Experimental Brain Research (2019) 237:1973–1980
https://doi.org/10.1007/s00221-019-05569-0

RESEARCH ARTICLE

The effects of conditioning startling acoustic stimulation (SAS) on the corticospinal motor system: a SAS–TMS study

Yen-Ting Chen[1,2] · Shengai Li[1,2] · Ping Zhou[1,2] · Sheng Li[1,2]

Received: 29 November 2018 / Accepted: 27 May 2019 / Published online: 29 May 2019

Abstract

A startling acoustic stimulus (SAS) could cause transient effects on the primary motor cortex and its descending tracts after habituation of reflex responses. In the literature, there is evidence that the effects of SAS depend on the status of M1 excitability and delivery time of SAS. In this study, we aimed to comprehensively investigate the effects of SAS on the excitability of primary motor cortex. Eleven healthy subjects participated in this study. Transcranial magnetic stimulation (TMS) was delivered to the hot spot for left biceps at rest and during isometric right elbow flexion (10, 30, and 60% of their maximum voluntary contraction, MVC). There were three SAS conditions: (1) No SAS; (2) SAS was delivered 50 ms prior to TMS (SAS50); (3) SAS 90 ms prior to TMS (SAS90). For each subject, the induced MEP amplitude was normalized to the largest response at rest with No SAS. Two-way ANOVAs (4 force levels × 3 SAS conditions) with repeated measures were used to determine the differences under different conditions. For the MEP amplitude, there were significant force level effect and FORCE LEVEL × SAS interactions. Specifically, the MEP amplitude increased with force level. Furthermore, post hoc analysis showed that the MEP amplitude reduced during SAS50 and SAS90 compared to No SAS only at rest. Our results provide evidence that a conditioning SAS causes a transient suppression of the corticospinal excitability at rest when it is delivered 50 ms and 90 ms prior to TMS. However, a conditioning SAS has no effect when the corticospinal excitability is already elevated with an external visual target.

Keywords Startling acoustic stimulus (SAS) · Reticulospinal excitability · Corticospinal excitability · TMS · Motor cortex · Human

Introduction

Acoustic startle reflex is likely to occur when an intense acoustic stimulus (i.e., startling sound) is delivered unexpectedly. Motoric reflex responses habituate quickly with subsequently repeated stimuli, usually in 3–5 times (Yeomans and Frankland 1995). However, there is evidence that ensuing startling acoustic stimulation (SAS) can still generate covert and transient effects on the primary motor cortex (M1) and corticospinal excitability. The ensuing SAS has differential effects at the cortical level and at the spinal level through projections from the stimulated reticular system. In general, it has been proposed that an early inhibition of the M1 excitability via ascending polysynaptic reticulocortical pathways (Kühn et al. 2004) and concomitant facilitatory effects on spinal motor neurons mediated by descending reticulospinal pathways (Chen et al. 2016, 2019; Ilic et al. 2011).

These effects have been studied in an established SAS–TMS paradigm (Chen et al. 2016; Fisher et al. 2004; Furubayashi et al. 2000; Ilic et al. 2011; Kühn et al. 2004). In this paradigm, a SAS is delivered about 30–100 ms before transcranial magnetic stimulation (TMS) to the M1, and the intensity of the SAS was between 80 and 110 dB (Furubayashi et al. 2000). The SAS-conditioning effect is mainly assessed by changes in the TMS-induced motor-evoked potential (MEP) amplitude. At least two factors which could alter the SAS effects on M1 are identified: the SAS–TMS inter-stimulus interval and the activation status of the target muscle. All studies report that conditioning

✉ Sheng Li
sheng.li@uth.tmc.edu

[1] Department of Physical Medicine and Rehabilitation, McGovern Medical School, University of Texas Health Science Center—Houston, Houston, TX 77030, USA

[2] TIRR Research Center, TIRR Memorial Hermann Hospital, 1333 Moursund, Houston, TX 77030, USA

SAS has a general transient inhibitory effect on the MEP amplitude if delivered 30–60 ms prior to TMS (Chen et al. 2016; Fisher et al. 2004; Furubayashi et al. 2000; Ilic et al. 2011; Kühn et al. 2004). The MEP amplitude is found to be suppressed further from 70 to 100 ms in one study (Ilic et al. 2011), but returns to the baseline in another study (Fisher et al. 2004; Furubayashi et al. 2000).

This SAS-conditioning effect also depends on the background excitability of the corticospinal motor system. The early inhibitory effect is observed when the target muscle is at rest (Chen et al. 2016; Ilic et al. 2011) and slightly activated (Fisher et al. 2004; Furubayashi et al. 2000; Ilic et al. 2011; Kühn et al. 2004). The effect disappears when the target muscle is activated at 10% of maximal voluntary contraction (MVC) and with visual attention (Chen et al. 2016). The differential effects at rest and pre-activation are also reported in an anticipatory timing study, where the SAS effect is inhibitory if delivered early in the preparation stage, while the effect is facilitatory if delivered closer to the movement onset when the corticospinal motor system is already in an advanced state of preparation for action (Marinovic et al. 2014).

In this study, we aimed to comprehensively investigate the effects of conditioning SAS on the corticospinal motor system using the established SAS–TMS paradigm with various combinations of the SAS–TMS intervals and the background excitability of the corticospinal motor system. Two intervals (50 ms and 90 ms) were chosen. The 50 ms condition would act as a confirmation of methods since the corticospinal suppression at 50 ms prior to TMS was consistent. The 90 ms condition was intended to clarify the contradictory results described above. As mentioned earlier (Marinovic et al. 2014), the SAS-conditioning effects differ when the M1 is at different levels of subthreshold activation prior to action. To investigate the SAS effect on M1 during different levels of its background excitability from subthreshold (increased M1 activity without observable muscle activity) to suprathreshold (increase M1 activity with observable muscle activity), we targeted to the M1 ipsilateral to the active biceps. During a unilateral muscle contraction, the excitability of the contralateral M1 area increases with the increment of muscle contraction (Ashe 1997; Dai et al. 2001; Ni et al. 2006). Reportedly, the excitability of the M1 ipsilateral to the contracting muscle also increases proportionally (Perez and Cohen 2008; Shibuya et al. 2014; Stinear et al. 2001; Uematsu et al. 2010). A series of positron emission tomography studies showed that activation of the ipsilateral M1 decreased during a very light ipsilateral muscle contractions (5% of MVC) and then increased with the increment of the required force level (from 10 to 60%) during a unilateral key-press task compared to the resting condition (Dettmers et al. 1996a, b).

Methods

Participants

Eleven right-handed healthy adults (32.5 ± 7.6 years, 3 females) participated in this study. A power analysis was conducted to estimate the number of subjects needed to find significant SAS-induced MEP reduction based on our previous work (Chen et al. 2016). The results of the power analysis indicated that 11 subjects are sufficient to reach α level of 0.05 and β level of 0.8. All the subjects were right-handed according to their preferred hand use in writing and eating. They self-reported being healthy without any known neuromusculoskeletal impairments. The committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston approved the procedures of this study. All participants provided written informed consent before participating in the study.

Experimental setting

Each subject was seated comfortably on a height adjustable chair in an upright position and to put the right arm in a customized device. The right forearm was secured against two adjustable metal plates with a padded strap approximately 2–4 in proximal from the wrist. The position of the subjects' both arms was as follows: the shoulder was placed approximately in 30° of abduction and 45° of flexion, while the elbow was flexed to 90°. The wrist and fingers were kept in the neutral position. To keep two arms under symmetrical position, a height adjustable table was provided for the left arm. A 20-in monitor (Model: 2001FP, Dell Computer Corp., Texas, USA), which was located approximately 1 m in front of the subjects at eye level, was used to provide visual feedback to the subjects. All subjects reported that the visual target was clearly displayed. A startle sound (Microsoft system warning sound, 1 kHz tone of 50 ms) was generated by a speaker (Model: HS50 M, YAHAMA Corp., Hamamatsu, Japan) through a sound card (Model: Sound Blaster Extreme, Creative Technology Ltd.) installed on a computer. The rise time of the startle sound was 8 ms. It had be proved in the literature that this rise time is sharp enough to successfully elicit startling reaction (Blumenthal and Berg 1986). The speaker was placed 30 cm behind the head of the subjects at ear level. The acoustic stimulus of 100 dB was confirmed at this distance (Fig. 1). The acoustic stimulus at this level is able to elicit startle reflex responses, based on EMG coherence analysis (Grosse and Brown 2003).

The force of right elbow flexion was measured with a torque sensor (Model: TRS-500, Transducer Techniques,

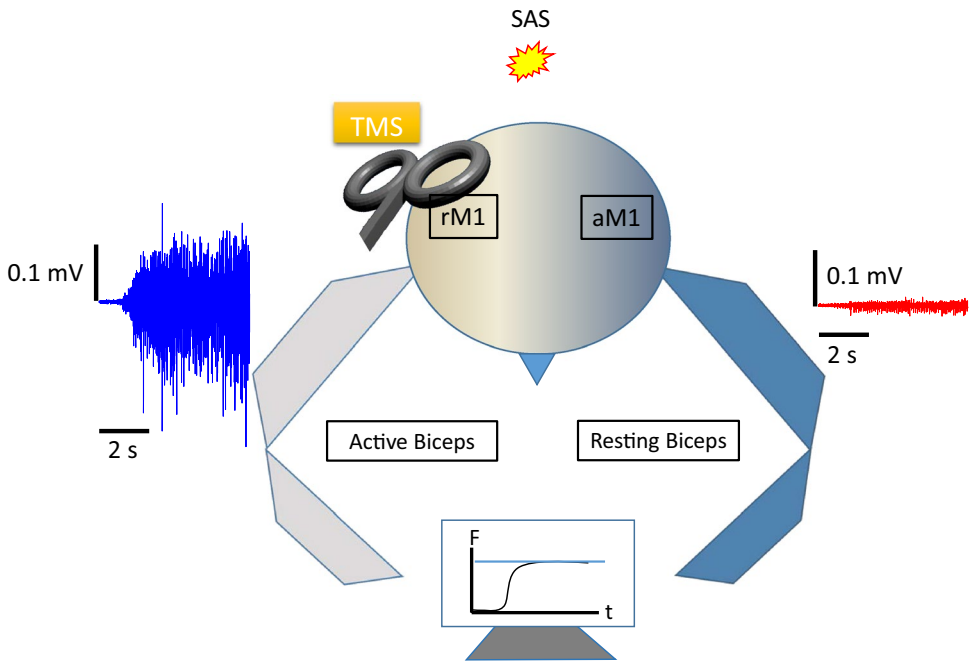

Fig. 1 Experimental setup. *rM1* the resting motor cortex, *aM1* the active motor cortex

Temecula, CA, USA). The sensor was located in line with the center of the rotation of the right elbow joint. Muscle activity was recorded with a Bagnoli EMG system (Delsys Inc., Boston, MA, USA) from right biceps muscle according to the European Recommendations for Surface Electromyography (Hermens et al. 2000). The EMG signals were band-pass filtered from 20 to 450 Hz, amplified 1000 times by the Bagnoli EMG system. All force and EMG signals were sampled at 1000 Hz with an NI-DAQ card. A custom-written program in LabView® (National Instrument™ Inc., Austin, Texas, USA) was used to generate visual feedback. All collected signals were stored on a personal computer.

Experimental tasks

Each subject performed the following tasks within a session: (1) localizing hotspot; (2) maximal voluntary contraction (MVC) elbow flexion tasks; and (3) TMS at rest and during isometric elbow flexion tasks with and without SAS conditioning.

Localizing the hotspot In the beginning of the experiment, the hotspot of the left biceps was localized for each subject. Subjects were asked to keep their elbow in about 90° flexion (against gravity). A single pulse of TMS stimulus (BiStim2, MagStim Corp., UK) was set at 75% of the maximum stimulator capacity and delivered over the right motor cortex using a figure-of-8 shaped stimulation coil (a 70-mm mean diameter of each wing, Model: BiStim2, MagStim Corp., UK). The hotspot was confirmed when the largest elbow flexion was produced in three consecutive trials. A gel ink pen was used to mark the spot on the scalp for the rest of the experiment.

MVC tasks After localizing the hotspot, subjects were asked to perform and maintain maximum isometric elbow flexion for 3–5 s on the right. For each subject, three MVC attempts were performed. The highest force among three trials was considered as the MVC force. To prevent possible fatigue effect, at least 1 min break was given to subjects between two consecutive attempts. The MVC force was used to determine the target force for TMS during isometric contraction task.

TMS at rest Subjects were asked to sit steady without any biceps muscle contractions. TMS was delivered to the hotspot of left biceps between 7 and 11 s during a 12-s trial. There were three startle acoustic stimulation (SAS) conditions during TMS at rest: (1) No SAS; (2) SAS delivered 50 ms prior to TMS (SAS50); and (3) SAS delivered 90 ms prior to TMS (SAS90).

TMS during isometric elbow flexion For isometric contraction tasks, the target forces were set to 10, 30, and 60% of each individual's MVC. The real-time force was provided as a white trace which ran from left to right in the middle of the monitor. The target force was provided as a horizontal red line in the middle of the monitor. The *y*-axis scale adjusted for different force levels so that the visual feedback was the same among different force levels and different subjects. Subjects were asked to perform isometric contraction with their right biceps and match the white line to the red line as precise as they can. Similar to the TMS at rest task, TMS was delivered to the hotspot of left biceps between 7 and 11 s during a 12-s trial. At least one familiarization trial

was provided to each subject. As the TMS at rest task, there were three SAS conditions for each force level: (1) No SAS; (2) SAS50; (3) SAS90.

The order of the force levels (rest, 10, 30, and 60% of MVC) was randomized for each subject. The order of the SAS conditions was randomized for each force level for each subject. Six trials were collected for each force level, and adequate rest breaks were provided to each subject to minimize fatigue effect. The hotspot was verified intermittently during the experiment to ensure accuracy of the TMS coil placement.

Data analysis

Force and EMG data were analyzed off-line with custom-written Matlab® programs (Math Works™ Inc., Natick, Massachusetts, USA). The raw force signal was low-pass filtered at 10 Hz with a fourth-order, zero-lag Butterworth digital filter before further analysis. The following parameters were calculated similar to our recent analysis methods (Chen et al. 2016).

Background force Background force was calculated as the mean force generated by the right biceps over a 100-ms window prior to the TMS delivery.

Background EMG Background EMG was quantified as the root mean square (RMS) of the left biceps EMG over the 100-ms window prior to the TMS delivery for each trial.

Motor-evoked potential (MEP) latency The MEP latency was quantified as the interval between the TMS delivery to the time point when the left biceps EMG signal exceeded 2 standard deviations of the amplitude of the background EMG values.

MEP amplitude To calculate the MEP amplitude, we quantified the peak-to-peak left biceps EMG amplitude with the time window from the MEP onset to 50 ms after the TMS delivery. The MEP amplitude was normalized to the largest response at rest with No SAS for each subject to make comparison between subjects.

Statistical analysis

In this study, we calculated the following dependent variables: (1) background force; (2) background EMG; (3) MEP latency; and (4) MEP amplitude. Two-way repeated measure ANOVAs were used for background force on the right side and background EMG on the left side with within-group factors of SAS effect (No SAS, SAS50, SAS90) and FORCE LEVEL (10, 30, and 60% of MVC), respectively. Another two-way repeated measure ANOVAs were used for MEP latency and MEP amplitude of the left biceps muscle with within-group factors of SAS effect (with and without) and FORCE LEVEL (rest, 10, 30, and 60% of MVC). Post hoc analyses were performed to detect the loci of significance. The alpha level for all statistical tests was set at 0.05. Data are reported as mean ± SD within the text and as mean ± SEM in the figures. Only the significant main effects are presented unless otherwise noted.

Results

Background force on the right side and background EMG on the left side

As expected, background force generated by the right biceps muscle increased with the force level (10%: 3.96 Nm ± 0.82 Nm; 30%: 11.59 Nm ± 2.65 Nm; 60%: 23.0 Nm ± 5.29 Nm; $F_{2,20} = 197.66$, $p < 0.01$). Similarly, background EMG of the left biceps also increased with the force level (10%: 0.0079 mV ± 0.0054 mV; 30%: 0.0086 mV ± 0.0050 mV; 60%: 0.017 mV ± 0.0089 mV; $F_{2,20} = 19.01$, $p < 0.01$). Post hoc analysis revealed that background EMG was significantly higher during 60% of MVC task compared with 10% and 30% of MVC tasks (both $p < 0.05$). However, there were no significant SAS effects, nor FORCE LEVEL × SAS interactions for both background force and background EMG. Representative EMG signals from both sides of biceps during 60% of MVC task in Fig. 1 illustrated this finding.

MEP latency

There was a significant FORCE LEVEL main effect ($F_{3,30} = 4.35$, $p = 0.01$) for the TMS latency. Post hoc analysis showed that the TMS latency was significantly longer at rest (15.05 ms ± 1.98 ms) compared with 60% of MVC task (14.45 ms ± 2.37 ms, 95% of the confidence interval of the difference between 10 and 60% of MVC tasks: 0.09–1.1 ms; $p = 0.01$). There were no significant SAS effects, nor FORCE LEVEL × SAS interactions for the TMS latency (Fig. 2).

MEP amplitude

There was a significant main effect of FORCE LEVEL on the MEP amplitude. The normalized MEP amplitude increased with force level (at rest: 67.70 ± 3.10%; 10%: 120.31 ± 13.59%; 30%: 178.30 ± 26.72%; 60%: 318.31 ± 56.11%; $F_{3,30} = 18.72$, $p < 0.01$). Specifically, post hoc analyses showed that the MEP amplitude during 60% of MVC tasks was significantly higher than the MEP amplitude at rest and during 10% and 30% MVC tasks. Furthermore, the MEP amplitude during 30% of MVC task was significantly higher than the MEP amplitude at rest. There were also significant FORCE LEVEL × SAS interactions for the MEP amplitude ($F_{6,60} = 2.35$, $p = 0.04$). Post hoc one-way ANOVA with repeated measure showed

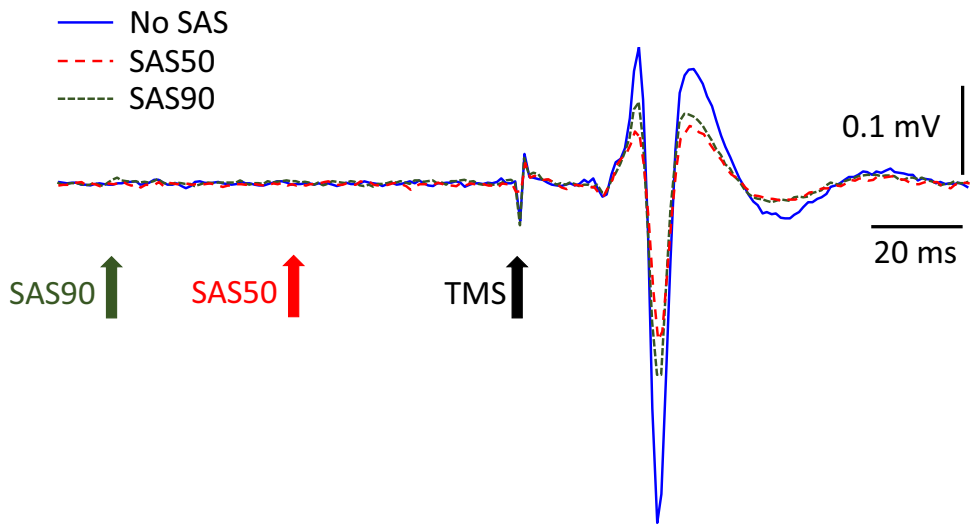

Fig. 2 Representative trials of MEP at rest during No SAS, SAS50, and SAS90

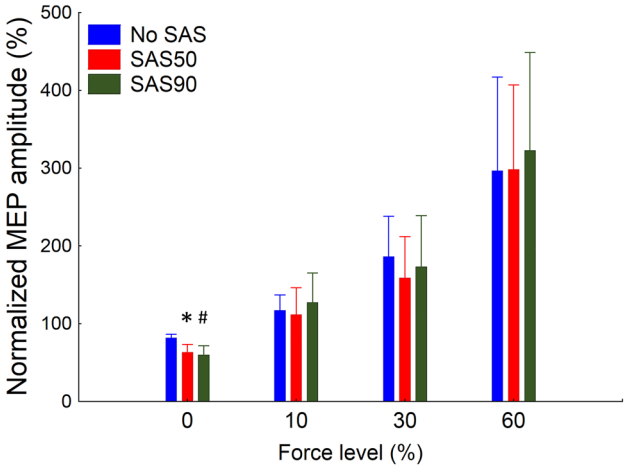

Fig. 3 MEP amplitude was smaller during SAS50 and SAS90 compared with No SAS at rest, but not during other force levels. *Statistically significant difference between No SAS and SAS50 at rest ($p < 0.05$). #Statistically significant difference between No SAS and SAS90 at rest ($p < 0.05$)

a significant main effect of SAS at rest ($F_{3,30} = 14.68$, $p < 0.05$). Post hoc paired t test showed that the MEP amplitude reduced during SAS50 ($60.83 \pm 15.15\%$; 95% of the confidence interval of the difference between No SAS and SAS50: 6.3–31.1%) and SAS90 ($58.14 \pm 17.40\%$; 95% of the confidence interval of the difference between No SAS and SAS90: 9.5–34.3%) compared to No SAS at rest ($80.78 \pm 6.68\%$), both $p < 0.05$). Post hoc one-way ANOVA analysis showed no significant main effect of SAS during voluntary contractions (all $p > 0.05$; Fig. 3).

Discussion

The purpose of this study was to comprehensively investigate the SAS-induced transient effects on the corticospinal output. Eleven healthy subjects performed isometric elbow flexion tasks on the right side at submaximal levels (10, 30, and 60% of MVC) or at rest. TMS was delivered to the right M1 area with and without a conditioning SAS at 50 ms or 90 ms prior to TMS. The background EMG of the rest biceps (left biceps) progressively increased as the level of isometric elbow flexion on the right side increased from 10%, 30% to 60% of its MVC. Similarly, the TMS-induced MEP of the rest biceps on the left side increased in parallel as well. Our results were consistent with the previous findings in the literature that the M1 excitability ipsilateral to the active muscle increased with its force level (Dettmers et al. 1996a, b; Perez and Cohen 2008; Shibuya et al. 2014; Stinear et al. 2001; Uematsu et al. 2010). In this study, we observed overt EMG activities from the left bicep muscle during unilateral elbow flexion at 60% of MVC on the right side (Fig. 1), and this finding confirmed that the excitability of right M1 transited from rest, subthreshold, to suprathreshold activation in this experimental paradigm. A small but significant MEP latency difference was observed between 60% of MVC task and at rest. This significant difference might due to the quantification methods used in this study. MEP latency was determined as the interval between the TMS delivery to the time point when the left biceps EMG signal exceeded 2 standard deviations of the amplitude of the background EMG values. During 60% of MVC task, the MEP amplitude is significantly larger than the MEP amplitude at rest. The sharper slope of the MEP during 60% of MVC may make the EMG signal reached to the defined 2 standard deviations of the background EMG values earlier. To sum up, with various combinations of SAS–TMS intervals and graded

background excitability of right M1, the two major findings in this study were: (1) the SAS-conditioning effects depended on the background excitability of the corticospinal motor system. There was a transient inhibition on the right M1 excitability if a SAS was delivered at rest, but no difference in the MEPs during voluntary elbow flexion on the right side at both intervals; (2) there was no difference in the SAS-conditioning effect between the SAS–TMS intervals of 50 ms and 90 ms. These findings are not able to account for inconsistent results in the literature. However, given different experimental settings, these results advance our understanding of the effects of habituated SAS on the corticospinal motor system in force generation and maintenance.

The result of a transient cortical inhibition when a SAS was delivered at 50 ms at rest is confirmatory and is consistent with our previous studies in a similar resting condition in healthy subjects (Chen et al. 2016) and stroke subjects (Chen et al. 2019). The result of no difference in the induced cortical inhibition between the 50 ms and 90 ms intervals is also in general agreement with a previous report (Ilic et al. 2011). In the cited study, healthy subjects were instructed to maintain a light ankle dorsiflexion contraction. EMG signals were recorded from the agonist soleus muscle and the resting antagonist tibialis anterior muscle. The 100 dB conditioning SAS was delivered ranging from 20 to 160 ms. The authors reported a general SAS-induced MEP reduction in both active soleus and resting tibialis anterior muscles from 40 to 120 ms. However, at the interval of 90 ms (ranging from 70 to 100 ms) and 110 dB conditioning SAS, Furubayashi et al. reported the MEP has returned to the baseline, i.e. no cortical inhibition, during light contraction of the first dorsal interosseous muscle (Furubayashi et al. 2000). These inconsistent observations of cortical inhibition at the 90-ms interval might be related to different muscle activation levels (at rest or pre-activated) and the intensity of SAS used in these studies.

The most striking result was that there was No SAS-induced cortical inhibition at both 50 ms and 90 ms intervals when the right M1 excitability increased from subthreshold to suprathreshold during right elbow flexion tasks. This result extended our recent observations that conditioning SAS at 50 ms had cortical inhibition when at rest but no effects when performing 10% MVC of elbow flexion (Chen et al. 2016, 2019). In these studies, subjects performed isometric elbow flexion while TMS was applied to the contralateral M1 area. In the present study, TMS was applied to the M1 area ipsilateral to active elbow flexion. Collectively, these results indicated that SAS conditioning had no significant effects on bilateral M1 excitability during unilateral voluntary elbow flexion.

Results of no cortical inhibition from conditioning SAS during voluntary activation from our series of studies were different from all previous reports (Fisher et al. 2004; Furubayashi et al. 2000; Ilic et al. 2011; Kühn et al. 2004). All studies reported that conditioning SAS at 50 ms induced early cortical inhibition during light voluntary contractions. The results from this study of graded increase in the M1 excitability suggest that the differences between our studies and others are not related to the level of activation. The contradicting results between these studies might be due to different experimental protocols. In our studies, subjects were asked to maintain the target force as precisely as they can with real-time feedback on the computer screen. But many other studies only encouraged the subjects to maintain a constant light force without a visual target (Fisher et al. 2004; Furubayashi et al. 2000; Ilic et al. 2011; Kühn et al. 2004). Different focus of attention between experimental protocols could play a fundamental role in the contradictory results. Recent researches have shown that the focus of attention can modulate the M1 excitability (Bell et al. 2018; Binkofski et al. 2002; Kuhn et al. 2017). Specifically, Kuhn et al. (2017) reported that an external attention focus during sustained index finger abduction task had increased short-interval intracortical inhibition (SICI) and longer time to fatigue. The increased inhibition was believed to modulate the inhibitory circuitry within M1 to sustain the descending output, thus longer time to fatigue. Conceivably, a SAS-induced interruption to the M1 excitability, i.e., cortical inhibition, could be modulated by increased SICI in the context with continuous attention to the visual target in our experimental protocol, but not in other studies. Future studies are needed to investigate the intracortical inhibitory and excitatory mechanisms to better understand the disparity in results.

The seemingly paradoxical results between our studies and other studies actually shed new light on understanding the effects of SAS on the corticospinal motor system. SAS has been used as a probe to investigate contributions of the brainstem reticular motor system to movement (Carlsen et al. 2012b). A robust finding is that if a person is prepared to start a particular movement in a simple reaction time task, a SAS can directly trigger the prepared action for the visual "go" signal. This phenomenon is called "StartReact". Valls-Solé et al. (1995) found that the StartReact effect can shorten reaction time from 150 ms to about 80 ms from the "go" signal to the EMG onset. However, the StartReact effect is absent in a choice reaction time task (Carlsen et al. 2004), or a Go/No-go reaction time task (Carlsen et al. 2008). In contrast, StartReact effects have been reported in other reaction time tasks, such as being engaged in a continuous movement (e.g., Maslovat et al. 2017) and when performing a force production task with visual feedback (e.g., Carlsen et al. 2012a; Maslovat et al. 2015). In a review article, Marinovic and Tresilian (2016) proposed an integrative view that SAS imposes excitatory effects on the central nervous system, the StartReact effect is only a particular manifestation which is

not mediated by acoustic startle reflex pathways. SAS could have other effects, depending on motor tasks.

Our findings from the SAS–TMS paradigm are in general agreement with this view, and provide further evidence that the effect of SAS on M1 excitability depends on the status of the cortical motor system. If engaged in maintaining a target force with visual feedback, a SAS is not likely to interrupt the ongoing corticospinal output, i.e., no MEP reduction; if there is no stable corticospinal output or an external target/goal (e.g., rest, or generating a light force), a SAS will interrupt the cortical motor system via a transient cortical inhibition, i.e., MEP reduction. When the cortical motor system is damaged, e.g., after stroke, the reticular motor system is shown to compensate for its function to some degree (Herbert et al. 2015; Jang et al. 2013; Zaaimi et al. 2012). However, more research is needed to further investigate the interactions between two motor systems and the role of reticular motor system in movement. Furthermore, the MEP response elicited by TMS reflects the overall excitability of corticospinal pathway. The role of excitability change on spinal level during different SAS–TMS intervals and different pre-exist M1 excitability should be also further investigated.

Conclusion

Our results provide evidence that conditioning SAS delivered 50 ms and 90 ms prior to TMS causes transient suppression of the corticospinal excitability at rest. There is no such transient cortical inhibition when the corticospinal excitability is already elevated with an external visual target.

Acknowledgements This study was supported in part by NIH NICHD/NCMRR R21HD087128, R21HD090453.

References

Ashe J (1997) Force and the motor cortex. Behav Brain Res 87:255–269

Bell SJ, Lauer A, Lench DH, Hanlon CA (2018) Visual attention affects the amplitude of the transcranial magnetic stimulation-associated motor-evoked potential: a preliminary study with clinical utility. J Psychiatr Pract 24:220–229. https://doi.org/10.1097/PRA.0000000000000321

Binkofski F et al (2002) Neural activity in human primary motor cortex areas 4a and 4p is modulated differentially by attention to action. J Neurophysiol 88:514–519

Blumenthal TD, Berg WK (1986) Stimulus rise time, intensity, and bandwidth effects on acoustic startle amplitude and probability. Psychophysiology 23:635–641

Carlsen AN, Chua R, Inglis JT, Sanderson DJ, Franks IM (2004) Can prepared responses be stored subcortically? Exp Brain Res 159:301–309. https://doi.org/10.1007/s00221-004-1924-z

Carlsen AN, Chua R, Dakin CJ, Sanderson DJ, Inglis JT, Franks IM (2008) Startle reveals an absence of advance motor programming in a Go/No-go task. Neurosci Lett 434:61–65. https://doi.org/10.1016/j.neulet.2008.01.029

Carlsen AN, Almeida QJ, Franks IM (2012a) Startle decreases reaction time to active inhibition. Exp Brain Res 217:7–14. https://doi.org/10.1007/s00221-011-2964-9

Carlsen AN, Maslovat D, Franks IM (2012b) Preparation for voluntary movement in healthy and clinical populations: evidence from startle. Clin Neurophysiol 123:21–33. https://doi.org/10.1016/j.clinph.2011.04.028

Chen YT, Li S, Zhou P, Li S (2016) Different effects of startling acoustic stimuli (SAS) on TMS-induced responses at rest and during sustained voluntary contraction. Front Hum Neurosci 10:396. https://doi.org/10.3389/fnhum.2016.00396

Chen YT, Li S, Zhou P, Li S (2019) A startling acoustic stimulation (SAS)-TMS approach to assess the reticulospinal system in healthy and stroke subjects. J Neurol Sci. https://doi.org/10.1016/j.jns.2019.02.018

Dai TH, Liu JZ, Sahgal V, Brown RW, Yue GH (2001) Relationship between muscle output and functional MRI-measured brain activation. Exp Brain Res 140:290–300

Dettmers C, Lemon RN, Stephan KM, Fink GR, Frackowiak RS (1996a) Cerebral activation during the exertion of sustained static force in man. Neuro Rep 7:2103–2110

Dettmers C, Ridding MC, Stephan KM, Lemon RN, Rothwell JC, Frackowiak RS (1996b) Comparison of regional cerebral blood flow with transcranial magnetic stimulation at different forces. J Appl Physiol (1985) 81:596–603. https://doi.org/10.1152/jappl.1996.81.2.596

Fisher RJ, Sharott A, Kühn AA, Brown P (2004) Effects of combined cortical and acoustic stimuli on muscle activity. Exp Brain Res 157:1–9. https://doi.org/10.1007/s00221-003-1809-6

Furubayashi T et al (2000) The human hand motor area is transiently suppressed by an unexpected auditory stimulus. Clin Neurophysiol 111:178–183

Grosse P, Brown P (2003) Acoustic startle evokes bilaterally synchronous oscillatory EMG activity in the healthy human. J Neurophysiol 90:1654–1661

Herbert WJ, Powell K, Buford JA (2015) Evidence for a role of the reticulospinal system in recovery of skilled reaching after cortical stroke: initial results from a model of ischemic cortical injury. Exp Brain Res 233:3231–3251. https://doi.org/10.1007/s00221-015-4390-x

Hermens HJ et al (2000) SENIAM 8: European recommendations for surface electromyography. Roessingh Research and Development, Enschede

Ilic TV, Pötter-Nerger M, Holler I, Siebner HR, Ilic NV, Deuschl G, Volkmann J (2011) Startle stimuli exert opposite effects on human cortical and spinal motor system excitability in leg muscles. Physiol Res 60:S101–S106

Jang SH, Chang CH, Lee J, Kim CS, Seo JP, Yeo SS (2013) Functional role of the corticoreticular pathway in chronic stroke patients. Stroke 44:1099–1104. https://doi.org/10.1161/STROKEAHA.111.000269

Kuhn YA, Keller M, Ruffieux J, Taube W (2017) Adopting an external focus of attention alters intracortical inhibition within the primary motor cortex. Acta Physiol 220:289–299. https://doi.org/10.1111/apha.12807

Kühn AA, Sharott A, Trottenberg T, Kupsch A, Brown P (2004) Motor cortex inhibition induced by acoustic stimulation. Exp Brain Res 158:120–124. https://doi.org/10.1007/s00221-004-1883-4

Marinovic W, Tresilian JR (2016) Triggering prepared actions by sudden sounds: reassessing the evidence for a single mechanism. Acta Physiol 217:13–32. https://doi.org/10.1111/apha.12627

Marinovic W, Tresilian JR, de Rugy A, Sidhu S, Riek S (2014) Corticospinal modulation induced by sounds depends on action

preparedness. J Physiol 592:153–169. https://doi.org/10.1113/jphysiol.2013.254581

Maslovat D, Drummond NM, Carter MJ, Carlsen AN (2015) Reduced motor preparation during dual-task performance: evidence from startle. Exp Brain Res 233:2673–2683. https://doi.org/10.1007/s00221-015-4340-7

Maslovat D, Carter MJ, Carlsen AN (2017) Response preparation and execution during intentional bimanual pattern switching. J Neurophysiol 118:1720–1731. https://doi.org/10.1152/jn.00323.2017

Ni Z et al (2006) Functional demanded excitability changes of human hand motor area. Exp Brain Res 170:141–148. https://doi.org/10.1007/s00221-005-0201-0

Perez MA, Cohen LG (2008) Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. J Neurosci 28:5631–5640. https://doi.org/10.1523/JNEUROSCI.0093-08.2008

Shibuya K, Kuboyama N, Tanaka J (2014) Changes in ipsilateral motor cortex activity during a unilateral isometric finger task are dependent on the muscle contraction force. Physiol Meas 35:417–428. https://doi.org/10.1088/0967-3334/35/3/417

Stinear CM, Walker KS, Byblow WD (2001) Symmetric facilitation between motor cortices during contraction of ipsilateral hand muscles. Exp Brain Res 139:101–105

Uematsu A, Obata H, Endoh T, Kitamura T, Hortobagyi T, Nakazawa K, Suzuki S (2010) Asymmetrical modulation of corticospinal excitability in the contracting and resting contralateral wrist flexors during unilateral shortening, lengthening and isometric contractions. Exp Brain Res 206:59–69. https://doi.org/10.1007/s00221-010-2397-x

Valls-Solé J, Solé A, Valldeoriola F, Muñoz E, Gonzalez LE, Tolosa ES (1995) Reaction time and acoustic startle in normal human subjects. Neurosci Lett 195:97–100. https://doi.org/10.1016/0304-3940(94)11790-P

Yeomans JS, Frankland PW (1995) The acoustic startle reflex: neurons and connections. Brain Res Rev 21:301–314

Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN (2012) Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. Brain 135:2277–2289. https://doi.org/10.1093/brain/aws115