Title: Beta rhythm events predict corticospinal motor output

Running Title: Beta events and corticospinal excitability

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Abstract

The beta rhythm (15-30 Hz) is a prominent signal of sensorimotor cortical activity. This rhythm is not sustained but occurs non-rhythmically as brief events of a few (1-2) oscillatory cycles. Recent work on the relationship between these events and sensorimotor performance suggests that beta events are the biologically relevant elements of the beta rhythm. However, the influence of these events on corticospinal excitability, a mechanism through which the primary motor cortex controls motor output, is unknown. We addressed this question by evaluating relationships between beta events and corticospinal excitability in healthy adults. We report that the number and amplitude of beta events, as well as their timing relative to transcranial magnetic stimulation (TMS) delivery, significantly predict corticospinal excitability. Findings document the relationship between beta events and corticospinal motor output, as required for tuning precise motor behavior.

Introduction

The primary motor cortex influences motor output through a balance between excitation and inhibition within cortical microcircuits that synapse onto pyramidal neurons. The excitability of these circuits can be measured non-invasively using transcranial magnetic stimulation (TMS), which elicits motor-evoked potentials (MEPs; Bestmann and Krakauer 2015). Excitability of these circuits also fluctuates spontaneously, partly determined by the phase and power of endogenous sensorimotor oscillatory activity (Sauseng et al. 2009; Kraus et al. 2016; Zrenner et al. 2018; Hussain et al. 2018).

We recently demonstrated that sensorimotor beta activity positively relates to corticospinal excitability, with higher beta power predicting larger MEP amplitudes (Hussain et al. 2018). However, the beta rhythm is not sustained but emerges as brief events that typically last 1-2 oscillatory cycles, termed beta events. Biophysical modeling of cortical microcircuits suggests that

beta events emerge from interactions between broad, excitatory synaptic drive to proximal dendrites of pyramidal neurons and shorter, stronger excitatory drive to distal dendrites of pyramidal neurons (Sherman et al 2016; Jones 2016). Further, characteristics of beta events (i.e., number, duration, amplitude and timing of events with respect to a stimulus) are associated with variability in somatosensory perception (Shin et al. 2017) and motor performance (Torrecillios et al. 2018). However, the relationship between beta events and corticospinal excitability, a basic mechanism by which the primary motor cortex influences motor output (Chen et al. 1998), is unknown. Here, we evaluated the relationship between corticospinal excitability and various characteristics of beta events using simultaneous TMS and EEG in healthy volunteers.

Methods

Healthy adults (N=20, 6 F, 14 M, age = 30 +/- 1.59 [SEM] years) participated in this study, which was approved by the National Institutes of Health Combined Neuroscience Section Institutional Review Board. All subjects provided their written informed consent before participation. Data acquired for this study have been published previously (Hussain et al. 2018).

After identifying the scalp hotspot and resting motor threshold (RMT) for the left first dorsal interosseous muscle (L. FDI), 600 single pulses of monophasic open-loop TMS were delivered to the right motor cortex (MagStim 200^2, MagStim Co. Ltd, UK) during EEG recordings. See Supplementary Methods for details of MEP measurement.

EEG data were segmented, re-referenced to average reference, and the Hjorth transform of the electrode closest to the contralateral motor cortex was obtained (C4; Hjorth 1975; Zrenner et al. 2018; Hussain et al. 2018). After identifying each subjects' individual beta frequency, mean beta power and individual beta events were extracted from the pre-stimulus period (-1.0 to -0.05 s

before TMS). Beta events were defined using two thresholds: a literature-based threshold (Torrecillos et al. 2018) and an empirically-defined threshold (Supplementary Figure 1, Shin et al. 2017). Next, multiple features of these events were extracted, including number, duration, maximum amplitude, and timing relative to the TMS pulse (Figure 1). See Supplementary Methods for a complete description of event identification and characterization procedures.

Linear mixed-effects modeling of trial-by-trial relationships between beta oscillation metrics and MEP amplitudes was performed (fixed effects of METRIC [number, duration, maximum amplitude, timing, mean power], random intercepts of SUBJECT). Separate models were fit for each beta oscillation metric. F-statistics resulting from each model fit were transformed to Z-values (Hughett 2007) to enable comparability across metrics.

Results

As previously described, the sensorimotor beta rhythm was comprised of transient, non-rhythmic burst-like events of high beta power. Events occurred at a rate of 1.24 per second (1.17 ± 0.016 [SEM] events per 0.95 s pre-stimulus period) and lasted for ~110-120 ms (114 ± 0.9 [SEM] ms).

Multiple beta event characteristics significantly predicted MEP amplitudes (Table 1). The number of beta events within the pre-stimulus period (Z-value=4.90), event maximum amplitude (Z-value=2.84), and timing of the last event relative to TMS delivery (Z-value=1.89) were all significantly associated with MEP amplitudes (see Table 1). Positive model estimates for number and maximum amplitude indicate that larger MEP amplitudes were associated with a greater number of events and larger events. In contrast, the negative model estimate for beta event timing indicate that larger MEP amplitudes were associated with events that occurred closer in time to

TMS delivery (Figure 1). Results were similar regardless of the threshold used for event identification (Table 1).

	Beta metric	**Model estimate**	**R^2**	**Z-value**	**P-value**
75th percentile threshold (69% event trials, N=5663)	Event number	0.05	0.37	4.90	4.7E-07*
	Event duration	0.31	0.38	1.32	9.3E-02
	Event max amp	0.01	0.38	2.84	2.3E-03*
	Event timing	-0.10	0.38	1.89	2.9E-02*
	Mean beta power	0.07	0.38	4.63	1.8E-06*
82nd percentile threshold (54% event trials, N=4477)	Event number	0.06	0.37	5.29	6.0E-08*
	Event duration	0.20	0.37	0.29	3.9E-01
	Event max amp	0.01	0.37	2.99	1.4E-03*
	Event timing	-0.09	0.37	1.45	7.4E-02
	Mean beta power	0.07	0.37	4.31	8.0E-06*
All trials, (N=8237)	Mean beta power	0.08	0.37	6.48	4.6E-11*

Table 1. Relationships between MEP amplitude and beta event characteristics and mean beta power across two different event-definition thresholds. Asterisks (*) indicate significance at an alpha of 0.05.

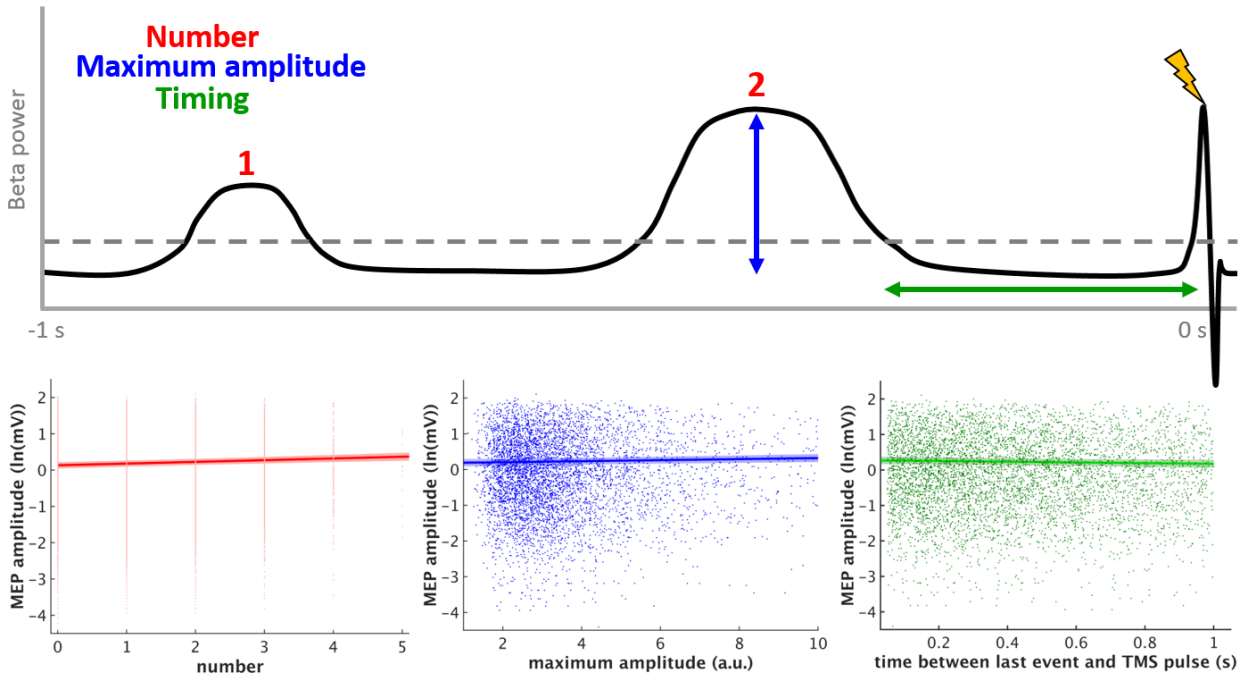

Figure 1. Beta event characteristics predict MEP amplitude. Beta events occurring in the pre-stimulus period (-1 s to -0.05 s relative to TMS delivery, yellow lightning bolt) were characterized based on their number (2 in schematic above, red), maximum amplitude of the last event (intra-individually normalized maximum amplitude, blue) and timing of the last event relative to TMS delivery (green). Beta event number and maximum amplitude were positively related to MEP amplitude, indicating that a greater number of events, as well as larger events, occurred prior to larger MEPs. The timing of the last event relative to TMS delivery was negatively related to MEP amplitude, indicating that MEPs were larger when an event occurred closer in time to TMS delivery.

Consistent with our recent work (Hussain et al. 2018), mean beta power also positively predicted MEP amplitude (all trials [N=8325]; model estimate=0.08, R^2=0.37, p=4.6^{-11}; Z-value=6.48). This relationship was also present when only trials containing beta events were considered (event trials [N=5663]; R^2=0.38, p=1.8^{-6}; Z-value=5.29). In contrast, when only trials containing no beta

events were considered, the relationship was consistently weaker across a range of thresholds (see Supplementary Figure 2; non-event trials defined using the 75th percentile threshold [N=2574]; R^2=0.35, p=0.01; Z-value=2.22).

Finally, beta event characteristics showed moderate variability in their correlations with mean beta power (Pearson's correlation, number [R=0.53], duration [R=0.33], and amplitude [R=0.63], all p<0.001).

Discussion

We evaluated the influence of non-rhythmically occurring brief events of strong beta activity, likely the biologically relevant elements of the beta rhythm (Shin et al. 2017; Torrecillos et al. 2018), on corticospinal excitability by recording sensorimotor oscillatory activity during single-pulse TMS. More beta events, larger beta events, or more recent occurrence of beta events preceding TMS delivery significantly predicted larger MEP amplitudes, indicating that their presence may generate periods of increased corticospinal excitability. Beta events have been proposed to arise from simultaneous weak proximal and strong distal excitatory drive to pyramidal neurons (Sherman et al. 2016). Building on this model, our findings may indicate that the combined distal and proximal excitatory drive during beta events brings pyramidal neurons closer to their firing threshold, allowing a greater proportion to fire action potentials when TMS is delivered. Then, a larger MEP is elicited.

Consistent with previous reports (Shin et al. 2017; Torrecillos et al. 2018), beta event characteristics and mean beta power similarly explained variation in corticospinal excitability. Despite this similar predictive power, measuring beta events enables simulation and interpretation of experimental observations in the context of specific cellular and circuit-level neural generators (Neymotin et al. 2018), which is a step forward relative to general descriptions of oscillatory power.

Using this simulation approach, Sherman et al. demonstrated that interactions between layer II/III and V pyramidal neurons and inhibitory interneurons precisely account for beta event waveforms (Sherman et al. 2016). Thus, even when beta events do not more strongly predict an experimental outcome compared to mean beta power (Shin et al. 2017; Torrecillos et al. 2018; and the current work), accounting for event characteristics refines interpretation of results. A more precise interpretation of observed neural signals enables a deeper understanding of the physiologic processes and dysfunctional circuits underlying neurological conditions (Cole et al. 2017), which could pave the way for new interventional techniques that selectively restore function in these circuits.

In sum, we demonstrate that the presence and specific characteristics of beta events predict MEP amplitude. Findings underline the importance of beta events in human motor control by documenting their role in determining corticospinal excitability, a mechanism through which the primary motor cortex controls human motor output.

Supplementary Material

Supplementary information associated with this manuscript is available in the attached file; Supplementary Material.

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