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Comparison of different baseline conditions in evaluating factors that influence motor cortex excitability

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Identifying task-related changes in cortical excitability requires comparing motor evoked potentials (MEPs) measured under an experimental condition with that obtained in a baseline, control condition. The goal of this study was to compare two different procedures for measuring baseline that are commonly used in transcranial magnetic stimulation (TMS) studies. We hypothesized that baseline measurements obtained during task performance may be elevated due to an overall heightened state of arousal or task-specific fluctuations in excitability. Single-pulse TMS was used to elicit MEPs during an experimental task involving action observation. Baseline MEPs were recorded before (preblock) and during (intrablock) the experimental blocks. Intrablock baseline MEPs were modulated in a manner correlated with the effect of the experimental manipulation. Although there are advantages to obtaining baseline measurements during the experimental block, such measurements are biased by the experimental manipulation. Unbiased baseline measurements are best obtained between experimental blocks.

Keywords baseline motor-evoked potentials; context-dependency; TMS

Transcranial magnetic stimulation (TMS) has become an established technique in cognitive neuroscience, used to assess a wide range of cognitive processes. One example comes from studies looking at the relationship of perception and action. TMS-induced motor evoked potentials (MEPs) have been used as a proxy of motor cortex excitability while subjects are involved in tasks such as action observation,[1-4] imagined movement,[5,6] or listening to sounds related to actions.[7] Enhanced MEPs in such tasks have provided one source of evidence in favor of theories of embodied cognition, including influential work on mirror neurons.[8]

These studies generally involve a comparison of MEPs elicited during task performance to a baseline condition, with the data often expressed as a percent change from baseline. Baseline MEPs are generally recorded while the participants are at rest, either obtained during the experimental blocks[2,9] or during an epoch before the start of the experimental block.[4,10] Given that modulatory effects relative to a baseline condition are essential for interpreting the results of an experimental manipulation (e.g., does a variable lead to an increase or decrease in excitability), it is important to consider the effect of different baseline conditions.

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We explore these issues in the current study, measuring baseline MEPs before and during the experimental block of trials, and using these as a point of comparison to MEPs elicited on experimental trials. For the experimental task, we used an action observation task that has been previously shown to produce an increase in MEPs.[2-4] We also included a second experimental task, landscape observation, to determine the specificity of M1 modulation.

Materials and Methods

Participants

Nine healthy subjects (age mean ± SD, 24 ± 2 years; four females, five males) participated in the study. All were right handed as measured by the Edinburgh Handedness Inventory.[11] The protocol was approved by the Institutional Review Board of University of California Berkeley and participants provided informed consent. They were financially compensated.

Stimuli

The stimulus set consisted of 60 pictures. Thirty of these depicted transitive actions (e.g., a hand pouring a bottle of water). The other 30 were pictures of landscapes (e.g., a scene of a hill after a forest fire).

Procedure

Participants were seated in a comfortable chair in front of a computer screen with their elbows flexed at 90° and hands prone in a supported and relaxed position. They were instructed to observe a series of pictures displayed on the screen. Each trial began with the appearance of a fixation cross for 250 milliseconds. After a blank screen of 500 milliseconds, a picture was presented and remained on the screen for 1500 milliseconds, followed by an intertrial interval of 5000 or 5250 milliseconds. The hand and landscape pictures were presented in separate blocks, with each condition repeated twice (four blocks total). The order was randomized between subjects.

TMS measurements were obtained at three epochs. First, for the Task trials, the TMS pulses were applied at a random interval of 600-1200 milliseconds after stimulus onset. Within each block, 30 MEPs were obtained, one per stimulus. Second, for the Intrablock Baseline, we included 20 "dummy" trials, randomly interspersed among the Task trials. In the dummy trials, the fixation cross was followed by a blank screen and the TMS pulse was applied 1100-1700 milliseconds after the offset of the fixation cross. With this design, the TMS pulse occurs at the same time relative to the fixation cross as in experimental trials. Third, for the Preblock Baseline, 10 MEP measurements were obtained before the start of each experimental block with an interpulse interval of 6 seconds. In sum, for each experimental condition (hand and landscape), we obtained a total of 20 Preblock Baseline MEPs, 40 Intrablock Baseline MEPS, and 60 Task MEPs.

TMS acquisition

Single-pulse TMS was applied over the primary motor cortex of the left hemisphere. Pulses were given via a 70 mm figure-eight coil, connected to a rapid Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was placed tangentially on the scalp, with the handle pointing backward and laterally at a 45° angle from the midline. The hot spot was defined as the optimal position to elicit MEPs in the right first dorsal interosseous muscle (FDI). The resting motor threshold (rMT) was defined as the minimal TMS intensity needed to evoke MEPs at least 50 μV peak-to-peak in the relaxed FDI, on 5 of 10 consecutive trials. The intensity of TMS was then set to 120% of the rMT.

EMG activity was recorded from surface electrodes placed over the right FDI. During the experimental blocks, recordings were stored for 4000 milliseconds after fixation onset. The EMG signal was amplified and band pass filtered (50-2000 Hz; Delsys Inc, Boston, MA). The signals were digitized at 5 kHz and stored for offline analysis. Trials associated with elevated background EMG activity were excluded from the analysis (5.6% of all MEPs).

A two-way repeated measures ANOVA was performed on the MEP amplitude data, with the factors Stimulus Type (hand, landscape) and Condition (Task, Intrablock Baseline, Preblock Baseline). Post hoc analysis was performed with Bonferroni corrections.

Results

The results showed a significant main effect for Condition ($F_{2,16} = 10.97$, $P = .001$) and a Condition × Stimulus Type interaction ($F_{2,16} = 7.48$, $P = .005$) (Figure 1). Post hoc

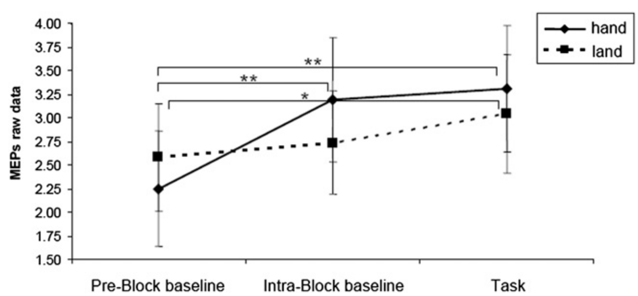

Figure 1 MEP amplitude (plus SE) recorded from FDI, obtained during three epochs (Preblock Baseline, Intrablock Baseline, and Task trials). Separate functions are presented based on whether the forthcoming or ongoing experimental block involved the presentation of action pictures (continuous line) or landscape pictures (broken line). * for $P < .05$, ** for $P < .01$.

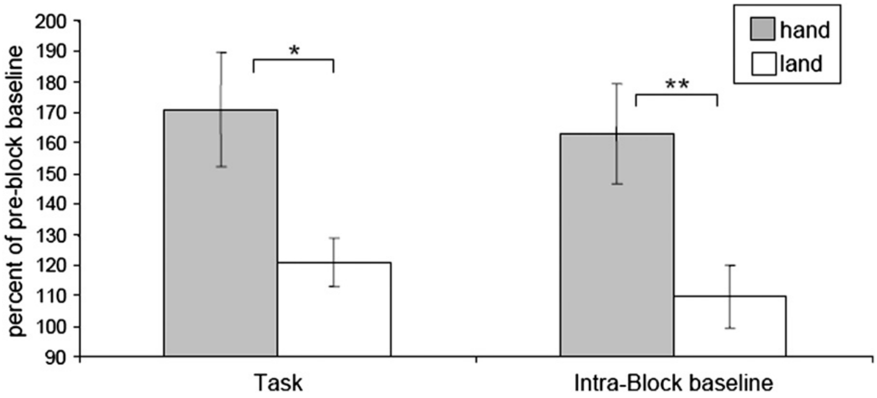

Figure 2 MEP values (plus SE), expressed as a percent change from the Preblock Baseline epoch, for the hand and landscape blocks. * for $P < .05$, ** for $P < .01$.

analysis revealed a significant difference between Preblock Baseline and Task MEPs for the Hand pictures ($t_8 = 4.12$, $P = .003$) and the Land pictures ($t_8 = 2.60$, $P = .032$). The comparison of the Preblock Baseline and Intrablock Baseline and for the Hand blocks was also reliable ($t_8 = 4.82$, $P = .001$).

After the convention adopted in many TMS studies, we normalized the MEPs observed during the experimental blocks to that obtained in the preceding Preblock Baseline epoch (Figure 2). This normalization procedure was performed for the two Task conditions (hand and landscape) and Intrablock Baseline MEPs. An analysis of these data showed only a main effect of Stimulus Type ($F_{1,8} = 13.91$, $P = .006$). Post hoc comparisons showed that the normalized MEPs were larger on Hand blocks compared with Landscape blocks. This effect was not only observed for MEPs linked to the stimuli (Hand versus Landscape pictures: $t_8 = 3.16$, $P = .013$), but also for MEPs obtained on the dummy trials (Intrablock Baseline Hand versus. Intrablock Baseline Landscape: $t_8 = 3.87$, $P = .005$). There was no difference in the MEP values when viewing hand pictures compared with their corresponding Intrablock Baseline measurements ($t_8 = 8.33$, $P = .429$).

Discussion

The goal of the current experiment was to compare two different baseline measurements used in studies examining cognitive factors that influence motor cortex excitability. Previous studies of action observation have reported an increase in excitability when people view pictures of actions.[12] We replicate this effect, finding a larger increase in MEPs recorded from a hand muscle when people observe hand pictures compared with landscape pictures. However, this effect was limited to comparisons in which the baseline measurements were obtained before the experimental block (Preblock Baseline). If our comparison had been limited to baseline measurements obtained during the experimental blocks (Intrablock Baseline), we would have failed to observe an MEP increase linked to action observation. Thus, relying on either one or the other baseline condition would have led to very different conclusions.

The influence of variation in baseline cortical excitability has recently been addressed, primarily in relation to experiments involving repetitive TMS (rTMS). For example, rTMS can either facilitate or suppress perceptual functions depending on the baseline level of activity of the targeted brain region.[13] Silvanto and Pascual-Leone[14] have proposed a state dependency model, arguing for an interaction between on-going task-related processing and measures of baseline excitability. This idea may help explain why we failed to observe a difference between the action observation condition and the Intrablock baseline measurements obtained between hand pictures. In our study, we assume that there remains a persistent increase in M1 excitability throughout the experimental blocks involving the repeated presentation of actions. This would be consistent with our finding that the Intrablock Baseline MEPs were higher in the hand blocks compared with the landscape blocks. Interestingly, we failed to observe a reliable MEP increase when the hand pictures were compared with the corresponding Intrablock Baseline trials.

A more general implication of the current findings is that, for cognitive tasks, caution should be exercised in selecting a baseline condition. In particular, researchers may be advised to avoid mixing experimental and control trials within the same block. First, doing so may increase the likelihood of a Type II error (i.e., failure to reject an experimental hypothesis) given that a stimulus or general task set may produce a protracted influence on cortical excitability. Null effects, although always hard to interpret, are especially problematic in TMS studies given concerns with stimulation placement and timing. Second, carryover effects between different types of experimental conditions (e.g., hand and landscape) may be even more complex that those observed between a single experimental condition and baseline measurements.

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