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RESEARCH ARTICLE

Short-latency afferent-induced facilitation and inhibition as predictors of thermally induced variations in corticomotor excitability

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Abstract

Recently (Ansari et al., PeerJ 6:e6163, 2018a; Somatosens Mot Res 35:69–79, 2018b), we showed using transcranial magnetic stimulation (TMS) that focal application of innocuous thermal stimuli to the distal hand produced variable responses in terms of motor-evoked potential (MEP) suppression or enhancement. Here, we sought to investigate possible causes of this variability by examining circuits mediating sensorimotor integration and intra-cortical inhibition. Participants ($n = 21$) first underwent TMS to assess baseline corticomotor excitability by measuring MEPs at rest with the index finger wrapped in a gel pack at room temperature (24 °C). Then, conditioned protocols were applied to assess short-latency afferent inhibition (SAI), short-latency afferent facilitation (SAF) and short-interval intra-cortical inhibition (SICI). Following baseline measures, MEP modulation in response to distal cooling was recorded with the index finger wrapped in a gel pack at ~ 10 °C. At baseline, participants exhibited variable levels of SAI, SAF and SICI. Participant also exhibited variable responses to cooling with about half of them (11/21) showing suppressed excitability and one-third showing enhanced excitability (7/21). A linear regression analysis revealed that SAI and SAF proved to be good predictors of cooling-induced variations in corticomotor excitability but not SICI. These results provide novel evidence linking variations in SAI and SAF with those in corticomotor excitability elicited in response to focal thermal stimulation, suggesting that these markers could be used to predict responses to sensory stimulation protocols.

Keywords Thermal stimulation · Motor evoked potentials · Short-latency afferent inhibition · Sensorimotor integration · Peripheral stimulation · Transcranial magnetic stimulation

Introduction

In recent years, the use of thermal stimulation in the form of either cooling or warming stimuli applied to superficial and deep tissues has been proposed as an effective facilitation method, notably for patients recovering from stroke (Chen et al. 2005, 2011). The rationale for using thermal stimulation has been based largely on indirect evidence from neuroimaging studies showing extensive neural activation both at the subcortical (e.g., ventrobasal thalamus) and cortical level (e.g., insular cortex, primary (S1) and secondary (S2) somatosensory areas) in response to skin cooling or warming (Bokiniec et al. 2018). On this basis, it was proposed (Hsu et al. 2013) that repeated applications of thermal stimuli could lead to neuroplastic changes in the injured brain and promote motor reorganization. In line with this, Tai et al. (2014) showed that alternating noxious warm and cold stimulation to the affected arm of stroke patients for 30 min increased the motor map size area and motor-evoked potential (MEP) amplitude in the lesioned hemisphere.

In recent investigations (Ansari et al. 2018a, b), we used transcranial magnetic stimulation (TMS) to examine the neurophysiological basis of thermal stimulation on corticomotor excitability. In the first study (Ansari et al. 2018b), we showed that innocuous cooling or warming restricted to a single digit elicited short-lasting and variable responses in our participants characterized by either MEP suppression or enhancement. When examining possible sources of this variability, we found that individual characteristics related to age (young vs. old) or sex had no influence. Likewise, individual

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changes in skin temperature had no effect. In a follow-up study (Ansari et al. 2018a), we showed that approximately tripling the cooling surface area on the distal hand still elicited mixed responses amongst participants with half showing suppression and the other half showing MEP enhancement, although these effects were more sustained in the post-stimulation phase. Our results also revealed that thermally induced variations in corticomotor excitability were fairly consistent in a given individual with repeated applications, even with many weeks between sessions.

While our findings on the variability of thermally induced modulation aligned with previous observations regarding the outcomes of stimulation protocols targeting cortical plasticity (Chipchase et al. 2011), they still raised the question as to why a simple intervention could produce such mixed responses at the individual level. We propose that this variability could be related to differences in the way thermal afferents are processed centrally through sensorimotor integration. Like other forms of somatosensory afferent inputs, thermal afferents have the potential to modulate corticomotor excitability either directly via thalamocortical projections or indirectly through projections from somatosensory areas (e.g., S1 and S2) to primary motor cortex (M1) (Hooks 2016). In humans, the excitability of cortical circuits thought to be involved in sensorimotor integration can be assessed through short-latency afferent inhibition (SAI) (Turco et al. 2018). SAI is obtained when MEPs evoked by cortical stimulation are conditioned by prior afferent nerve stimulation at short intervals (i.e., 18–24 ms). When the interval between the afferent nerve conditioning and the TMS pulse is increased between 40 and 70 ms, the afferent modulation becomes facilitatory, a phenomenon that has been referred to as short-latency afferent facilitation (SAF) (Devanne et al. 2009). Both SAI and SAF magnitudes are influenced by the nature of the afferent volley (e.g., cutaneous vs. proprioceptive) and its amplitude (Devanne et al. 2009; Bailey et al. 2016). Several studies have established links between variations in SAI level and excitability of circuits mediating sensorimotor integration. For instance, in patients in the acute stage after stroke, Di Lazzaro et al. (2012) reported a significant reduction in SAI level in the lesioned hemisphere, likely reflecting an adaptation to enhance responsiveness to sensory inputs. In healthy participants, Mang et al. (2012) investigated how SAI and SAF were modulated in response to an increase in corticomotor excitability elicited by repeated neuromuscular electrical stimulation. Their results showed that both markers exhibited a parallel change (i.e., decreased SAI coupled with increased SAF) after the intervention, both pointing to a net increase in the excitatory drive exerted by sensory inputs onto corticospinal neurones in response to enhanced corticomotor excitability.

The above results, collectively, point to the importance of considering changes in the circuits mediating sensorimotor integration when examining the impact of sensory stimulation protocols on corticomotor plasticity. Interestingly, several investigations (Yarnall et al. 2016; Koizume et al. 2017), including our own (Young-Bernier et al. 2014), have shown that SAI level can vary substantially from one individual to another, even in healthy participants of the same age group. Such variations in SAI suggest that the state of M1 intra-cortical excitability at baseline may vary substantially between individuals, which may, in turn, influence how individuals will respond to sensory stimulation. Indeed, there is evidence that inter-individual variations in SAI level, or with other markers of intra-cortical excitability, such as short-interval intra-cortical inhibition (SICI), can be predictors of whom will exhibit suppression or enhancement in response to plasticity-inducing TMS protocols (Guerra et al. 2017). Along the same reasoning, one can ask whether inter-individual differences in the excitability of circuits mediating sensorimotor integration could provide some insights for the variability observed in response to thermal stimulation.

In the present report, we sought to address the above question using TMS to examine the relationship between inter-individual variations in SAI and SAF level, and MEP modulation elicited in response to distal focal cooling. SICI was also assessed as an additional marker to probe individual differences in the excitability of circuits mediating intra-cortical inhibition. Based on the reviewed evidence, we anticipated that levels of SAI and SAF, as markers of sensorimotor integration, would be good predictors of cooling-induced variations in corticomotor excitability in contrast to SICI, which would show no relationship.

Materials and methods

This study was approved by the Institutional Review Ethics Board (Bruyère Hospital Ottawa, Protocol M16-18-015) in accordance with the principles of the Declaration of Helsinki. All participants gave a written informed consent before the experimental session, which was performed in a controlled laboratory environment. Participants received a small honorarium for their participation.

Participants

Twenty-one healthy young adults were recruited for this study (28 ± 7 years, 11 females). Before testing, all participants were screened for conditions likely to affect their participation (e.g., nerve diseases, sensory problems or pain in the upper extremities, recent trauma and aversion to cold). Participants were also screened with a questionnaire (adapted from Keel et al. 2001) for contra-indications to TMS. All tests were performed on the preferred hand (right, $n = 19$), as determined by the Edinburg Hand Inventory

(online version http://www.brainmapping.org/shared/Edinburgh.php).

Electromyography and transcranial magnetic stimulation

Recording and stimulation procedures have been described in detail previously (Ansari et al. 2018b). Briefly, electromyographic (EMG) activity was recorded using surface sensors (DE-2.1, Delsys Inc., Boston, MA, USA) placed over the first dorsal interosseous (FDI) of the dominant hand. After amplification and filtering (Bagnoli™ 4 System, Delsys Inc., bandwidth = 6–450 Hz, gain = 1000), EMG signals were digitized at a rate of 2 kHz (PCI-63203, National Instrument Corp. Austin, TX) and were relayed to a laboratory computer and saved for later off-line analysis.

For TMS, participants were comfortably seated in a custom-made chair equipped with armrests and footrests. Participants were fitted with a Waveguard™ TMS compatible EEG cap (ANT Neuro, Madison, WI, USA) with markers to facilitate coil placement and ensure consistent positioning. Also, a U-shaped neck cushion was used to maintain head position and prevent neck fatigue. TMS pulses were applied on the hemisphere contralateral to the preferred hand over the motor hot spot for the FDI (marked with a sticker) using a focal coil (70 mm, inner loops) connected to a BiStim^2 stimulator (Magstim Co. Ltd, Whitland UK). Stimulation was performed with the coil held in the conventional orientation (i.e., ~45° from the sagittal plane). The resting motor threshold (rMT) was determined using the Motor Threshold Assessment Tool software (MTAT 2.0; Clinical Researcher, Knoxville, TN, USA). During TMS, participants were asked to stay relaxed and count the number of stimuli delivered to prevent a shift of attention or sleepiness. All tests were performed during regular working hours (from 9 a.m. to 5 p.m.) to avoid diurnal variations (Doeltgen and Ridding 2010).

Experimental protocol

The current experiment was conducted in three steps. As shown in Fig. 1, the first step consisted of establishing baseline values for corticomotor excitability as reflected in unconditioned MEPs at rest. As in our previous experiments, this assessment was performed with the index finger wrapped in a gel pack sleeve designed for finger application (TXRT-2540, Torex® Health Products, Tallmadge, OH) that was kept at room temperature (i.e., neutral ~ 24 °C) to account for the tactile feedback associated with the finger wrapping. As reported before, skin temperature was monitored through thermocouple sensors attached at the level of the proximal interphalangeal joint and connected to a K-type digital thermometer (Model# TC41FBA, Perfect-Prime, Dayton, NJ, USA, resolution ± 0.1 °C). With the neutral gel pack in place, skin temperature was recorded and MEPs were elicited ($n = 20$) at a suprathreshold intensity equivalent to 130% rMT to derive a reliable estimate of resting corticomotor excitability (Brown et al. 2017). The second step consisted of assessing SAI, SAF and SICI using

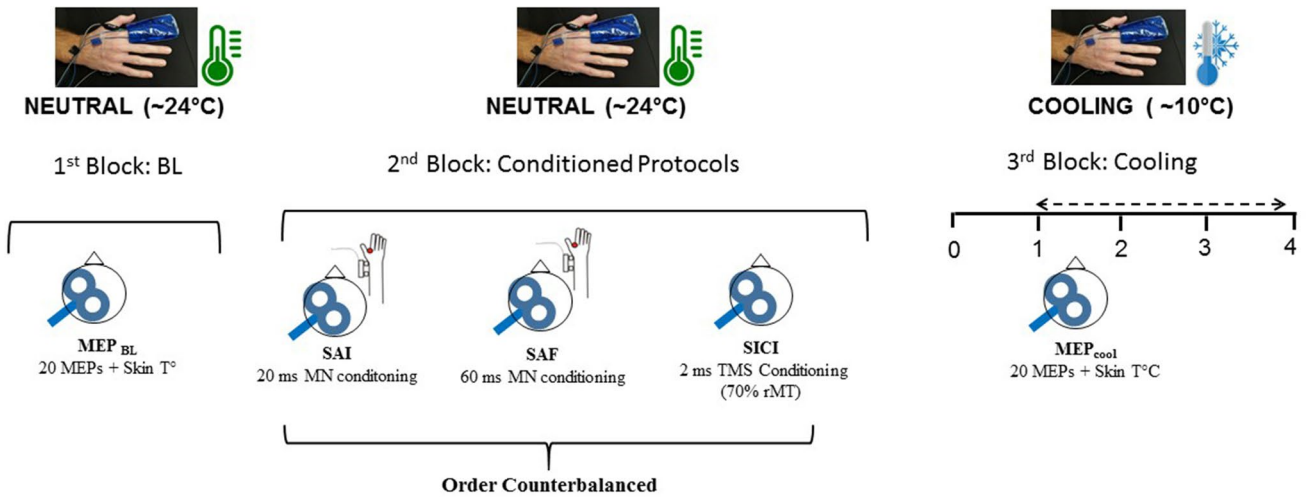

Fig. 1 Schematic representation of the experimental protocol conducted in three steps. The first step consisted of establishing skin temperature (T°) and baseline (BL) values for corticomotor excitability as reflected in unconditioned MEPs at rest. The second step consisted of assessing short-latency afferent inhibition (SAI), short-latency afferent facilitation (SAF) and short-interval intra-cortical inhibition (SICI) with conditioned protocols. The intervals used for median nerve (MN) conditioning for SAI and SAF are indicated. For SICI, the inter-stimulus interval is indicated along with the TMS conditioning intensity (rMT: resting motor threshold). Note that all conditioned MEPs were recorded with the neutral gel pack sleeve in place to account for the tactile feedback associated with the finger wrapping. The final step consisted of assessing variations in skin temperature (T°) and MEP modulation in response to cooling

paired-pulse protocols. To this end, blocks of trials were performed sequentially to record conditioned and unconditioned MEPs (15–20 /block) for SAI, SAF and SICI; the order of testing with each block being counterbalanced across participants. As indicated in Fig. 1, all conditioned MEPs were recorded with the neutral gel pack sleeve in place. The final step consisted of assessing MEP modulation in response to cooling. As in our previous reports, the cooling was induced by replacing the neutral gel pack with a pre-cooled one (~ 10 °C). After a 1-min application, skin temperature was recorded, and 20 MEPs were elicited (130% rMT). This final block took 2–4 min to complete, so the cooling stimulation was limited to 5 min max. At the end of the last block, participants were asked to rate the perceived intensity and comfort associated with the cooling stimulation using a 5-point numerical rating scale for intensity/comfort level (Geurts et al. 2005): (1) slightly cool/comfortable, (2) cool/slightly uncomfortable, (3) cold/uncomfortable, (4) very cold/very uncomfortable, (5) extremely cold/extremely uncomfortable.

Conditioned protocols for SAI, SAF and SICI

The protocol to assess afferent-related modulation was similar to that reported in our previous studies (see Young-Bernier et al. 2014). Briefly, for SAI and SAF, afferent nerve conditioning was produced by electrically stimulating the median nerve at the wrist through bipolar electrodes (cathode proximal to the anode, 200 µs pulse) connected to a Digitimer stimulator (DS7A, Digitimer Ltd, Hertfordshire, UK). The conditioning intensity was set at the motor threshold to induce a minimal visible twitch in thenar muscles (Tokimura et al. 2000). For SAI, the conditioning interval between the peripheral and cortical stimulation was set to 20 ms, whereas for SAF, the conditioning interval was set to 50 or 60 ms after initial testing with participants indicating which interval seemed most effective. The latter intervals were selected based on the systematic investigation of Devanne et al. (2009) on the effects of varying inter-stimulus intervals (ISIs) on afferent-induced modulation. For both afferent-conditioning protocols, the TMS test intensity was set to 120% rMT. For SICI, the conditioning protocol consisted of pairing subthreshold TMS pulses with suprathreshold pulses with a fixed ISI of 2 ms. The subthreshold conditioning was produced by delivering pulses equivalent to 70% rMT, as such subthreshold intensity is known to activate cortico-cortical circuits without eliciting descending activity (Lazzaro et al. 1998). For suprathreshold pulses, the test intensity was set at 130% of the rMT in line with recent evidence showing that SICI remains stable over a range of test intensity from 110 to 130% rMT (Miyaguchi et al. 2017). In each protocol, 15–20 conditioned and unconditioned MEPs were recorded.

Data analysis

For skin temperature, readings from the two thermocouple sensors were averaged in each participant to derive individual mean values for the neutral (baseline) and cooled conditions, respectively. For MEPs, mean amplitude values were obtained for each participant by averaging the peak-to-peak amplitude recorded under each block for both conditioned and unconditioned trials. As in our previous reports, variations in corticomotor excitability in response to cooling stimulation were determined by computing percent change relative to baseline $(MEP_{cool} - MEP_{BL}/MEP_{BL}) \times 100$. From these relative percentages, individual responses were classified using the 10% cut-off value (Hinder et al. 2014) as either suppressed (< 10% BL), enhanced (> 10% BL) or not modulated (± 10% BL). For SAI, SAF and SICI, estimated levels of inhibition or facilitation were determined using MEP ratios obtained by expressing conditioned MEPs as percentage of unconditioned MEPs (i.e., MEPs recorded at baseline, neutral temperature). MEP ratios above 100% indicated facilitation, whereas MEP ratios below 100% signalled inhibition.

Statistical analysis

Before analysis, all variables (TMS markers, MEP modulation) were checked for the normality of their distribution with the D'Agostino–Pearson test. All variables were normally distributed ($p > 0.08$). Then, we performed a linear regression analysis with each marker (i.e., SAI, SAF and SICI) to determine their respective ability to predict cooling-induced variations in corticomotor excitability, as reflected in MEP relative change. We also performed a series of correlations with the Pearson's r to examine associations between the different markers of intra-cortical excitability. For each set of correlations, we used Bonferroni corrections to adjust p-values to reduce the risk of type I error (see "Results" section). GraphPad Prism version 8.00 for Windows (GraphPad Software, San Diego, CA, USA, http://www.graphpad.com) was used for the statistical analysis and preparation of figures. All data are reported as mean ± one standard deviation (MEAN ± SD).

Results

Corticomotor excitability, SAI, SAF and SICI at baseline

At baseline, the average rMTs (± SD) in our group of healthy participants were 39.4 ± 10.9% MSO (maximal stimulator output). The average test (unconditioned) MEP amplitude for the SAI/SAF and SICI protocols was,

respectively, 1.11 ± 0.52 mV and 1.18 ± 0.53 mV. For SAI and SAF, the average intensity to condition the median nerve was 15.2 ± 5.6 mV, and the average intensity for TMS test pulses was 47.1 ± 12% MSO. For SICI, the average conditioning intensity was 27.4 ± 7.6% MSO and the test intensity 52.2 ± 14.2%. Figure 2a shows the distribution of individual levels measured, respectively, for SICI, SAI and SAF when dichotomized according to the size of the test MEPs. It can be seen that the latter factor (i.e., test MEP size) had no major influence on observed levels, although SAI levels tended to be more variable in individuals exhibiting larger test MEPs (> 1 mV). We applied independent t-tests for each marker to search for possible differences related to test MEP size, and these comparisons revealed no significant differences between groups ($t_{19} < 1.7$, $p > 0.09$). Inspection of Fig. 2a also shows that participants exhibited greater inter-individual variations in SAI and SAF than in SICI. The SAF protocol was particularly variable with only about half of the participants (9/21) showing the expected facilitation, the other half exhibiting either no clear facilitation or even inhibition. Figure 2b, c, d illustrates the correlation found between the different pairs of markers at the individual level. While a trend was seen for the association between SAI and SAF (Fig. 2b), none of the pairs of correlation reached statistical significance (adjusted p-value (0.05/3) = 0.017).

Variations in corticomotor excitability with cooling

Figure 3a shows individual variations in MEP amplitude measured in response to cooling as a function of the decrease in skin temperature. As expected, individual responses were quite variable with a relatively large subset of participants (11/21) exhibiting depressed MEPs, while another subset (7/21) exhibited the opposite pattern (i.e., enhanced MEPs). Another small subset (3/21) showed no clear modulation. Further inspection of Fig. 3a shows that individual reductions in skin temperature at the cooling site had no significant ($p = 0.55$) impact on cooling-induced MEP modulation. As shown in Fig. 3b, the local cooling stimulation and the accompanying reduction in skin temperature were perceived as just "cold" by most participants and elicited only mild discomfort.

SAI, SAF and SICI as predictors of cooling-induced variations in corticomotor excitability

Figure 4 illustrates the results of the regression analysis to examine the respective role of SAI, SAF and SICI as predictors of individual responses to cooling in terms of MEP modulation. As shown in Fig. 4, both SAI and SAF levels were significant predictors (adjusted p-value (0.05/4) = 0.0125) of cooling-induced MEP modulation. For SAI, individual variations predicted > 30% of the variance ($p = 0.007$) so that individuals with high SAI (i.e.,

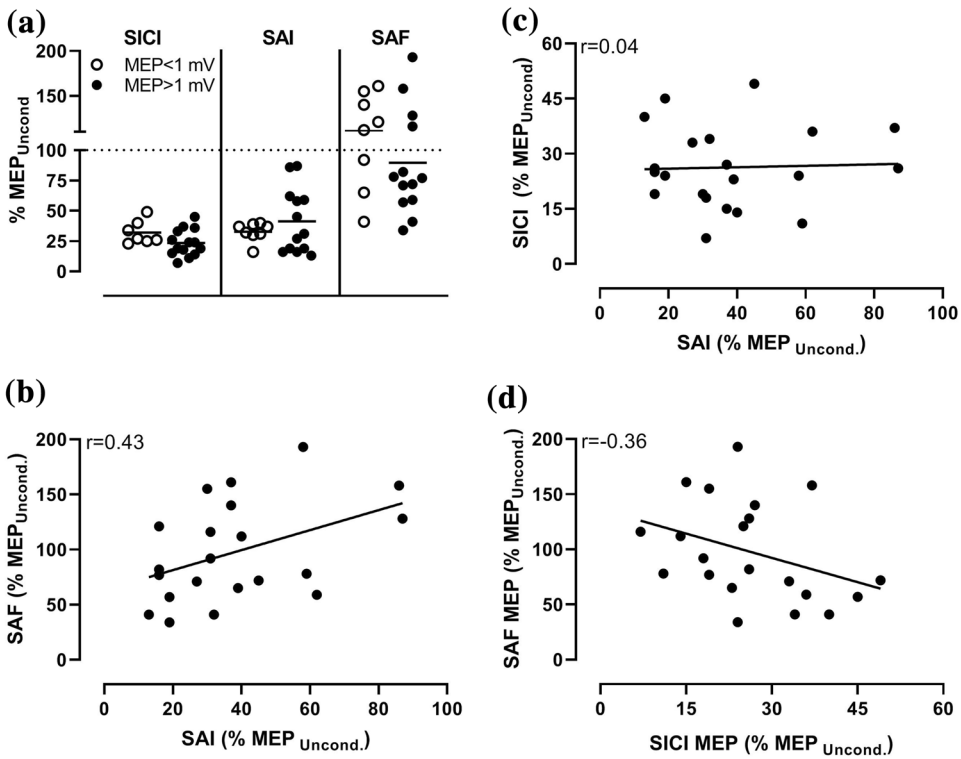

Fig. 2 **a** Distribution of individual levels of SICI, SAI and SAF measured in all participants when dichotomized according to the size of the test (unconditioned) MEP (i.e., larger or smaller than 1 mV). **b–d** Results of the correlative analysis between the different markers (i.e., SAI, SAF and SICI) at baseline with corresponding Pearson's r values

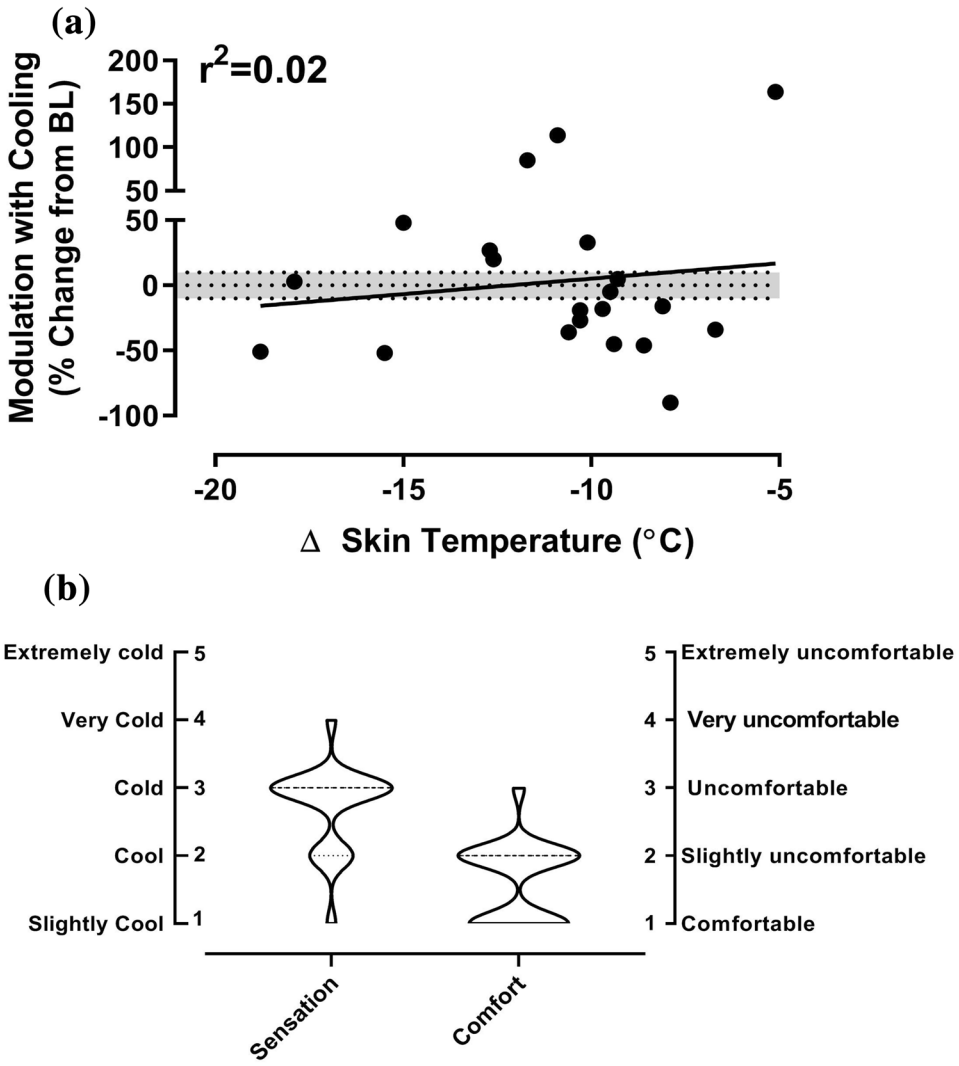

Fig. 3 **a** Relationship between relative changes in MEP amplitude (% from baseline) in response to cooling and corresponding changes in skin temperature. Note that changes in temperature were not predictive of MEP modulation, as reflected in the very low coefficient of determination (r^2). **b** A violin plot showing the distribution frequency of subjective ratings for the perceive intensity and comfort associated with the cooling stimulation

strong inhibition) were also those that showed depressed MEPs in response to cooling, and correspondingly, those with low SAI (i.e., low inhibition) tended to show MEP facilitation. Similarly, SAF ($p = 0.011$) explained 30% of the variance ($p = 0.011$), individuals showing large SAF being those that exhibited the largest enhancement in response to cooling, whereas low or lack of SAF was associated with depression. In contrast, variations in SICI level poorly predicted cooling-induced modulation ($p = 0.25$). The role of SAI and SAF, as predictors of cooling-induced modulation, can be further appreciated in Fig. 5, where individual examples of MEP modulation in the form of either cooling-induced inhibition (Fig. 5a) or facilitation (Fig. 5b) are shown with corresponding levels of SAI and SAF measured in response to afferent conditioning.

Discussion

In the present study, we sought to determine whether individual differences in TMS markers of intra-cortical excitability could explain some of the variability observed in response to distal focal thermal stimulation. In accord with our predictions, variations in SAI and SAF levels proved to be good predictors of cooling-induced modulation, whereas variations in SICI were not. In the discussion, we will address the significance these findings for research examining the impact of sensory stimulation protocols on corticomotor excitability.

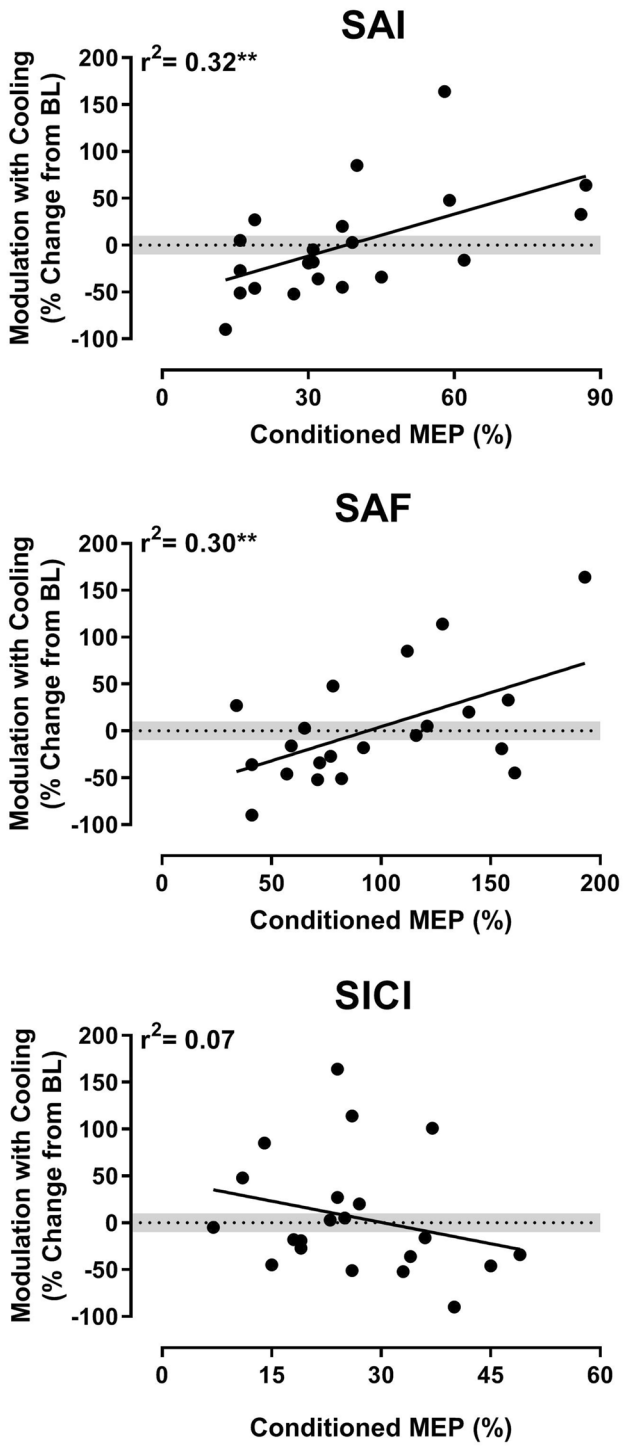

Fig. 4 Results of the regression analysis showing the relationship between cooling-induced changes in MEP amplitude and individual variations in the different TMS markers at baseline. Note that variations in SAI and SAF levels, as reflected in r^2 values, were good predictors of corresponding cooling-induced variations in MEP amplitude, whereas variations in SICI were not. Asterisks denote significance with adjusted p-value at $p = 0.0125$

Variations in SAI, SAF and SICI at baseline and intercorrelation between markers

Consistent with previous reports, levels of SAI, SAF and SICI varied considerably between individuals. In the case of SAI, the relatively large inter-individual variability exhibited by our participants (range 13–87%) was comparable to that seen in our earlier reports (Young-Bernier et al. 2012) with young adults of the same age (range 3–67% MEP inhibition) using the same conditioning protocol. In their report examining the impact of age on SAI, Yarnall et al. (2016) also observed a wide variability of SAI levels in young adults (< 40 years, see their Fig. 1), some subjects even showing facilitation. For variations in SAF levels, the variability between participants was large with only about half of the participants showing the expected facilitation, an observation consistent with our previous reports in young adults (Young-Bernier et al. 2012; Davidson and Tremblay 2013). Such variability contrasts with the consistent effects reported by Devanne's group (Devanne et al. 2009; Degardin et al. 2011) with > 75% of their participants showing SAF in the FDI. The reason for the discrepancy between their observations and ours is not clear but may reflect differences between protocols. One source of variability may be at the peripheral level since SAF is thought to result from the recruitment of muscle afferents not only in response to direct nerve stimulation but also from the induced muscle twitch (Devanne et al. 2009). The latter source of afferents may be particularly susceptible to variations from trials to trials and between individuals (e.g., slight differences in the intensity of the twitch), thus accounting for some of the variability observed at the cortical level.

With regard to variations in SICI, both early (Boroojerdi et al. 2000) and more recent reports (e.g., Samusyte et al. 2018) have insisted on the high inter-individual variability. Although SICI appeared to be less variable than either SAI or SAF in our group of participants, the between-subject variability (Coefficient of variation SICI, 43%) was in the range reported in previous studies. As stressed by Wassermann et al. (2001), variations in SICI levels have been shown to correlate strongly with certain personality traits, such as those associated with anxiety disorders; pointing to the importance of individual factors in influencing TMS markers of intra-cortical excitability.

Another potential source for the variability observed in SICI, SAI and SAF is related to size of the test MEP for unconditioned trials. Indeed, previous reports (Garry and Thomson 2009; Udupa et al. 2009) have shown that TMS markers of intra-cortical motor inhibition (e.g., SAI, SICI) tended to decrease with higher test MEP amplitude (and higher intensity). In this study, we used a test intensity for each of our protocol (i.e., 120% rMT for SAI/SAF and 130% rMT for SICI) that was previously reported optimal for

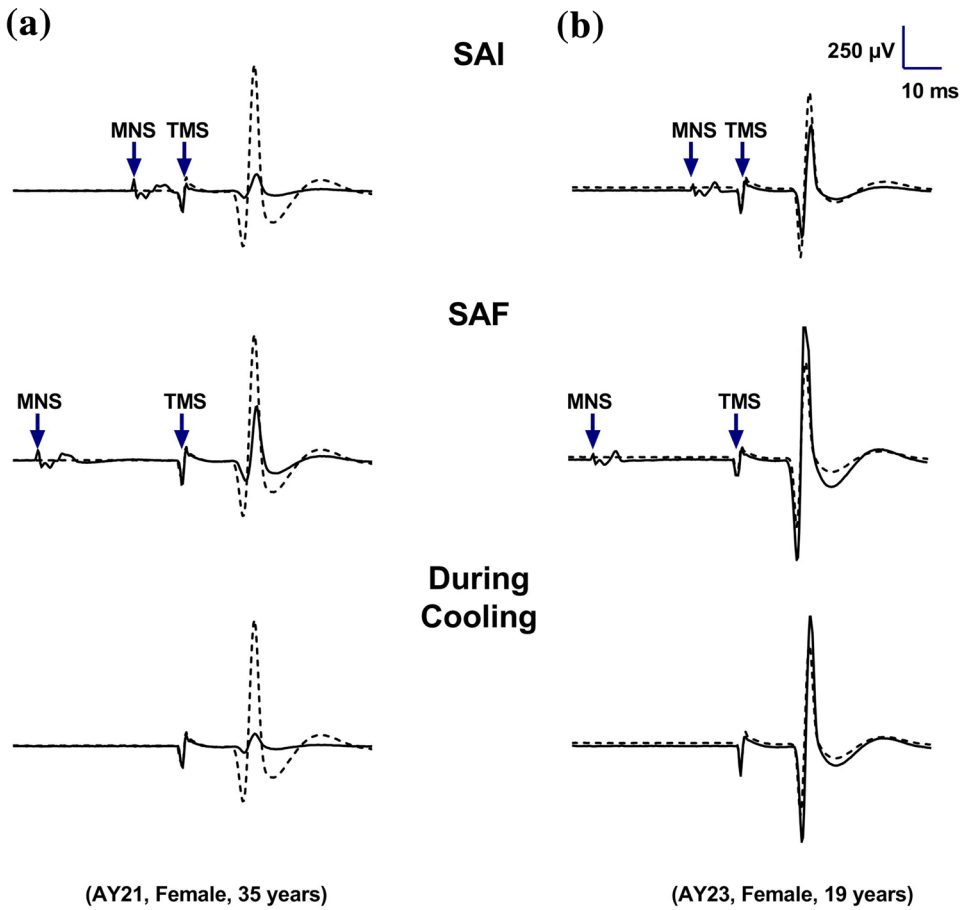

Fig. 5 Individual examples showing the association between markers of sensorimotor integration and cooling-induced MEP Modulation. **a** This participant exhibited high SAI (strong inhibition) but no SAF (weak inhibition instead) and this was associated with marked MEP inhibition during cooling. **b** This participant exhibited low SAI (weak inhibition) but clear SAF and correspondingly exhibited facilitation in response to cooling. In each trace, the dotted lines represent the baseline (pre-cooling) or unconditioned (SAI, SAF) MEP amplitude. All traces represent an average of 15–20 responses

probing changes in intra-cortical motor excitability (e.g., see Garry and Thomson 2009; Miyaguchi et al. 2017). Although our participants exhibited variations in test MEP size, this variability had no systematic influence on levels of SICI, SAI and SAF measured (see Fig. 2a). From these considerations, we conclude that the size of the test MEP amplitude was not a major factor in influencing variations observed in SAI, SAI and SAF levels in our group of participants.

When examining the association between the different markers, our analysis revealed no significant association between SICI and either SAI or SAF. The lack of association between SICI and SAI is consistent with pharmacological evidence showing that the two markers reflect different forms of GABAergic inhibition mediated by different circuits within the M1 (Ziemann et al. 2015). The same logic can be invoked to explain the absence of relationship between SICI and SAF, although the pharmacological basis of afferent-mediated facilitation remains largely unknown at the moment. Finally, the lack of a clear association between SAI and SAF suggests that the two markers, although they may share common properties, likely reflect activation of different circuits within the M1. As discussed above, one major difference between the two lies at the sensory level since SAI can be evoked with purely cutaneous stimulation (Bailey et al. 2016), whereas SAF requires mixed nerve stimulation pointing to a proprioceptive modulation in origin (Devanne et al. 2009). In this respect, the lack of strong association between the two suggests that afferent inhibition may vary independently of afferent facilitation in a given individual, much like measures of intra-cortical inhibition and intra-cortical facilitation, as reported by Wassermann (2002).

Variations in MEP modulation in response to distal cooling

Consistent with our previous investigations (Ansari et al. 2018a, b), MEP modulation in response to distal cooling was characterized by a mixed pattern of response with participants showing either enhanced or suppressed MEPs. Also consistent with our earlier observations (Ansari et al. 2018b), variations in MEP amplitude were largely independent of individual changes in skin temperature, confirming that the degree of skin cooling is not a critical factor in determining the sign of modulation. The addition of subjective ratings in the present report provided an opportunity to assess how participants perceived the focal cooling stimulation. As reported earlier, the fact that sensation elicited no

major discomfort and was perceived as "cold" by the majority of participants confirms that the cooling was effective in stimulating low-threshold cold receptors, while avoiding the noxious range. In sum, these observations provide further evidence demonstrating that individual responses to innocuous cold stimulation are inherently variable, likely reflecting individual differences in the way thermal afferent information is processed centrally.

SAI, SAF and SICI as predictors of MEP modulation in response to cooling

A major finding of the present study is that variations in SAI and SAF levels proved to be good predictors of MEP modulation elicited in response to cooling, whereas variations in SICI level were not. For the two markers of sensorimotor integration, the relationship was such that those showing a combination of high SAI and low (or lack of) SAF tended to show depressed MEPs in response to cooling, whereas those with low SAI and high SAF tended to show facilitation. In this regard, our results converge with those of Mang et al. (2012) who observed a parallel modulation in SAI and SAF levels (i.e., down- and upregulation, respectively) after inducing an increase in corticomotor excitability with prolonged nerve stimulation. While these authors did not directly test the predictive value of SAI and SAF at onset, their results still converge with ours in showing a correspondence between circuits mediating SAI/SAF and those mediating changes in corticomotor excitability in response to afferent stimulation. Such a link may seem evident when considering changes in corticomotor excitability induced by electrical nerve stimulation, but it seems less evident when considering changes induced by thermal stimulation, as reported here. While it may seem odd at first to consider a link between SAI and SAF, which reflects the activation of large afferent fibres, and, cooling-induced effects, which reflect activation of small afferent fibres, it appears less odd when considering the polymodal nature of thermal afferents. For instance, recent investigations in rodents (Wang et al. 2018) have shown that > 50% of cooling-sensitive neurones in the dorsal root ganglia also respond to mechanical stimuli, indicating that cold afferent fibres can convey not only thermal but also mechanical information, allowing a certain degree of sensory convergence between tactile and thermal modalities at higher levels of the somatosensory system.

The present observations that individuals with high SAI and low SAF tended to show MEP inhibition in response to cooling suggest that in those cases the predominant mode of modulation in response to afferent stimulation is inhibition. Since the level of SAI has been shown to depend on the volume of sensory afferent (Bailey et al. 2016), we can assume that in these individuals, the peripheral nerve stimulation was particularly effective in eliciting somatosensory excitation, leading to a strong inhibition at the cortical level at both the SAI and SAF conditioning intervals. High SAI also suggests highly efficient cholinergic activity within the M1 (Di Lazzaro et al. 2002), which likely contributes to enhance afferent-mediated inhibition at the intra-cortical level. Thus, for individuals exhibiting high SAI, the depressed modulation with cold stimulation may reflect a general predisposition to express inhibition in response to afferent stimulation, either tactile or thermal in origin. Conversely, for individuals in whom facilitation was detected both in response to afferent nerve conditioning and in response to cooling stimulation, the association with lower levels of SAI suggests an increased motor excitability at baseline. For reasons discussed earlier, it is also possible that in these individuals the nerve stimulation was particularly effective in recruiting proprioceptive afferents and inducing a muscle twitch, thus explaining the facilitation detected. However, this explanation could hardly account for the facilitation observed with cooling in the same individuals. As suggested, the co-occurrence of lower levels of SAI in these individuals rather points to an increase in cortical excitability, possibly linked with reduced cholinergic-dependent inhibition. Such an increase in excitability is by no way indicative of abnormality, especially given that rMTs in this subgroup were typical of young adults; it just seems to predispose these individuals to express facilitation (or to show less inhibition) in response to afferent stimulation, including thermal stimulation. Here again, our observations align with those of Mang et al. (2012). In their report, MEPs elicited at the afferent facilitation interval were comparable in amplitude to test MEPs, i.e., individuals did not exhibit clear facilitation. Only after motor cortical excitability was increased after 40 min of neuromuscular stimulation, did afferent facilitation was detected with a corresponding decrease in SAI (Mang et al. 2012). In our subset of participants, lower SAI and higher SAF at baseline provided a condition at the cortical level to allow facilitation to be expressed in response to cooling stimulation.

In the case of SICI, the lack of a clear association with cooling-induced modulation was somewhat expected given that this marker reflects interactions within the M1 between cortical interneurons rather that afferent-mediated modulation. While studies have shown that circuits mediating SAI interact with those mediating SICI and that both modulate late indirect waves generated by TMS (Turco et al. 2018), there is evidence that SICI is a poor predictor of afferent-mediated changes in corticomotor excitability (López-Alonso et al. 2014).

Study limitations

The present study has certain limitations. For instance, our sample size, while typical of investigations in human

physiology, could have been larger to include a larger spectrum of participants notably middle-aged adults and seniors since ageing can affect TMS markers of sensorimotor integration (Young-Bernier et al. 2012). In terms of outcomes, we limited our investigation on three specific markers derived from TMS, but we could have extended the list to include long-latency afferent inhibition, long-interval intracortical inhibition and intra-cortical facilitation (ICF). However, these measurements are time-consuming and imply more TMS pulse deliveries, which is not always possible or suitable when planning a testing session with human participants. Also, some markers, such as ICF, have very poor reliability on repeated sessions (Dyke et al. 2018), which complicates the interpretation of variations. Another possible limitation is the lack of strict control over the conditioning stimulation when assessing SAI and SAF. As we explained earlier, some of the variability in SAF and SAI could have reflected variations in the afferent volley generated by the mixed nerve stimulation. Greater control, for instance using the "*M*" wave, could have provided more consistent stimulation and reduced variability, especially when assessing SAF. However, such considerations, while important for methodological studies, were not critical for this study since the goal was not to assess the source of SAI/SAF variability. Along the same line, one may ask why we did not investigate the impact of cooling stimulation on SAI, SAF and SICI? As stated, our goal in this study was to investigate potential factors contributing to the variability of responses to thermal stimulation at the individual level and not to determine how cooling could affect SAI, SAF or SICI. A problem that arises when examining the effect of an intervention aiming at modulating corticomotor excitability is how to account for changes in excitability post-stimulation. This requires manipulations and time to adjust the TMS test intensity to account for increase or decrease in excitability. However, when examining the effect of a thermal intervention like cooling, time is critical as tissue temperatures change rapidly with time, thus limiting the ability to perform protocol adjustments and manipulations. The adoption of a threshold tracking approach to measure SICI (Samusyte et al. 2018) would be a suitable strategy to address thermal effects in the future.

Conclusion

The present study provides novel evidence linking variations in SAI and SAF at baseline with those in corticospinal excitability elicited by focal thermal stimulation. In this regard, our results raised the possibility of using SAI and SAF, as markers of sensorimotor integration, to predict how individuals will respond to sensory afferent stimulation protocols aiming at inducing lasting changes in corticomotor excitability. In particular, our results point to high SAI as a strong predictor of individuals who will express inhibition in response to repeated afferent stimulation, whereas high SAF seems to predict those who will exhibit facilitation. Such observations have potential implications for the application of sensory stimulation protocols in neurorehabilitation.

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