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Establishing the definition and inter-rater reliability of cortical silent period calculation in subjects with focal hand dystonia and healthy controls

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Abstract

The purpose of this paper is to describe a clearly defined manual method for calculating cortical silent period (CSP) length that can be employed successfully and reliably by raters after minimal training in subjects with focal hand dystonia (FHD) and healthy subjects. A secondary purpose was to explore intra-subject variability of the CSP in subjects with FHD vs. healthy subjects.

Methods—Two raters previously naïve to CSP identification and one experienced rater independently analyzed 170 CSP measurements collected in six subjects with focal hand dystonia (FHD) and nine healthy subjects. Intraclass correlation coefficient (ICC) was calculated to quantify inter-rater reliability within the two groups of subjects. The relative variability of CSP in each group was calculated by coefficient of variation (CV). Relative variation between raters within repeated measures of individual subjects was also quantified by CV.

Results—Reliability measures were as follows: mean of three raters: all subjects: ICC= 0.976; within healthy subjects: ICC=0.965; in subjects with FHD: ICC= 0.956. The median within-subject variability for the healthy group was CV=7.33% and in subjects with FHD: CV= 11.78%. The median variability of calculating individual subject CSP duration between raters was CV=10.23% in subjects with dystonia and CV=10.46% in healthy subjects.

Conclusions—Manual calculation of CSP results in excellent reliability between raters of varied levels of experience. Healthy subjects display less variability in CSP. Despite greater variability, the CSP in impaired subjects can be reliably calculated across raters.

Keywords

cortical silent period; cortical excitability; focal hand dystonia; reliability; definition; methodology; transcranial magnetic stimulation

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Introduction

Transcranial magnetic stimulation (TMS) to the motor cortex can be used to elicit a cortical silent period (CSP) which is an interruption of electromyographic (EMG) activity in the corresponding contracting muscle [4]. The length of this silent period is a reflection of cortical excitability and is thus a useful measure in a variety of experimental settings, including healthy subjects and those with neurologic compromise, and may provide a clinical marker of certain movement disorders, such as focal hand dystonia (FHD).

The CSP is thought to represent GABA-B receptor-mediated inhibition of cortical excitability, in addition to spinal inhibitory mechanisms such as Renshaw inhibition [13,25,32]. Altered CSP duration has been observed in neurologic conditions associated with corticospinal lesions and in some movement disorders [6,9,12,21]. In subjects with hemiparetic stroke, decreases in ipsilesional CSP length paralleled clinical improvement [6]. Shortened CSP has been observed in patients with focal hand dystonia (FHD) indicating a lack of cortical inhibition as a feature of this disorder [2,9,16]. Other clinical conditions have also been correlated to CSP length; longer CSP duration is typically associated with motor neglect while shorter CSP lengths often occur with spasticity [7]. These findings demonstrate a role for CSP measurement in understanding pathophysiology of certain neurologic disorders as well as monitoring cortical excitability changes over time [6] and after an intervention [24].

There are multiple approaches for calculating CSP which creates within-study reliability and between-study reproducibility concerns, reducing the generalizability of this measurement. The approach frequently used is a visually guided or “manual” calculation. However, often the definitions of CSP onset and offset are not explicitly stated. The CSP onset is described as either the stimulation artifact or the onset of the motor evoked potential (MEP) and CSP offset is defined as the return of spontaneous EMG activity or pre-stimulus muscle activity, but the exact parameters are not consistently reported [10,12,18,26].

Computerized methods have been developed to automate the time consuming CSP calculation [8,11,14,17]. One program, known as the Cusum method, has demonstrated excellent reliability with manual measurement by experienced raters and poor to moderate reliability with other automated methods [11,17].

Despite these attempts to automate CSP calculation, the majority of researchers employ a manual calculation technique. Manual calculation, though time consuming, allows researchers to examine for errors, variability or patterns within a subject or group. Given the additional time required to perform manual calculation, it may be required that more than one researcher be involved to expedite data processing. To our knowledge, no reliability has been reported between different manual raters or compared raters of different experience level. Additionally, no study has determined the reliability of CSP calculation in a neurologically impaired population. The purpose of this paper is to present a manual method with clear definitions for calculating CSP length that can be employed successfully and reliably by raters after minimal training, encouraging a uniform definition of measurement. Standardization in definition will allow for improved ability to compare findings across different studies. The reliability and relative variation of CSP measurement between raters is reported in subjects with FHD and in healthy subjects during a single testing session. A secondary purpose of this study was to examine the relative variation between subject groups. We hypothesized that healthy subjects would display less variability than subjects with FHD.

Methods

Subjects

Nine healthy subjects (age: 33 ± 10.5 y, 3 F) and six subjects with a diagnosis of FHD (age: 45.67 ± 13.02 y, 1 F) were studied. For subjects with FHD, all symptoms primarily affected the dominant arm (four right-hand dominant, two left-hand). Handedness was determined by the Edinburgh Handedness Inventory [18]. The CSP was calculated in the hemisphere contralateral to the dominant arm. Exclusion criteria for all subjects were: (1) any neurologic condition other than FHD, (2) medication for dystonia, (3) botulinum toxin injections in the past 6 months, (4) seizure history, (5) pregnancy, (6) metal in head, or (7) implanted medical devices [31].

All subjects gave informed consent according to Declaration of Helsinki prior to participation. The study was approved by the University of Minnesota General Clinical Research Center and Institutional Review Board.

Cortical Excitability Assessment

The CSP measurement was performed with the subject seated in a chair. Small surface EMG electrodes were attached to the skin over the first dorsal interosseus (FDI) in a belly/tendon montage with a ground electrode placed on the dorsum of the hand. The EMG signals were acquired at a sampling rate of 2560 kHz using a Cadwell Sierra EMG amplifier (Cadwell Laboratory, Washington) (sensitivity: 100 μ v/div, filter: 20-2000Hz).

To find the optimal position for FDI activation, a 70-mm figure eight TMS coil connected to a Magstim 200 Rapid magnetic stimulator (Magstim Co. Ltd, Dyfed, UK) was used. The coil was positioned with the handle directed 45° posterolaterally to the mid-sagittal line of the head over the approximate location of maximal sensitivity for FDI muscle activation. Single-pulse magnetic stimuli were delivered manually at approximately 0.1 Hz starting at 55% of maximal stimulus output. This level was adjusted systematically until the resting motor threshold (RMT) was found, defined as the minimum intensity required to elicit a motor evoked potential (MEP) amplitude of >50 μ V peak-to-peak in at least 3 of 5 trials with the target muscle at rest [23]. Stimulator output intensity was set to 120% of RMT for CSP assessment to prevent stimulation spread to neighboring cortical regions [15]. These parameters were chosen based upon previous investigations on subjects with FHD [1,16]. It should be noted that stimulation parameters in the facilitation of CSP also has variability in methodology with some authors using different intensities [19]. The reliability of different stimulation techniques is beyond the scope of this article, however, the technique for calculation could apply to any CSP trace.

For CSP assessment (for review: [30]), subjects were asked to isometrically contract the FDI by abducting their second digit against a ring coupled to a S-Beam load cell (Interface Inc., Scottsdale, Arizona, USA). The information from the load cell was transduced into an electrical signal, which was displayed on a computer screen (Dell Latitude D600) visible to the subject. Subjects were asked to maintain a constant force (indicated by a bar on the screen) until told to relax. Force was 25% of maximum voluntary contraction, or approximately 6 N in most subjects. A single-pulse TMS was administered 3-5s following contraction initiation. Subjects were instructed to relax 2-3s after stimulus delivery. Ten CSP measurements were obtained in a single session with a minimum 20s rest interval between each trial. All EMG traces were stored for off-line analysis. In subjects with FHD, the CSP measurements were taken in the hemisphere contralateral to the more affected hand and in the hemisphere contralateral to the dominant hand in healthy subjects.

CSP Calculation

All EMG traces were full-wave rectified and CSP was defined as the length of time between the first peak of superimposed TMS-induced FDI activation until the recurrence of at least 50% of the mean of the sustained prestimulus background EMG activity (Fig. 1) [16]. The EMG background activity is defined as the mean amplitude of the signal during the 25ms epoch preceding TMS delivery.

Two raters previously naïve to CSP identification and one experienced rater (history of >1000 calculations) independently analyzed the onset and offset of 170 different CSP measurements collected across subjects with FHD and healthy subjects. Identification involved visual analysis of EMG data points over the 250 ms time course of each trial.

Ten CSP measurements were obtained for each subject during a single testing session and were used to analyze the reliability between the raters for identifying the CSP for each subject. These data were also used to examine the intra-subject variability to determine if, on average, one group had more variation in their CSP measure within the 10 trials. The raters were instructed in determining CSP onset and offset during one 30 minute training session prior to data analysis. Raters were allowed to practice for 30 minutes following initial instruction during which time, questions were answered. Competence was defined as measurement agreement (± 5 ms of the experienced rater's finding) on ten pre-selected identification trials. Raters were blinded to the subject group and the CSP results obtained by the other raters.

Data Analysis

Intraclass correlation coefficient (ICC) was calculated using a repeated measures analysis of variance (ANOVA) to quantify inter-rater reliability between the 3 raters within the 2 groups of subjects:

$$ICC(3, 1) = (BMS - EMS) / [BMS + (k - 1)EMS];$$

Whereby, BMS = between subject mean square; EMS = error mean square; k = the number of comparisons [20]. ICC model 3 was used for this calculation because the raters were not randomly selected from the population and the raters had variable levels of experience. Coefficient of variation [CV = (session standard deviation / session mean) $\times$ 100] of CSP was also calculated for each subject within the 10 trials that occurred within the single testing session. The median CV and range for the two groups was then calculated from these data. The CV measures the relative variation between two distributions while taking into account possible differences in the magnitude of the means within each group [20].

Results

The three raters had an ICC of 0.976 ($F=123.92$, $P<0.001$) across all trials. Reliability between the novice raters (rater 2 and 3) resulted in an ICC of 0.980; between the experienced rater and each novice rater, ICC = 0.975 and 0.975. Rater measurements in the healthy population yielded an ICC of 0.965; in the population with dystonia ICC = 0.956. The variability of CSP calculation within a single subject across all 3 raters had a median CV of 10.23% (range: 0.65% – 36.42%) in subjects with dystonia and 10.46% (range: 0.00% – 31.90%) in healthy subjects.

Healthy subjects displayed a significantly longer CSP duration ($p<0.001$) than subjects with dystonia (Mean $\pm$ SD: 141.00 $\pm$ 22.72 ms vs. 113.70 $\pm$ 26.26ms). Relative variation of CSP within healthy subjects was CV=7.99% (range: 5.22%-14.37%), and within subjects with FHD

was CV= 11.78% (range: 4.35%-16.27%). and between raters; CV=12.17% (range: 0.00%-36.42%).

Discussion

Excellent reliability has been defined as an ICC of 0.75 or greater [10]. In this study, manual calculation of CSP by three independent raters resulted in excellent inter-rater reliability. This high reliability was found both in healthy subjects and subjects with FHD. The manual method presented in this paper requires minimal training and no specialized software. The low CV measure between raters for a single subject is another indication that despite variability of CSP duration between subjects, the proposed method of calculation is stable.

The CSP measurement is regularly utilized in neurologic populations to understand pathophysiology [6,12] and to evaluate intervention effects [19, 34]. Subjects with Parkinson's disease demonstrate shortened CSPs [5] that can be significantly lengthened following repetitive TMS (rTMS) [26]. Shortened CSPs are also associated with FHD [9,28] that also can be lengthened by rTMS [16,27]. In all of these studies, CSP was calculated manually, thus a standardized definition, such as the one presented in this paper, is important to facilitate comparisons across studies.

Previously, CSP reliability investigations have only been performed in healthy populations with the reliability of CSP calculation in subjects with pathology largely unknown. Low intra-subject CSP variability has been reported in healthy subjects [3,22]. However, CSP variability has been demonstrated in patients with brain lesions secondary to stroke or tumor [29], thus it is possible that in the more highly variable population, the reliability may not be as high. Indeed, we hypothesized that subjects with FHD would display great variability in a single testing session than healthy subjects; and that was the case. Importantly however, despite this higher variability within a trial, the proposed method provides a reliable method of calculation.

Conclusion

The findings of this paper suggest that manual CSP calculation can be reliably performed by raters with varying experience. These results support the use of CSP as a reliable measure of cortical excitability in healthy subjects and patients with neurologic compromise.

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Figure 1. Example of cortical silent period (CSP) onset and offset in A) one healthy subject (duration: 182.52ms) and B) one subject with dystonia (duration: 106.08ms). Triangle denotes stimulus artifact. CSP onset and offset are indicated with arrows.