthermore, the mean length of PP-ER was significantly longer in subjects than in surrogates (2.10; 5–95th percentile range of surrogates: 1.82–2.05) and the number of PP-ER was significantly lower (306; 5–95th percentile range of surrogates: 313–353).

Two examples of the relation between MEP amplitude and phase of infraslow activity are presented in Fig. 5, *A* and *B*. In both subjects MEP amplitude significantly depended on the phase, since parameter *b* fell outside the 5–95th percentile range of the surrogates (see Table 2). Significant phase dependence was found in 46% of the subjects. In half of these subjects (23% of all subjects) we found a weak but significant correlation, represented by $R^2 >$ 95th percentile of surrogates (see Table 2).

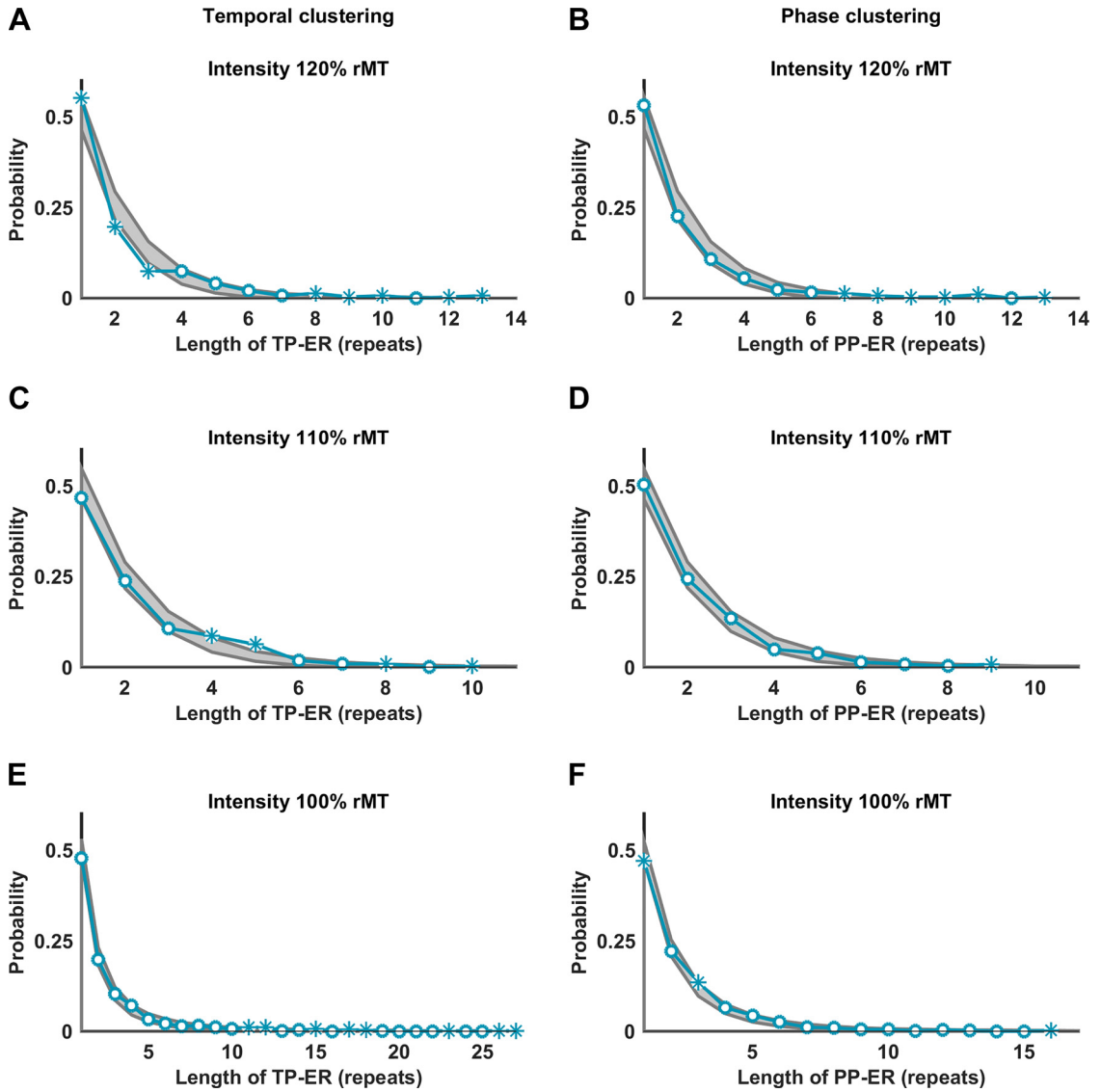

Fig. 3. Significant temporal (*left*) and phase (*right*) clustering at the group level for all 3 stimulation intensities: *A* and *B*: 120% resting motor threshold (rMT) ($n = 13$). *C* and *D*: 110% rMT ($n = 10$). *E* and *F*: 100% rMT ($n = 10$). *A*, *C*, and *E*: the probability curve of time periods of consecutive equal responses (TP-ER) as a function of their length (blue), including the 5–95th percentile range of the surrogate data (gray). *B*, *D*, and *F*: the probability curve of phase periods of consecutive equal responses (PP-ER). *Significant probability values that fall outside the 5–95th percentile range of surrogates.

Relation Between Infraslow Activity and MEP Amplitude: Stimulation Intensity 110% rMT

At the subject level, significant temporal clustering was found in 70% of the subjects (see Fig. 2*B* for an example). Significant temporal clustering was also found at the group level (see Fig. 3*C*). Furthermore, the mean length of TP-ER was significantly longer in subjects than in surrogates (2.19; 5–95th percentile range of surrogates: 1.84–2.06) and the number of TP-ER was significantly lower (336; 5–95th percentile range of surrogates: 357–400).

We found significant phase clustering in 60% of the subjects (see Fig. 4*B* for an example) as well as at the group level (see Fig. 3*D*). However, the mean length of PP-ER was not significantly longer in subjects than in surrogates (2.01; 5–95th percentile range of surrogates: 1.85–2.06), and the number of PP-ER was not significantly lower (366; 5–95th percentile range of surrogates: 358–399).

Figure 5, *C* and *D*, show the relation between MEP amplitude and phase of the infraslow activity for two subjects. Overall, we found a significant phase dependence in 40% of the subjects and a significant phase correlation in 30% of the subjects (see Table 2).

Relation Between Infraslow Activity and MEP Occurrence: Stimulation Intensity 100% rMT

All subjects (100%) showed significant temporal clustering in at least two of four blocks of 50 pulses. Clusters were formed by periods of consecutive present MEPs or absent MEPs (see Fig. 2, *C* and *D*). In most subjects the stimulation intensity was only slightly adjusted between blocks, because of some drift in rMT (see Table 1). We also found significant temporal clustering at the group level (see Fig. 3*E*). Furthermore, the mean length of TP-ER was significantly longer in subjects than in surrogates (2.98; 5–95th percentile range of

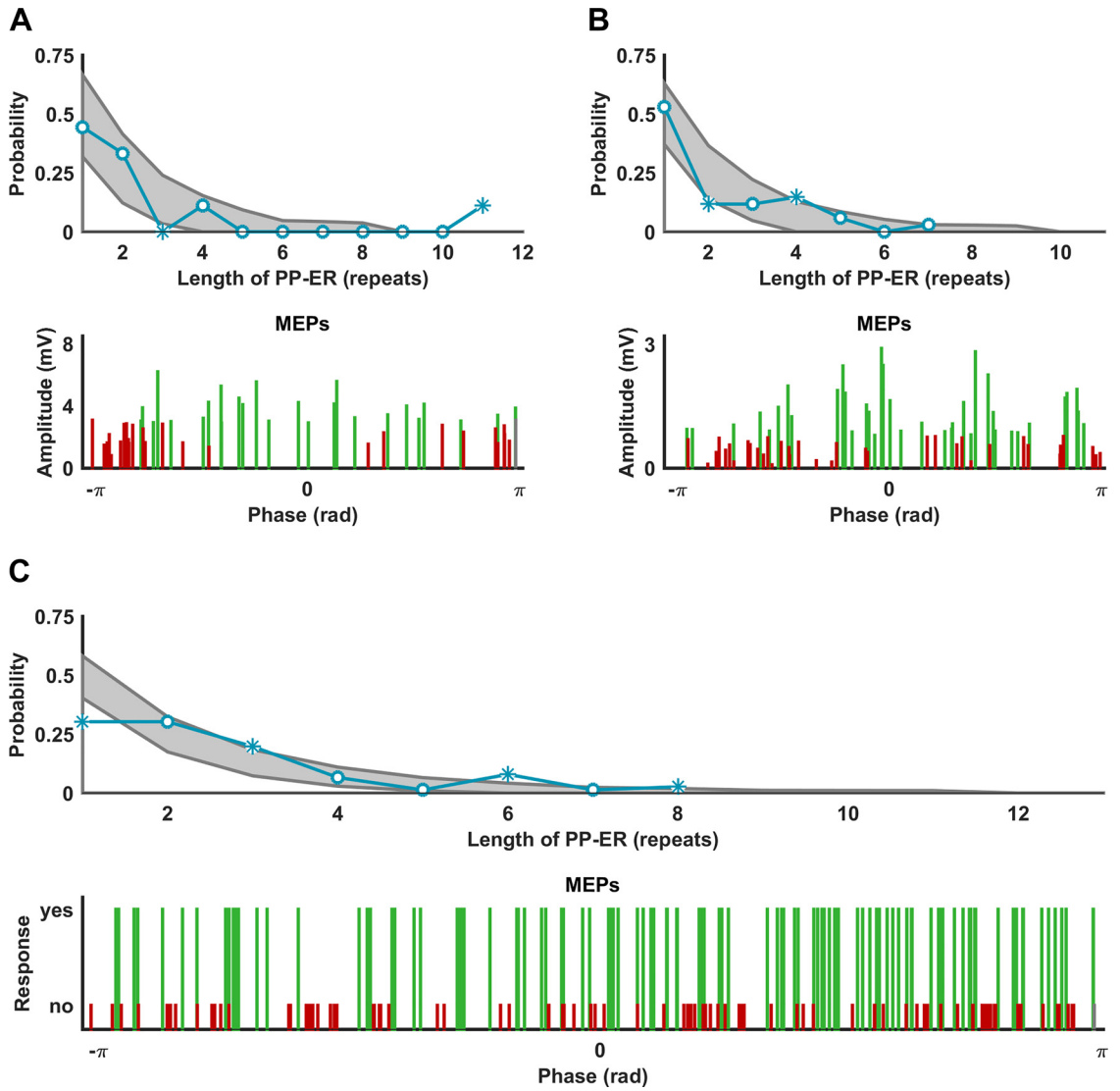

Fig. 4. Three examples of significant phase clustering in subjects stimulated at 3 intensities: 120% resting motor threshold (rMT) (*subject 8*; *A*), 110% rMT (*subject 19*; *B*), and 100% rMT (*subject 30*; *C*). *Top*: the probability curve of phase periods of consecutive equal responses (PP-ER) as a function of their length (blue), including the 5–95th percentile range of the surrogate data (gray). *Significant probability values that fall outside the 5–95th percentile range of surrogates. *Bottom*: the pattern in motor evoked potential (MEP) size (*A* and *B*) or occurrence (*C*) over phase. Green, "large" and "present" MEPs; red, "small" and "absent" MEPs. Note that the phase is periodic, so that amplitudes around π (in gray) are also presented around $-\pi$, forming a longer PP-ER.

surrogates: 2.49–2.68) and the number of TP-ER was significantly lower (644; 5–95th percentile range of surrogates: 717–771).

Of all subjects, 80% showed significant phase clustering (see Fig. 4*C*). At the group level, we found significant phase clustering (see Fig. 3*F*). Furthermore, the mean length of PP-ER was not significantly longer in subjects than in surrogates (2.32; 5–95th percentile range of surrogates: 2.16–2.33), but the number of PP-ER was significantly lower (828; 5–95th percentile range of surrogates: 833–894).

DISCUSSION

In this study we explored whether infraslow activity modulates corticomotor excitability by evaluating the presence of temporal and phase clustering of TMS-evoked responses. We found significant temporal clustering at a group level, in all individual subjects stimulated at rMT and in most of the subjects stimulated above rMT (69% for 120% rMT and 70% for 110% rMT). Furthermore, for all three stimulation intensities the mean length of TP-ER was significantly longer in subjects than in surrogates, and the number of TP-ER was significantly lower. Temporal clustering of MEP size and MEP occurrence suggests underlying determinism of corticomotor excitability instead of randomly generated fluctuations.

To explore the contribution of infraslow activity as a modulator of corticomotor excitability, we additionally evaluated phase clustering. Significant phase clustering was present in 60–69% of individual subjects when evaluating MEP size, whereas this was 80% when evaluating the occurrence of a MEP. Furthermore, we found significant phase clustering at a group level for all three stimulation intensities. Only at 120% rMT and 100% rMT did we find significant differences in mean length and/or number of PP-ER between subjects and surrogates. Although the presence of both temporal and phase

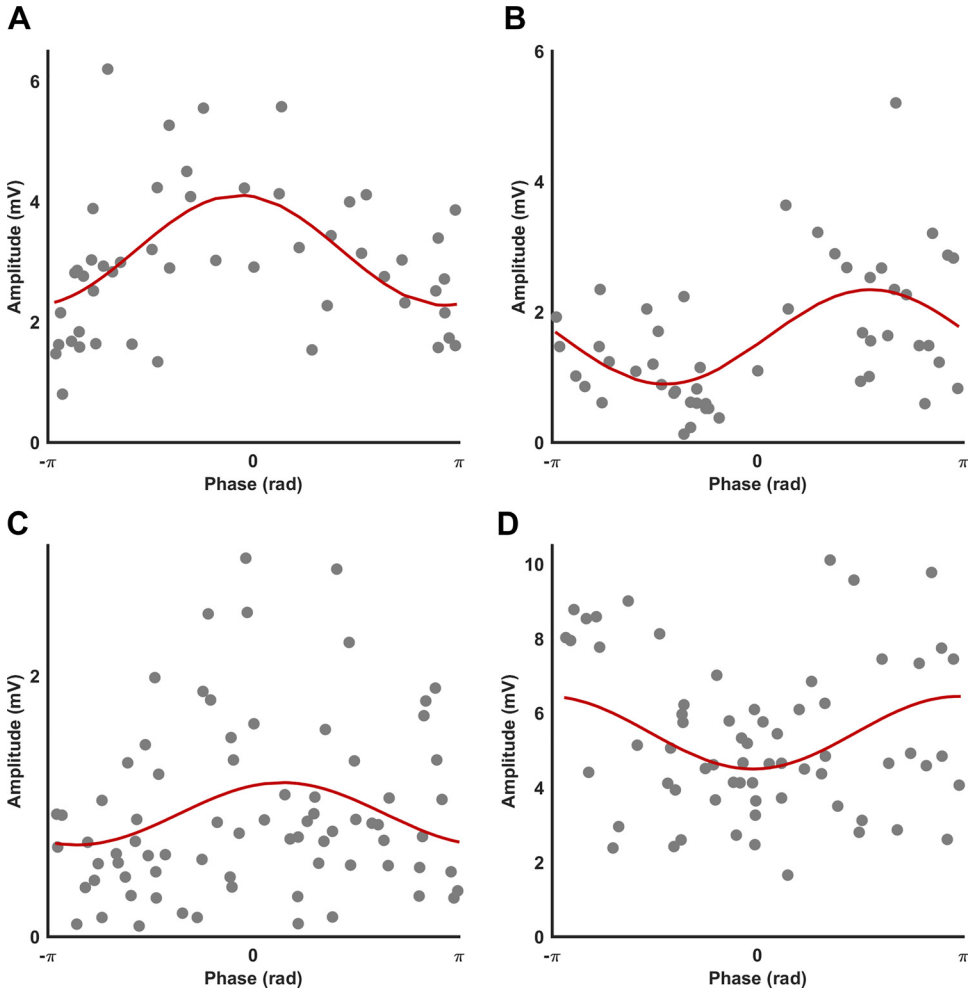

Fig. 5. Four examples of significant dependence of motor evoked potential (MEP) amplitude on the phase of the infraslow activity in subjects stimulated at 2 intensities: 120% resting motor threshold (rMT) (*subjects 8* and *10*; *A* and *B*) and 110% rMT (*subjects 19* and *15*; *C* and *D*). The least-square method was used to fit a sine function (red line) through the MEP amplitudes and their corresponding phases (gray dots).

clustering indicates a contribution of infraslow activity as a modulator of corticomotor excitability, significant clustering was not found in all subjects. In 40–46% of subjects we found a significant dependence of MEP amplitude on the phase of the infraslow activity. In addition, we found a weak ($R^2 < 0.31$) but significant amplitude-phase correlation in 23–30% of subjects. We assumed a sinusoidal relation between amplitude and phase, due to the periodic nature of the phase. The fitted sinus curves had no constant shape, as can be seen in Fig. 5, whereas Bergmann et al. (2012) reported that MEP amplitudes were

Table 2. *Parameter b and correlation coefficient R^2 of fitted sine function through linear and circular data of subjects stimulated at 120% rMT and 110% rMT*

	Stimulation intensity 120% rMT												
Subject no.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
b, subject	−0.38	0.25*	0.24	−0.15	−0.26*	0.31	−0.15	−0.91*	−0.19*	0.72*	0.22	−0.54	0.06*
b, 5th perc	−0.61	−0.24	−0.24	−0.17	−0.24	−0.34	−0.29	−0.53	−0.17	−0.42	−0.24	−0.63	−0.04
b, 95th perc	0.67	0.25	0.27	0.20	0.26	0.39	0.31	0.57	0.19	0.47	0.26	0.63	0.05
R^2, subject	0.04	0.10	0.07	0.06	0.09	0.07	0.03	0.26*	0.09	0.31*	0.07	0.09	0.13*
R^2, 95th perc	0.13	0.12	0.12	0.11	0.12	0.12	0.12	0.12	0.10	0.11	0.11	0.11	0.12
	Stimulation intensity 110% rMT												
Subject no.	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*			
b, subject	0.16	0.97*	0.18	−0.21*	−0.12	−0.24*	0.10	−0.13	0.23*	0.24			
b, 5th perc	−0.16	−0.71	−0.19	−0.16	−0.15	−0.22	−0.12	−0.15	−0.15	−0.37			
b: 95th perc	0.18	0.80	0.20	0.17	0.16	0.23	0.13	0.17	0.15	0.42			
R^2, subject	0.06	0.12*	0.05	0.10*	0.03	0.07	0.04	0.04	0.14*	0.02			
R^2, 95th perc	0.07	0.08	0.08	0.08	0.08	0.08	0.08	0.07	0.08	0.07			

For the 1,000 surrogates either the 5th and 95th percentiles (parameter *b*) or only the 95th percentile (R^2) is given. *Significant values (parameter *b*: outside 5–95th percentile range surrogates; R^2: larger than 95th percentile surrogates). perc, Percentile; rMT, resting motor threshold.

consistently larger when evoked during the rising state (phase between $-\pi$ and 0 rad) compared with the falling state (phase between 0 and π rad) of the slow oscillation (Bergmann et al. 2012). This discrepancy might be explained by the fact that we measured subjects during wakefulness instead of during NREM sleep, where MEP responses do not resemble wakelike responses. In addition, we applied a relatively small number of pulses over the entire range between $-\pi$ and π, and the phase at the moment of stimulation was determined off-line. In contrast, Bergmann et al. (2012) used an automatic real-time detection algorithm to trigger TMS pulses very specifically during either the rising or falling state (Bergmann et al. 2012). This targeted approach makes it possible to discriminate two conditions (rising and falling state), each containing a higher number of trials.

The presence of both temporal and phase clustering was more prominent for MEP occurrence than for MEP amplitude. The fact that a stronger association was found for MEP occurrence might be related to differences in methodology and statistics. A smaller number of pulses were given to evaluate the relation between infraslow activity and MEP amplitude compared with MEP occurrence, 50–75 versus 200 single pulses, respectively. Furthermore, the large/small distribution was always 50%/50% for the MEP amplitude, whereas the present/absent distribution could be unbalanced for MEP occurrence. The influence of both factors on the variation in surrogate data might explain our finding.

Reduction of variability has been explored with brain state-triggered TMS, as applied by Bergmann et al. (2012). In this type of closed-loop systems, the TMS pulse is applied as a function of the simultaneously recorded instantaneous EEG (Zrenner et al. 2016). Recently this approach was applied by Zrenner et al. (2018) to synchronize TMS pulses to the phase of ongoing mu oscillations in the alpha band for the sensorimotor cortex. Stimulation during the positive peak of mu oscillations (low-excitability state) resulted in significantly smaller MEP amplitudes than during the negative peak (high-excitability state). Furthermore, a long-term potentiation-like increase in excitability was seen for repetitive stimulation (100 Hz) during the high-excitability state only, whereas no change in excitability was observed when targeting the low-excitability state or random phases of the mu oscillations (Zrenner et al. 2018). This indicates that the therapeutic potential of TMS could be optimized by targeting a specific oscillatory phase, due to a reduction of the TMS response variability.

Generation and Relevance of Infraslow Activity

Various mechanisms have been proposed to be involved in the generation of low-frequency fluctuations. Aladjalova showed that infraslow activity can be recorded in cortical slabs without any subcortical input (Aladjalova 1964), suggesting that cortical neurons have an intrinsic ability to generate very slow activity. Infraslow oscillations have also been recorded in the thalamus in rats (Albrecht et al. 1998; Albrecht and Gabriel 1994), in anesthetized guinea pigs in vivo (He 2003), and in individual thalamocortical neurons in slices of cat sensory thalamic nuclei (Hughes et al. 2011; Lőrincz et al. 2009; Parri et al. 2001; Parri and Crunelli 2001).

Furthermore, infraslow activity may result from glia cells or the blood-brain barrier (Amzica and Steriade 2000; Vanhatalo et al. 2004; Voipio et al. 2003). In addition, nonbrain contributions to infraslow electrical activity recorded from the scalp may result from respiration or changes in skin resistance. Depending on the relative power of these other sources of infraslow activity, correlations between our readouts for cortical excitability may be modified, which may explain the variability in phase dependence that we found for MEP amplitude.

The biological significance of infraslow activity in relation to cortical excitability is not fully clear (Berger et al. 2014; Iscan et al. 2016; Zrenner et al. 2018). Most likely, however, the functional role of infraslow brain rhythms is similar to what has been reported for brain rhythms in general: to realize local-global interactions between neuronal networks and preservation of persistent activity (Buzsáki and Draguhn 2004). For example, beta frequencies appear to be involved in synchronization of remote networks in the brain, whereas gamma rhythms are used for relatively local computations (Avella Gonzalez et al. 2014; Buzsáki and Watson 2012; Kopell et al. 2000). Infraslow EEG fluctuations are correlated with resting state network dynamics (Grooms et al. 2017; Hiltunen et al. 2014), suggesting a role in synchronizing network activity across large areas across the neocortex. As such synchrony involves variations in excitability of the involved networks (Pesaran et al. 2018), responses to external perturbations as applied in our study will vary as well.

Limitations

We only explored whether infraslow activity modulates corticomotor excitability, instead of evaluating multiple frequency bands. Significant associations between the phase of brain oscillations and MEP amplitude have been reported for rhythms in the alpha, beta, and gamma bands (Berger et al. 2014; Mäki and Ilmoniemi 2010; Monto et al. 2008; Zrenner et al. 2018). However, the large TMS artifact hampers off-line estimation of the phase at the moment of stimulation. Linear interpolation over a period of 25 ms around the TMS pulse did not influence the infraslow activity filtered between 0.01 and 0.1 Hz, although it did affect faster frequency bands. Furthermore, EEG signals are typically not strictly periodic. Therefore, extracting and interpretation of the physical meaning of phase from such signals is not straightforward (Kraskov et al. 2004). However, other studies used a similar approach to exact phase from the EEG and observed phase dependencies as well, ranging from perception of touch (Monto et al. 2008) and selectivity of neuronal firing (Ng et al. 2013) to long-term potentiation (Zrenner et al. 2018).

Another limitation is the potential contribution of sweat, which can cause voltage fluctuations in the infraslow frequency range. However, since all subjects were measured at rest, it is unlikely that subjects sweated a lot during the TMS session. Furthermore, if sweat artifacts had been present, correlations with our readouts are improbable.

Temporal clustering could be influenced by changes in coil positioning or physiological factors such as respiration rate, blood pressure, or attention level (Conte et al. 2007; Mars et al. 2007), which we did not evaluate. In most subjects, however, the rMT did not vary much between the four blocks of 50 pulses that were applied to study the relation between infraslow activity and MEP occurrence. Nevertheless, because of a dif-

ference in the timescale of variations in MEP and rMT, we cannot exclude the influence of nonspecific factors. In case of drift, the stimulation intensity was slightly adjusted to provoke that MEPs were only evoked 50% of the time. Although changing the intensity might have influenced infraslow activity and corticomotor excitability, we tried to obtain a present/absent MEP distribution that was as close to 50%/50% as possible.

We evaluated infraslow activity measured at the electrode closest to the stimulation location. This choice was made because others found modulatory effects that were topographically delimited to the stimulated motor cortex. No significant effects for MEP amplitude were found for oscillations measured in the contralateral motor cortex or in the occipital or frontal cortex (Bergmann et al. 2012; Mäki and Ilmoniemi 2010; Sauseng et al. 2009). For the amplitude of TMS evoked potential (TEP) components, however, modulatory effects were not necessarily restricted to the stimulation site. During NREM sleep, TEP amplitudes were significantly larger when evoked during the rising state of slow oscillations (<1 Hz) compared with the falling state. Although this effect was still most prominent at the stimulation location for the P40 and N120 peaks, fronto-central and centro-parietal channels showed the largest differences for the late N400 peak (Bergmann et al. 2012). It thus seems to depend on the TMS outcome measure whether the modulatory effect is strictly local or global.

In conclusion, significant temporal clustering was found at the group level, in all individual subjects stimulated at the rMT, and in most of the subjects stimulated above rMT. In addition, the majority of subjects showed significant phase clustering for MEP occurrence and MEP size, and significant phase clustering was found at the group level. Furthermore, in approximately one-quarter to one-half of the subjects we found a significant correlation and dependence of MEP amplitude on the phase of infraslow activity, respectively. The presence of both temporal and phase clustering and phase dependence makes the contribution of infraslow activity as a modulator of cortical excitability likely, even though additional mechanisms are most probably involved as well.

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DISCLOSURES

M. J. A. M. van Putten is cofounder of Clinical Science Systems, Leiden, The Netherlands. No other conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.A.d.G. and M.J.v.P. conceived and designed research; A.A.d.G. performed experiments; A.A.d.G. analyzed data; A.A.d.G. and M.J.v.P. interpreted results of experiments; A.A.d.G. prepared figures; A.A.d.G. drafted manuscript; A.A.d.G. and M.J.v.P. edited and revised manuscript; A.A.d.G. and M.J.v.P. approved final version of manuscript.

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