

Handedness and the excitability of cortical inhibitory circuits

Campbell S. Reid<sup>1</sup> and Deborah J. Serrien

School of Psychology, University of Nottingham,

University Park, Nottingham, NG7 2RD, UK

Correspondence address:

Deborah Serrien

School of Psychology

University of Nottingham

University Park

Nottingham, NG7 2RD, UK

Phone: + 44 (0)115 951 5285

Fax: + 44 (0)115 951 5324

Email: [deborah.serrien@nottingham.ac.uk](mailto:deborah.serrien@nottingham.ac.uk)

<sup>1</sup>CSR is now at the Department of Bioengineering, University of Strathclyde, Wolfson Building, 106 Rottenrow East, Glasgow, G4 0NW.

## Abstract

Inhibitory processes play a significant role in the control of goal-directed actions. To increase insights into these mechanisms as a function of handedness, we measured the transient inhibition of volitional motor activity induced by single pulse transcranial magnetic stimulation during bimanual isometric contractions with symmetrical and asymmetrical force demands. Here, we assess the cortical silent period (cSP), which associates with intrahemispheric inhibition, and the ipsilateral silent period (iSP), which provides an estimation of interhemispheric inhibition. The data showed that inhibitory processes support the functional regulation of bimanual motor output. Furthermore, right-handers demonstrated asymmetries in intra- and interhemispheric inhibition due to asymmetrical force requirements and hand dominance, whereas left-handers did not show marked differences. In particular, right-handers demonstrated increased inhibitory processing that favoured control of the dominant (left) hemisphere whereas both motor cortices exhibited equal capabilities in left-handers. These observations were specific to the bimanual nature of the task. The present results underline distinct organisational mechanisms of coordinated behaviour in right- and left-handers.

Keywords: cortical silent period (cSP), ipsilateral silent period (iSP), bimanual control

## 1. Introduction

Handedness and hemispheric specialisation are current topics in the area of motor neuroscience [1]. Most research work has addressed hemispheric organisation in right-handers who have a defined motor superiority of the dominant (left) hemisphere as compared to the non-dominant (right) hemisphere in controlling contralateral effectors. This dominance has been attributed to anatomical and functional characteristics of primary motor cortex (M1) and descending pathways [2-8]. Furthermore, a left hemispheric specialisation also includes a stronger involvement in ipsilateral control [9-11] and in bimanual coordination [12]. Particularly, an influential role in coordinated behaviour is notable. With respect to bimanual movements, it is acknowledged that symmetrical movements represent basic coordination modes [13] whereas asymmetrical ones require motion uncoupling that often results in interference [14-16]. Accordingly, inhibitory processes are likely to play a crucial role in facilitating the performance of asymmetrical bimanual patterns.

Assessing hemispheric regulation during coordinated behaviour enables insights into the mechanisms that underlie motor control. Accordingly, the current work aims to evaluate the inhibitory processes during coordination patterns. To this end, a single pulse transcranial magnetic stimulation (TMS) experiment was conducted during performance of a bimanual task with similar and dissimilar demands of both hands. It is known that TMS of M1 produces a brief suppression of electromyogram (EMG) activity in the contralateral target muscle [17,18]; known as the cortical silent period (cSP). Whereas the initial part of the cSP is mainly due to spinal mechanisms, the latter part relates to intracortical inhibition [19,20]. In addition, TMS of M1 also generates a short disruption of EMG activity in the ipsilateral muscle, labelled as the ipsilateral silent period (iSP), [21-26]. The iSP is largely mediated by transcallosal fibers from the stimulated to the non-stimulated side, herewith inhibiting motor output of the contralateral M1. Hence, the measurement can be used to assess interhemispheric inhibition.

The previous observations suggest that evaluating the iSP and cSP following TMS provides insights into the cortical inhibitory processes during bimanual motor organisation. Furthermore, it is acknowledged that hemispheric regulation is distinct due to handedness. In particular, in contrast to a dominant motor organisation of the left hemisphere in right-handers, the hemispheric organisation of left-handers is more heterogeneous for contralateral as well as

ipsilateral activity as indicated by structural and functional imaging work [2,5,7,9,27]. Accordingly, the hypothesis was made that the hemispheric inhibitory processes would be distinct in left- and right-handers.

## 2. Methods

### 2.1. Participants

Eight right-handed (age:  $21.6 \pm 2.7$  years) and eight left-handed (age:  $21.0 \pm 1.5$  years) participants took part in the experiment. Their mean laterality index, as determined by the Edinburgh handedness inventory [28] was  $-81 \pm 14$  for the left-handers and  $81 \pm 8$  for the right-handers. In accordance with the declaration of Helsinki, all gave informed consent to participate in the study, which was approved by the local ethics committee.

### 2.2. Materials

Participants were seated in a height-adjustable chair in front of a monitor. Both arms were placed in a prone position with the palms facing down on a custom designed frame that provided adjustable support to ensure that only the index fingers were used during the task (Fig. 1). The tip of both index fingers was placed against a separate force transducer (LCAE-10KG, Omega Engineering Ltd, UK). The force transducers were mounted as cantilevered beams with the positive force direction aligned with the direction of abduction of the index fingers. Output from the force transducers was signal conditioned (DRG-SC-BG bridge input signal conditioners, Omega Engineering Ltd, UK) to provide a 5V output range over the 10 kg range per transducer. Surface EMG activity was recorded (Bagnoli, DelSys, USA) from the left and right first dorsal interosseous (FDI) muscles, which was amplified (gain 1000) and filtered (20-450 Hz). The force and EMG signals were connected to a shielded connector block and digitized (National Instruments Corporation, UK). All data were sampled at 4000 Hz and stored for later analysis. Experimental control was achieved using custom programs written in Matlab (Mathworks, UK) and the Cogent graphics platform.

Insert Fig. 1 about here

### 2.3. TMS stimulation

Single pulse magnetic stimuli were delivered to M1 by means of a Magstim Rapid stimulator (Magstim, UK) with a figure-of-eight-shaped coil located at the optimal position to evoke a motor evoked potential (MEP) in the right or left FDI muscle. The lowest stimulation intensity at which MEPs with peak-to-peak amplitude of approximately 50  $\mu$ V could be evoked in three out of five trials was taken as the resting motor threshold (RMT). In the experiment, TMS was delivered at 120% of RMT. A series of 10 pulses were delivered to each hemisphere with both hands at rest in order to establish baseline cortical excitability for the left and right FDI muscle. To aid in the positioning of the TMS coil over the participant's brain, use was made of the Brainsight frameless interface system (Rogue Research, Canada). The infra-red tracking technique of this system integrates an interactive navigational guide for coil position and allows recording of the position and orientation of the coil at the instant of stimulation.

### 2.4. Task procedures

The session started with three maximum voluntary contractions (MVC) for 3 s with each index finger. Participants were instructed to perform MVC contractions at a level they felt comfortable to maintain over an extended period. The average of the MVCs was accordingly used to define the force levels required in the performance conditions of the experiment. Participants performed two sessions of 66 trials; one with stimulation to the left hemisphere and one with stimulation to the right hemisphere. In these sessions, the trials were divided into experimental blocks that required the participants to maintain one index finger at 100% MVC while the other index finger performed contractions of 0% (ipsilateral baseline, 22 trials), 50% (asymmetrical condition, 22 trials) or 100% MVC (symmetrical condition, 22 trials). Single pulse TMS was delivered in 50% of the trials to M1 ipsilateral to the index finger which in all trials of that block performed at 100% MVC. Force levels were pseudo-randomised to avoid fatigue and habituation effects. A separate control block of 22 trials was performed before each experimental block in order to provide a baseline condition for the cSP. In these trials, single pulse TMS was delivered to the same hemisphere stimulated in the following experimental block. The index finger contralateral to TMS stimulation contracted to 100% MVC while the ipsilateral index finger

remained at 0%. The inter-trial interval varied between 6 and 8 s, ensuring that there was a minimum of 6 s between TMS pulses. A control block lasted approximately 4 min whereas an experimental block took approximately 11 min to complete. Performance was at all times monitored by the experimenter, and participants were offered a break during each block if fatigue appeared to be present. Sufficient breaks were also presented between blocks. The order of the blocks and the force levels were counterbalanced across subjects.

At the start of each trial, the monitor would show two vertically aligned scale lines, with the left/right scale line representing the force produced by the left/right index finger. For each finger, a stationary target mark highlighted the force level to be produced, whereas a continuously moving mark provided feedback on the generated force level. Participants were instructed to generate the required forces as quickly as possible upon perceiving the target marks, imposing dynamic constraints for achieving the combined task demands. The required force levels were to be maintained within  $\pm 5\%$  for 500 ms, which would then send a trigger to the stimulator to deliver a TMS pulse. Participants were told to ignore the TMS pulse and to maintain force levels until the end of the trial, 0.5 s after the TMS pulse. They were instructed to relax both fingers subsequently.

## 2.5. Measurements and analysis

The main TMS-evoked measurements reflected the iSP and cSP, which are observed in the EMG of actively contracting muscles after stimulation of M1. Due to the nature of the experimental block, the iSP was measured in the 0, 50 and 100% trials as the ipsilateral FDI maintained 100% contractions in all three conditions. However, the cSP could only be assessed in the 50 and 100% trials, hence the requirement for a control condition for the cSP baseline. Each trial was assessed individually in the control and experimental blocks to check for sufficient EMG activity after stimulation ( $\sim 500$  ms) to fully assess cSP, and that no ipsilateral MEPs were evoked. Trials violating these criteria were excluded from further analysis. A total of 25% of the trials were rejected due to ipsilateral MEPs. There was no systematic bias in the number of rejected trials, and approximately 8 trials per condition were retained. Subsequent analysis was performed on the averaged EMG activity. The same algorithm was used for calculating onset,

offset and area of iSP and cSP. The mean EMG level was calculated over the 500 ms preceding TMS stimulus. A moving window of 20 data points (5 ms) was then applied to the data starting at 25 ms post-stimulus for iSP and 40 ms post-stimulus for cSP.

SP onset was defined as the first data point at which 75% of data points in the window were below 90% of the mean EMG level. The algorithm allowed for a second peak above the 90% threshold in the evoked potential morphology within 35 ms of the initial onset. The offset point was defined as the first point where 75% of the data points in the window were above 90% of the mean EMG level. The SP duration was defined as the onset point subtracted from the offset point, and onset latency was defined as the stimulation time subtracted from the onset time. The SP area was estimated using the trapezoid numerical integral estimation method. The mean EMG level was subtracted from each data point over the duration of the SP before the area was calculated. The area was then normalised with respect to the corresponding baseline condition (either the cSP baseline condition or 0% ipsilateral baseline condition), where a ratio below/above 1 indicated a reduction/increase of area with respect to baseline. Fig. 2 shows single trial data and details the calculations of the SP areas.

The behavioural measurement was time to target force, as an indication of task accomplishment. This measure represents the latency between the imperative stimulus (trial initiation) and the time of stimulation. It incorporates the reaction time, electromechanical delay, force rise time and maintaining both force levels at the required level for 500 ms. The analyses were conducted using ANOVAs on handedness group (left- vs. right-handers), side (preferred vs. non-preferred), and force (50 vs. 100%). The Greenhouse-Geisser correction was used when necessary to correct for non-sphericity. A  $P$  value of  $<0.05$  was considered significant. Post hoc  $t$ -tests corrected for multiple comparisons were performed where appropriate.

Insert Fig. 2 about here

### 3. Results

iSP area. The results revealed a main effect of Force,  $F(1,14)=5.76$ ,  $P<0.05$ ,  $\eta^2=.170$ , a Side x Force interaction,  $F(1,14)=8.61$ ,  $P<0.01$ ,  $\eta^2=.116$ ; and a Group x Side x Force interaction,  $F(1,14)=5.27$ ,  $P<0.05$ ,  $\eta^2=.189$ . Fig. 3 illustrates that there were no group differences in the

bimanual symmetrical condition, whereas in the bimanual asymmetrical condition the right-handers demonstrated stronger inhibition when the left rather than the right hemisphere was stimulated ( $P < 0.05$ ). The onset time of iSP revealed a main effect of Group,  $F(1,14) = 4.24$ ,  $P = 0.05$ ,  $\eta^2 = .195$ ; and a Group x Force interaction,  $F(1,14) = 5.18$ ,  $P < 0.05$ ,  $\eta^2 = .125$ . Right-handers had shorter onset latencies than left-handers, but this difference was larger for the bimanual asymmetrical than symmetrical condition. The mean times  $\pm$  SD for the left vs. right-handers were  $.035 \pm .004$  s and  $.031 \pm .003$  s (asymmetrical condition),  $.034 \pm .003$  s and  $.032 \pm .002$  s (symmetrical condition). The Group x Side x Force interaction,  $F(1,14) = 0.55$ ,  $P = 0.47$ , was not significant.

Insert Fig. 3 about here

cSP area. The results showed a main effect of Force,  $F(1,14) = 34.56$ ,  $P < 0.01$ ,  $\eta^2 = .028$ . In addition, the 2-way interactions were significant; Group x Hand,  $F(1,14) = 8.60$ ,  $P < 0.01$ ,  $\eta^2 = .116$ ; Group x Force,  $F(1,14) = 5.06$ ,  $P < 0.05$ ,  $\eta^2 = .195$ ; and Hand x Force,  $F(1,14) = 13.15$ ,  $P < 0.01$ ,  $\eta^2 = .074$ . The Group x Hand x Force interaction was also significant,  $F(1,14) = 5.10$ ,  $P < 0.05$ ,  $\eta^2 = .194$ . Fig. 4 demonstrates that there were no group differences in the bimanual symmetrical condition whereas right-handers showed stronger inhibition when the right rather than the left hemisphere was stimulated in the bimanual asymmetrical condition ( $P < 0.05$ ). The onset time of cSP only revealed a significant main effect of Force,  $F(1,14) = 10.47$ ,  $P < 0.01$ ,  $\eta^2 = .137$ . The mean times were  $.048 \pm .004$  s and  $.046 \pm .003$  s for the bimanual asymmetrical and symmetrical condition, respectively.

Insert Fig. 4 about here

Force rise time. The results demonstrated no main effects (Group,  $P = 0.21$ ; Side,  $P = 0.87$ ; Force,  $P = 0.56$ ) or interactions (Group x Side,  $P = 0.58$ ; Group x Force,  $P = 0.17$ ; Side x Force,  $P = 0.27$ ; Group x Side x Force,  $P = 0.93$ ). However, an additional analysis that compared unimanual (baseline) and bimanual conditions showed a significant main effect of Condition,

$F(2,28)=8.35$ ,  $P<0.01$ ,  $\eta^2=.175$ . Post-hoc analysis showed that force rise time in the unimanual baseline was significantly shorter than in the bimanual conditions ( $P<0.01$ ). The mean times  $\pm$  SD were  $1.751\pm.432$ ,  $2.704\pm.621$  and  $2.607\pm.668$  s for the unimanual and bimanual asymmetrical and symmetrical conditions, respectively.

#### 4. Discussion

Inhibitory control plays a relevant role in regulating goal-directed actions. To allow insights into these mechanisms in right- vs. left-handers, we measured the transient inhibition of volitional motor activity induced by single TMS pulses during bimanual isometric contraction tasks. These inhibitory periods can provide information about intra- as well as interhemispheric pathways, which contribute to the control of corticospinal output [29,30]. In view of handedness, it has been suggested that intrahemispheric parameters do not rely on handedness whereas interhemispheric parameters do with a more pronounced inhibitory drive from the dominant to nondominant hemisphere [31]. In this study, we explore how intra- and interhemispheric inhibitory systems contribute to bimanual symmetrical and asymmetrical patterns. Moreover, we assess the coordination of force pulses; an important feature of bimanual tasks such as required during object manipulation. For example, when opening a jar, the force and timing of each movement must be coordinated between both hands.

##### 4.1. Suppression of inhibitory interactions

The iSP and cSP can be used to assess excitability of cortical inhibitory mechanisms. Whereas the cSP is taken to represent intracortical inhibition, the iSP reflects intracortical inhibition controlling the excitatory transcallosal fibres from the stimulated to the contralateral side [25,32-34]. This indicates that callosal interactions have a net inhibitory action [23,24,35], which support the performance of independent hand movements and accordingly facilitate the execution of complex bimanual patterns [36].

The present data revealed that inhibitory mechanisms, as indexed by the changes in the SP areas, were suppressed during bimanual as compared to baseline conditions which only involved unimanual performances. This observation indicates that the coordinated activity induced a state of disinhibition and suggests that inhibitory processes are restrained under bimanual conditions.

In view of the iSP, it suggests that inhibitory interactions between both hemispheres are reduced, which is in line with the occurrence of intermanual cross talk during bimanual task performance [37]. These interactions presumably arise at the level of response planning rather than of response execution [38]; a premise that is supported by data that assimilation effects are reduced when receiving sufficient time for response preparation [39]. That the task constraints play a significant role in driving the degree of intermanual interactions [40] is evident from comparing the present data with those of Giovanelli et al. [41] who observed an increased iSP area, reflecting increased interhemispheric inhibition, when performing bimanual as compared to unimanual isometric contractions. That is, the latter observation was likely due to the steady state conditions in contrast to the dynamic state conditions in the present study that required participants to cope instantaneously with the combined task demands. In addition, the current cSP findings underline a decreased excitability of intracortical inhibitory circuitry under bimanual conditions. Combined these effects on iSP and cSP indicate that complex bimanual activities induce pronounced modulations in cortical inhibitory circuits. That these changes are caused by the multi-task demands is supported by the increased time to achieve target forces in the bimanual as compared to unimanual performances. It supports the premise that coordinated behaviour involves extra computational demands.

The early onset of iSP rules out that its modifications would rely on current spread and on changes in cSP. Therefore, the observed effects likely represent differences in the inhibitory circuitry produced by TMS to M1 ipsilateral and contralateral to the target muscle. However, despite these differences, interdependence of homologous representations exists during which each hemisphere is affected by activity-related changes in the other [42]. This implies that contraction of a target muscle will modify excitability to the contralateral homologous muscle by the type of interactions between various inhibitory circuits.

#### 4.2. Inhibitory differences due to handedness

The data revealed that handedness has a pronounced influence on the cortical inhibitory circuits. In particular, the interhemispheric mechanisms were not affected by the type of the bimanual task or stimulated hemisphere in the left-handers, which suggests no defined asymmetries between both hemispheres. In contrast, right-handers showed distinct iSP effects in

the bimanual asymmetrical conditions. Moreover, stimulation of the right (non-dominant) hemisphere evoked a strong reduction of interhemispheric processing whereas suppression was least when the left (dominant) hemisphere was stimulated. This proposes that the inhibitory drive under bimanual conditions is most robust from the left towards the right M1, and is in agreement with asymmetrical interhemispheric differences in right-handers [43]. As interactions between both hemispheres are important in suppressing unwanted activity [23,24], it implies that the dominant M1 can suppress more easily co-activation in the non-dominant M1 whereas the latter is not reciprocal to the same extent; a premise that is in line with an increased degree of mirror movements in the left than right hand in right-handers [44]. Combined, these observations suggest distinct differences in interhemispheric interactions between right- and left-handers, which will impact accordingly on their respective bimanual performances.

The symmetrical bimanual condition demonstrates that the additional EMG activity in the ipsilateral FDI suppresses intracortical inhibition, decreasing the cSP area when compared with the unimanual baseline condition. Although it was not specifically tested, it can be assumed that reducing the unimanual force level to 50% would also reduce the cSP area by a similar amount due to a decrease in EMG activity, and that the suppression of intracortical inhibition by the additional ipsilateral EMG would still be present. The results show that this is indeed the case in the left-handers regardless of which hemisphere is stimulated. In the right-handers, this effect is demonstrated for left hemisphere stimulation (dominant hand) but not for right hemisphere stimulation (non-dominant left hand). In fact, there is no scaling of the cSP area when the right hemisphere is stimulated, suggesting a strong interhemispheric inhibitory effect from the left hemisphere. This finding proposes reduced inhibition in the left (dominant) hemisphere, which would result in greater excitability and hence facilitate contraction as compared to the right (non-dominant) hemisphere [44-47]. These intrinsic properties indicate that cortical inhibitory circuits contribute to asymmetrical dexterity in right-handers. The observations further suggest that right-handers experience more difficulties than left-handers in bimanual tasks that require uncoupling of the patterns, and support the general idea that handedness associates with functional lateralisation as well as interhemispheric interactions [1, 48-50].

In conclusion, the present data assessed inhibitory cortical circuitry during bimanual tasks and revealed intra- and interhemispheric asymmetries in right-handers in contrast to left-

handers who did not show such distinctiveness. Moreover, right-handers demonstrated enhanced inhibitory processes that facilitated control of the left (dominant) hemisphere. As these differences are obtained from SP measurements, which provide information from voluntary muscle contraction, the results support evidence for distinct organisational mechanisms of motor behaviour in right- and left-handers; lateralised control with dominance of the left M1 in right-handers whereas both motor cortices have more equal capabilities in left-handers. These observations were specific to the bimanual nature of the task. Overall, these data underline that inhibitory processes that facilitate synergistic actions of both hands in the functional regulation of coordinated motor output are distinct in right- vs. left-handers.

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## Figure caption

Fig. 1. The experimental setup, with the two load cells for measuring force (A), the mounting bracket to attach the load cells to the base plate (B), and the adjustable columns to support and constrain the wrists and thumbs (C). Dashed arrows indicate the direction of adjustment for the wrist and thumb support columns. Grey filled arrow indicates the direction of force from index finger abduction against the load cell.

Fig. 2. Single trial raw data from a left handed participant. 0 s indicates TMS stimulation. A: Ipsilateral force percentage expressed as percentage of MVC, arrow indicates force onset. B: Ipsilateral FDI EMG in millivolts (mV), arrow indicates EMG onset, grey area indicates iSP. C: Detail of ipsilateral FDI EMG from -0.01 to 0.075 s, arrows indicate iSP onset and offset, grey area indicates iSP, dashed line indicates threshold for calculating iSP (90% of mean EMG over 0.5 s preceding TMS stimulus). D: Contralateral FDI EMG expressed as percentage of MVC, arrow indicates force onset. E: Contralateral FDI EMG in millivolts (mV), arrow indicates EMG onset, grey area indicates cSP. F: Detail of contralateral FDI EMG from -0.05 to 0.2 s, arrows indicate cSP onset and offset, grey area indicates cSP, dashed line indicates threshold for calculating cSP (90% of mean EMG over 0.5 s preceding TMS stimulus).

Fig. 3. Normalised iSP area of the left- and right-handers as a function of hand and bimanual task demands (asymmetry, 50%; symmetry, 100%). Distinct differences can be observed for the right-handers in the bimanual asymmetrical conditions. Means $\pm$ SE.

Fig. 4. Normalised cSP area of the left- and right-handers as a function of hand and bimanual task demands (asymmetry, 50%; symmetry, 100%). A marked divergence can be noted for the right-handers in the bimanual asymmetrical conditions. Means $\pm$ SE.

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Figure 1

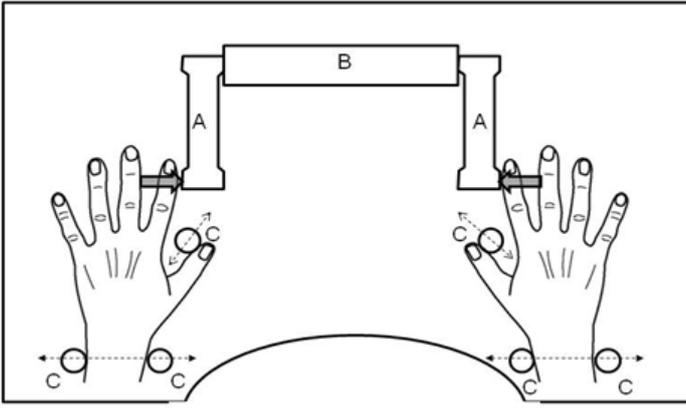


Figure 2

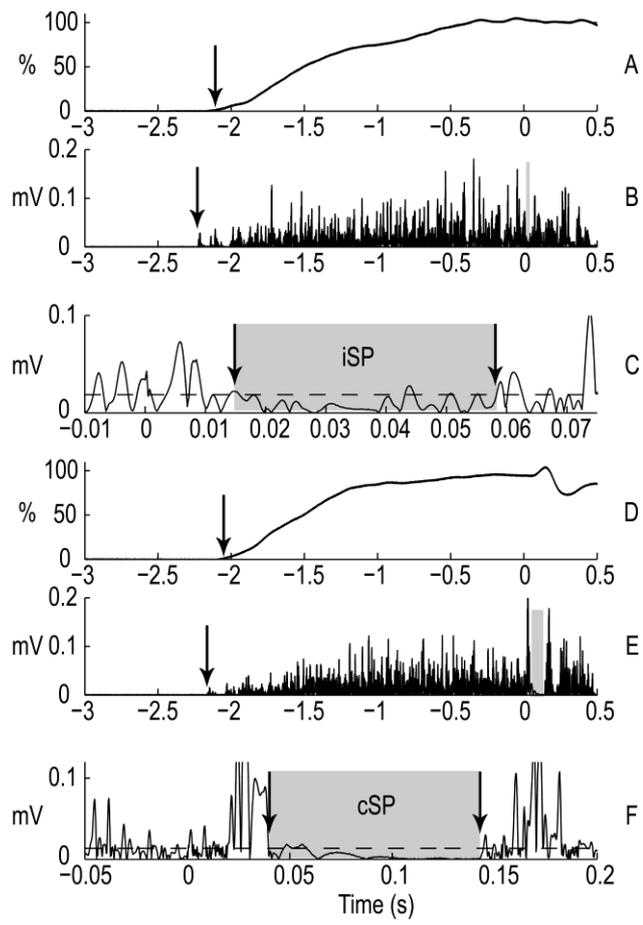


Figure 3

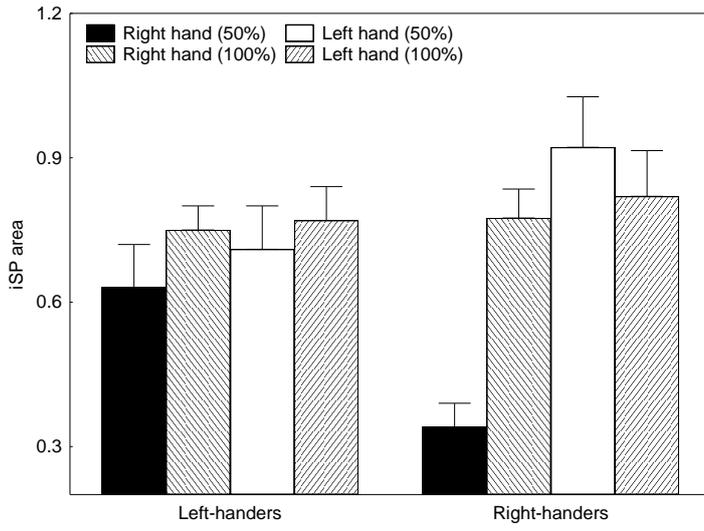


Figure 4

