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Cardiac cycle does not affect motor evoked potential variability: A real-time EKG-EMG study

Motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) are highly variable, reflecting physiological fluctuations in the corticospinal excitability. Besides changes in coil 3D-orientation, MEP variability also depends on several physiological factors related to the state of the stimulated cortex [1,2]. Another factor, poorly investigated so far, is the physical brain displacement secondary to fluctuations in intracranial pressure (ICP). ICP fluctuations are mostly related to forward-travelling arterial blood pressure pulses secondary to the cardiac cycle [3]. A magnetic resonance imaging (MRI) study estimated a brain displacement secondary to the cardiac cycle of ≈0.2 mm in the frontal lobe in young subjects, with a time to peak of ≈500 ms from the R-wave of electrocardiogram (EKG) [4].

Recent MRI-based modelling demonstrated that slight changes in TMS-induced currents' direction influence the electric field voltage at the axon hillock [5], thus eliciting different patterns of corticospinal neurons activation. Therefore, a physical displacement of the brain parenchyma might lead to variations in the angle between the TMS-induced electric field and the stimulated fibers and, in turn, affect MEP variability. Few studies have previously tested this hypothesis by evaluating the relationship between the cardiac cycle and MEP amplitude variability [6–8]. However, the cohorts included a limited number of participants. Moreover, MEPs were gated only to a single period of the cardiac cycle [6], the cycle was split into a few intervals [7], or the relationship between specific cardiac phase and MEP amplitude was explored only by post-acquisition analyses [8]. Finally, none have verified possible changes in MEPs inter-trial variability in the various cardiac cycle phases.

We here readdressed this issue by examining possible changes in MEP amplitudes during several phases of the cardiac cycle through a real-time EKG-EMG co-registration approach in a large sample of subjects. Also, as a measure of inter-trial variability of MEP, we calculated the coefficient of variation (CV) of MEP amplitude at each EKG or cardiac phase.

We enrolled 30 participants (13 females, mean age 24.7 ± 2.7) with no history of neuropsychiatric or cardiac diseases. TMS pulses were delivered through a Magstim 200^2 (Magstim Company Ltd) connected to a figure-of-eight coil with postero-anterior orientation. The hotspot of the right first dorsal interosseous muscle (FDI) and the intensity for evoking ≈1 mV MEPs (MT_{1mV}) were identified [1]. EMG activity from FDI and the EKG (lead I according to standard methods) were recorded using surface electrodes. The EMG and EKG raw signals were amplified and band-pass filtered (20Hz-1kHz and 0.5–40Hz, respectively), digitalized and stored for off-line analyses. Heart rate (HR) was calculated from the average R-R interval duration during the recording through offline EKG track analysis.

TMS pulses were synchronized with EKG signal using the R-wave peak as a trigger through a custom-made script on Signal software (Cambridge Electronic Design). Twenty single pulses at MT_{1mV} (inter-stimulus interval: 4.5–5.5 ms) were randomly delivered at 0, 100, 200, 300, 400, 500, and 600 ms after the R-wave peak (T1-T7; 140 total pulses) (Fig. 1A). Peak-to-peak MEP amplitude was averaged for each time-point. Systole and diastole duration was estimated as a function of HR and the amplitude of MEPs evoked during systole or diastole was averaged. To investigate possible changes of MEP amplitude across the different EKG (T1-T7) or cardiac phases (systole, diastole), we compared the averaged MEP amplitude for each tested time-point against the overall average (i.e. average of the 140 trials considering all time-points together). We also calculated the CV of MEP amplitude (CV% = SD/mean*100) at each time-point, a measure of inter-trial variability in the various EKG intervals and/or cardiac phases. Two repeated-measure ANOVAs were performed on MEP amplitude and CV% with the factor "time-point" (levels: T1-T7). Paired t-tests were used to compare MEP amplitude and CV% between systole and diastole. The level of statistical significance was set at $p < 0.05$.

None of the subjects reported side-effects during the study. Four subjects were excluded from the analyses since they had HR > 100 bpm, implying a cardiac cycle lasting <600 ms and thus precluding MEP recordings at T7. Repeated-measure ANOVA showed a non-significant effect of the factor "time-point" on MEP amplitude ($F_{6,150} = 0.80$, $p = 0.57$) and CV% ($F_{6,150} = 1.71$, $p = 0.12$). Similarly, MEP amplitude ($t = 1.44$, $p = 0.16$) and CV% ($t = -1.28$, $p = 0.21$) were comparable between the two phases of the cardiac cycle (Fig. 1B–E).

We designed this experiment following the hypothesis that the minimal brain displacement secondary to the cardiac cycle would determine subtle changes in the geometrical disposition of neuronal elements within M1 in relation to the orientation of the TMS-induced electric field. Accordingly, the specific pattern of corticospinal activation would slightly change in the various phases of the cardiac cycle, resulting in different MEP amplitudes. This physiological phenomenon would therefore contribute to the variability of MEPs [6]. Our results showing comparable MEP amplitude and CV% between the 7 different intervals of EKG and between the systolic and diastolic phases suggest a non-significant effect of cardiac cycle-related brain displacement. Several arguments may explain our negative findings. First, the amount of brain parenchyma displacement due to the cardiac cycle [4] would cause a variation between the geometrical disposition of M1 neurons and the TMS-

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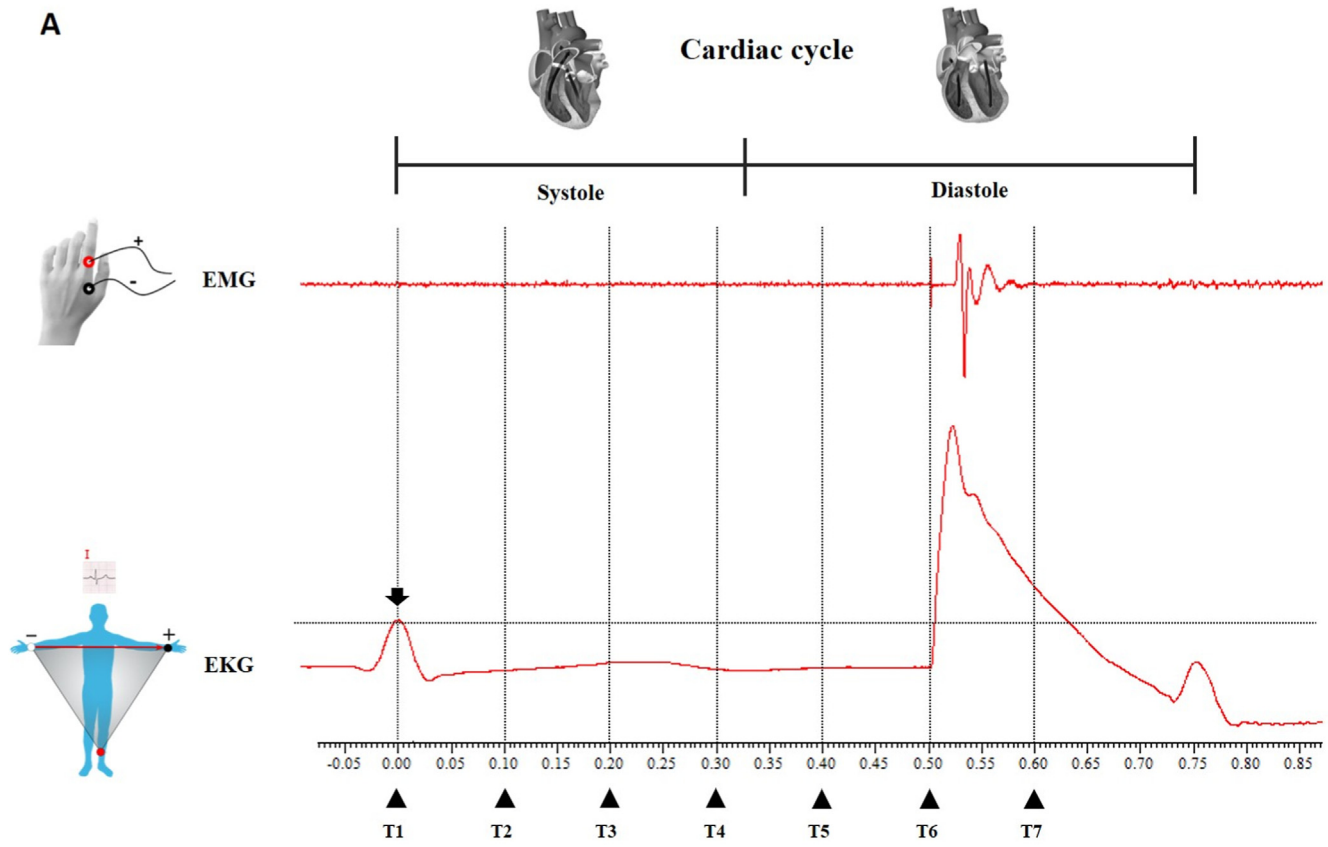
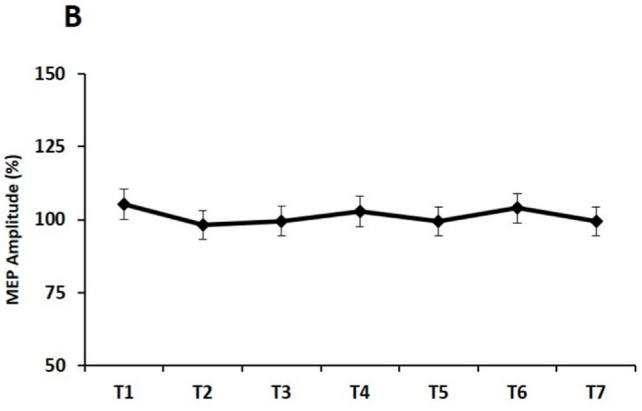
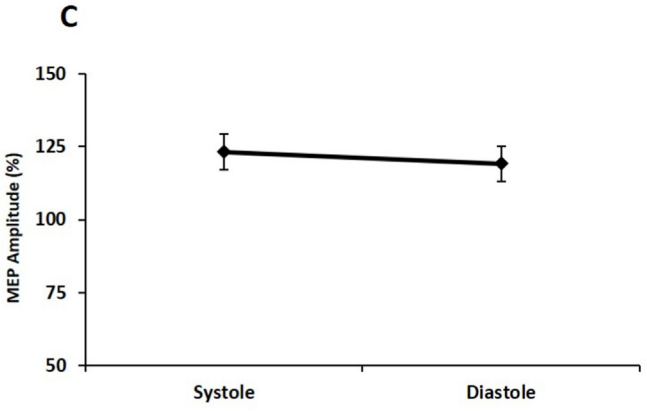
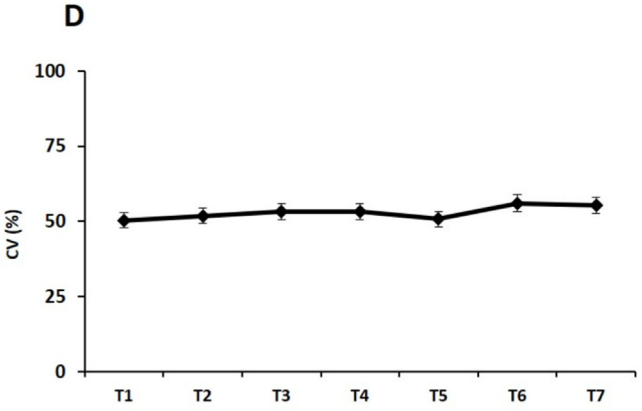

A
Cardiac cycle
Systole
Diastole
EMG
EKG
-0.05 0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85
T1 T2 T3 T4 T5 T6 T7


B
MEP Amplitude (%)
150
125
100
75
50
T1 T2 T3 T4 T5 T6 T7


C
MEP Amplitude (%)
150
125
100
75
50
Systole
Diastole


D
CV (%)
100
75
50
25
0
T1 T2 T3 T4 T5 T6 T7

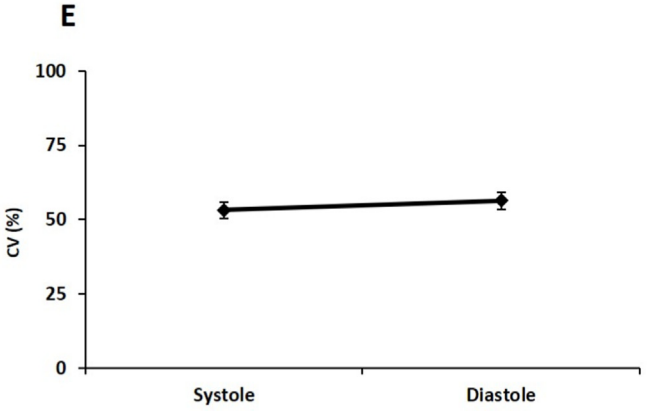

E
CV (%)
100
75
50
25
0
Systole
Diastole

Fig. 1. Panel A: EKG and EMG recording during a TMS pulse given at T6 (500 ms after the R-wave peak). When the R-wave reached the threshold line (black arrow) the TMS pulse was triggered. All the time points (T1-T7) and systolic and diastolic phase estimates are shown. Panels B–C: Normalized MEP amplitude at T1-T7 (panel B) and at systolic and diastolic phases (panel C). Panels D–E: CV% at T1-T7 (panel D) and at systolic and diastolic phases (panel E). No difference occurred across the various time-points or different phases of the cardiac cycle.

induced electric field not sufficient in modifying the physiological pattern of corticospinal activation. Second, the young age of subjects would have contributed to further reduce the effect of this displacement. Despite ultrasound evidence of increased brain tissue pulsatility [9], younger people have more trophic brains than older adults. Accordingly, the cardiac cycle-related brain displacement would be dampened in younger subjects and, in turn, MEP amplitude less variable. Finally, the non-linear coupling of the electric cardiac cycle and ICP wave peak would have also contributed to our findings. The initial phase of the ICP pulse wave is primarily generated by the forward-travelling arterial blood pressure pulse traversing the intracranial compartment [2,10]. The physiological and structural properties of arterial vessels, along with the vascular regulatory mechanisms make ICP not linearly coupled with the EKG activity [10]. Thus, the EKG recording would not be sensible enough to monitor the association between cardiac cycle and MEP variability.

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Author contributions

E.B., A.S. and M.M. conceived the study. E.B. and M.M. performed the experiments. E.B. and A.G. performed data analysis. E.B., A.G., A.Z. and A.S. wrote the manuscript.

Data accessibility

Data related to this study are available from the authors.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support far this work that could have influenced its outcome.

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