Short latency afferent inhibition: comparison between threshold-tracking and conventional amplitude recording methods.

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Abstract

Introduction: Short-latency afferent inhibition (SAI), which is conventionally measured as a reduction in motor evoked potential amplitude (A-SAI), is of clinical interest as a potential biomarker for cognitive impairment. Since threshold-tracking has some advantages for clinical studies of short-interval cortical inhibition, we have compared A-SAI with a threshold-tracking alternative method (T-SAI).

Methods: In the T-SAI method, inhibition was calculated by tracking the required TMS intensity for the targeted MEP amplitude (200 uV) both for the test (TMS only) and paired (TMS and peripheral stimulation) stimuli. A-SAI and T-SAI were recorded from 31 healthy subjects using ten stimuli at each of 12 inter-stimulus intervals, once in the morning and again in the afternoon.

Results: There were no differences between morning and afternoon recordings. When A-SAI was normalized by log conversion it was closely related to T-SAI. Between subject variability was similar for the two techniques, but within subject variability was significantly smaller for normalized A-SAI.

Conclusions: Conventional amplitude measurements appear more sensitive for detecting changes within subjects, such as in interventional studies, but threshold-tracking may be as sensitive at detecting abnormal SAI in a patient.

Keywords: short latency afferent inhibition; amplitude measurement; threshold-tracking; variability

Introduction

Transcranial magnetic stimulation (TMS) provides information about the excitability properties of particular cortical regions, such as the motor cortex, occipital cortex, and the connections between cortical areas. For instance, the interaction between the sensory and motor cortices can be studied with the short-latency afferent inhibition (SAI) paradigm. The amplitude of TMS-induced motor evoked potentials (MEP) reduces if the TMS is given at certain interstimulus intervals (ISIs) after peripheral nerve stimulation. At ISIs of ~20–25 ms, the nerve stimulation induces SAI(Chen et al. 1999; Tokimura et al. 2000). SAI has been used in both patient and healthy populations as a tool for investigating sensorimotor integration. Since SAI is measured by the change in MEP amplitude, variability in MEP amplitude also affects the reproducibility/reliability of SAI. In the threshold-tracking method, cortical inhibition is not measured by the reduction in MEP amplitude but by the increase in TMS intensity required to achieve the target MEP amplitude. Recently, a comparison between threshold-tracking and conventional amplitude measures of short-interval intracortical inhibition (T-SICI and A-SICI) found that T-SICI was more sensitive than A-SICI in detecting loss of intracortical inhibition in patients with motor neurone disease but few upper motor neurone signs (Tankisi et al., 2021b). This has raised the possibility that threshold-tracking SAI (T-SAI) might similarly have some advantage over conventional amplitude measurements (A-SAI) in clinical applications of SAI such as in dementia. It has also been suggested that threshold-tracking has an advantage in overcoming the high variability of conventional amplitude measurements (Vucic et al., 2018; Samusyte et al., 2018), although this has not been supported by recent A-SICI versus T-SICI comparisons (Tankisi et al 2021a,b). Since SAI variability (Brown et al., 2017; Turco et al., 2019) is a crucial limiting factor in assessing its modulation by disease and non-invasive methods such as repetitive TMS (rTMS) (Bäumer et al. 2007; Young-Bernier et al. 2014) and transcranial direct current stimulation (tDCS) (Scelzo et al. 2011; Kojima et al. 2015), we considered it important to establish whether T-SAI is any more repeatable and reliable than A-SAI. To this

end, T-SAI and A-SAI were obtained from healthy individuals in the morning and afternoon of the same day.

Methods

Subjects

Thirty-one healthy volunteers (13 females, 18 males) aged 25-54 years (mean 35.1, SD 8.5 years) without history of systemic or neurologic disease were included. None had any contraindications for TMS, and none were on any regular medication. Participants were asked to abstain from coffee (12 h) and alcohol (24 h) before the examinations. The study was performed in accordance with the Helsinki Declaration. All participants provided written informed consent, and the study was approved by The Central Denmark Region Committees on Health Research Ethics and the Gazi University Ethics Committee in Ankara. Examinations were performed by four operators (BC, HCA, HEB, HT).

Transcranial Magnetic Stimulation

The left motor cortex (M1) was stimulated with a Magstim® D70 figure-of-8 coil connected to two Magstim® 200 stimulators in BiStim configuration (Ørskov et al. 2021). The coil was held tangentially on the scalp and oriented 45° to the midline to induce a posteroanterior electromagnetic field in M1. The optimal position of the coil, to obtain a MEP from Abductor Pollicis Brevis (APB) muscle, was marked on a cap on the participant's head. Stimulus delivery and data acquisition were controlled by QTRACW software (©UCL, London, UK, distributed by Digitimer Ltd. at www.digitimer.com) using QTMSG-13 recording protocol.

Peripheral Electrical Stimulus

The median nerve was stimulated at the wrist using surface electrodes. Surface electromyographic recordings were made from the right APB muscle with Ag-AgCl electrodes. The peripheral electrical stimulus was adjusted to evoke a 1 mV compound muscle action potential (CMAP). EMG signals were filtered (3 Hz to 10 kHz) and sampled at 10 kHz.

Resting motor threshold

Resting motor threshold (RMT) for a 200 μV peak-to-peak response (RMT200) and 1 mV response (TS1mV) were measured by '4→2→1' tracking and logarithmic regression, described previously (Tankisi et al. 2021a). According to this, tracking first started at the stimulus intensity at which the hotspot was determined, with a step size of 4% maximum stimulator output (MSO), but this step size was reduced to 2% and then 1% when changes of step direction were required, or when the response was within the target error limits (20% on a logarithmic scale, i.e. from target-20% to target +25%). Tracking then continued with steps of 1% (or 0% if within target zone) until steps were zero, or had reversed direction, six times.

Short Latency Afferent Inhibition

A-SAI: after setting the peripheral electrical stimulus and estimating TS1mV, paired peripheral electrical and TMS stimuli were given at ISIs of 16,17,18,19,20,21,22,23,24,26,28 and 30 ms, with a pseudo-random (shuffled) order. Test-alone TMS was given after each four paired stimuli. Each paired stimulus was delivered 10 times, making a total of 150 stimuli. A-SAI data was generated from all 10 conditioned and all 30 unconditioned MEPs. Because the responses tend to be normally distributed on a logarithmic scale, they were averaged as geometric means. For each ISI, A-SAI was calculated as the percentage of control MEP amplitude, i.e.:

$$\text{A-SAI} = \frac{\text{Geometric mean [10 } \textit{Paired(peripheral+TMS) MEP amplitudes}\text{]}}{\text{Geometric mean [30 } \textit{Test-alone MEP amplitudes}\text{]}} \times 100 \qquad [1]$$

T-SAI: RMT200 was tracked continuously. The parallel threshold tracking method was as previously used for SICI (Tankisi et al. 2021a). Accordingly, inhibition was measured by threshold-tracking on separate channels for each ISI. The paired stimuli were delivered 10 times for each ISI, which with the test-alone stimuli made a total of 150 stimuli, the same as for the A-SAI protocol. For each ISI, T-SAI was estimated by log regression as the paired stimulus required to elicit the 200μV target response as a percentage of the test-alone stimulus required to elicit the same response. The regression was weighted, with weights reducing from 1 for responses at the level of the target, to 0 at 1/10th and 10×

target, so that any of the 10 paired or 30 test-alone points outside this 100-fold range were ignored. Then:

$$\text{T-SAI} = \frac{\text{Threshold [}\textit{Paired(peripheral+TMS) stimulus}\text{]}}{\text{Threshold [}\textit{Test-alone MEP stimulus}\text{]}} \times 100 \qquad [2]$$

Gating

To exclude responses obtained from contracted muscle, online gating of prestimulus activation was used for both paired and test-alone sweeps in both protocols. Sweeps in which 5 or more negative EMG peaks exceeded 20 μV during the 270 ms before the magnetic stimuli were automatically discarded from the analysis.

Data Analysis

To explore within individual variability, we used the standard error of measurement (SEMeas), defined as the within-subject SD, which is simply related to the Minimal Detectable Change for an individual (MDC) and the Minimal Detectable Change for a group of size n (MDC_n) (Matamala et al. 2018):

$$\text{MDC} = \text{SEMeas} \times \sqrt{2} \times 1.96 \quad \text{and} \quad MDC_n = \frac{\text{MDC}}{\sqrt{n}} \qquad [3]$$

These quantities, which are also referred to as Smallest Detectable Changes SDC_{indiv} and SDC_{group}, (Schambra et al. 2015), are the minimal changes that can be detected with 95% probability and that are not due to measurement error. The morning and afternoon recordings on the same subjects were used (a) to separate the within-subject and between-subject sources of variance for amplitude and threshold-tracking SAI at each ISI, and (b) to estimate intraclass correlation coefficients (ICC) for the mean SAIs from 18-22ms, as recommended measures of reliability (Schambra et al., 2015):

$$ICC_{2,k} = ICC_{agreement} = \frac{\sigma^2_{subjects}}{\sigma^2_{subjects} + \sigma^2_{am/pm} + \sigma^2_{residual}} \qquad [4]$$

A two-way repeated-measures analysis of variance (rmANOVA) was also performed for the 18-22 ms data using the factor TIME (am x pm) and PROTOCOL (A-SAI x T-SAI). Pearson correlation analysis was used to analyse the relationship between variables. The Lilliefors test was used to check whether variables were normally distributed. For statistical tests, $P<0.05$ was considered significant. .

Results

Figure 1A shows geometric means and geometric means ×/÷ geometric SD for all 31 A-SAI recordings obtained from two separate (morning x afternoon) recording sessions. Figure 1B shows the corresponding T-SAI recordings but with arithmetic means ± SD. It is clear from this figure that there is no appreciable difference between morning and afternoon recordings, and the two sets of recordings were therefore simply used to provide an indication of within-subject variability.

Relationship between A-SAI and T-SAI

In Figure 1 there is a near mirror-image relationship between the A-SAI and T-SAI recordings, and this relationship is explored further in Figure 2A, in which for each ISI, the 62 A-SAI and T-SAI values have been condensed into an ellipse, one standard error from the mean. The relationship is clearly non-linear, and in Figure 2B the data is replotted with A-SAI values on a logarithmic axis, when the relationship becomes much more linear. The straight line, which is the best straight line through the zero-inhibition origin and the 310 values for the ISI range 18-22ms with the strongest inhibition, is given by: $T\text{-}SAI = 100 - 17.35 \times \text{Log}_{10}(A\text{-}SAI/100)$. This is very similar to the relationship previously reported for the relationship between T-SICIp and A-SICI, namely: $T\text{-}SICIp = 100 - 17.85 \times \text{Log}_{10}(A\text{-}SICI/100)$, where T-SICIp was SICI estimated, like T-SAI, by parallel threshold-tracking (Tankisi et al., 2021a).

Transformation of A-SAI to resemble T-SAI

One aim of this study was to compare the repeatability of A-SAI and T-SAI estimates of SAI. This is difficult to do directly, since amplitudes are often not normally distributed, showing a 'floor' effect as

inhibition cannot exceed 100% (e.g. Figure 3A). For all ISIs, however, A-SAI values were well described by a log-normal distribution (e.g. Figure 3B). To compare variabilities of amplitude and threshold-tracking measures, we therefore followed the procedure used previously with SICI measures (Tankisi et al., 2021a), and transformed the A-SAI values to A-SAI-T ones, using the straight line relationship in Fig. 2B, i.e.

$$\text{A-SAI-T} = 100 - 17.35 \times \text{Log}_{10}(\text{A-SAI}/100). \quad [5]$$

These A-SAI-T values were directly comparable with the T-SAI ones (e.g. Figure 3C), and Figure 4A shows a near perfect overlap between the means of all A-SAI-T and T-SAI values at each ISI.

Variability of A-SAI-T and T-SAI

In Figure 4A it is clear that although the SDs of the threshold estimates are similar near the peak inhibition at 20ms, the T-SAI values are more variable at longer ISIs. The variabilities are compared in more detail in Figure 4B, where within-subject and between-subject variabilities are compared for A-SAI-T and T-SAI. On average, between-subject variability was similar for A-SAI-T and T-SAI, but within-subject variability was greater for T-SAI than A-SAI-T. *F* tests showed a significant difference between within-subject SDs for A-SAI-T and T-SAI at 16, 19, 21, 22, 23, 24, 26, 28 and 30 ms ISIs ($p<0.05$), while a paired *t-test* showed reduced average within-subject SDs for A-SAI-T (2.61%RMT) compared to T-SAI (4.01%RMT) ($p<0.0001$). On the other hand, average between-subject SDs for A-SAI-T (5.42%RMT) were not significantly different from that for T-SAI (6.07% RMT)($p=0.17$).

For ISIs from 18-22ms, MDC values for A-SAI-T and T-SAI were 5.4 and 8.08% RMT respectively, while the mean threshold increase in each case was 5.55%RMT. The number of the subjects required to detect a 20% change in that mean SAI was 24 for A-SAI-T and 53 for T-SAI. A-SAI-T values for 18-22ms were also more reliable at distinguishing subjects, with an ICC of 0.78, as against 0.66 for T-SAI. These values are somewhat higher than the previously recorded values for SAI of 0.67 (Brown et al., 2017) and 0.61 (Turco et al., 2019), but they are not directly comparable, because of the transformation to equivalent thresholds and averaging over 5 ISIs. Repeated measures ANOVA revealed no main effects or interactions of TIME ($F_{1,30} =0.45$, $p= 0.56$) and PROTOCOL ($F_{1,30}$

=0.04, p= 0.84) on SAI ISIs between 18-22 ms, indicating that SAI was not different between sessions regardless of the protocol. For mean values from 18-22ms, there was a higher correlation between A-SAI-T(am) and A-SAI-T(pm) (r=0.81, p<0.0001) than between T-SAI(am) and T-SAI(pm) (r=0.45, p=0.011), or between A-SAI-T(am+pm) and T-SAI(am+pm)(r=0.36, p=0.0036).

Sex differences

The between-subject SDs in Figure 3b show a clear peak at short ISIs (17-20ms) compared with longer ISIs (22-30ms) for A-SAI-T and there is a suggestion of a similar early peak for T-SAI. One likely contribution to this betweeen-subject variability comes from the sex differences illustrated in Figure 5, which show that SAI comes appreciably earlier in women than in men, presumably because of differences in arm length and latencies of the N20 component of the somatosensory evoked potential, which affects the ISI of peak SAI (Tokimura et al., 2000).

Discussion

SAI has been studied in many clinical conditions (for review, see (Turco et al. 2021b)). In particular, it was shown that SAI is reduced in Alzheimer's dementia but normal in frontotemporal dementia (Di Lazzaro et al. 2006) or vascular dementia (Di Lazzaro et al. 2008). These findings suggest that SAI may be a potential biomarker in dementia.

In this study, we investigated SAI for the first time with the automatic threshold-tracking method, and compared the results with conventional amplitude measurement. Our main finding was a very close logarithmic relationship between mean A-SAI and T-SAI values (e.g. Figs. 2B, 4A). Maximum inhibition occurred at 20 ms ISI with both methods, with a similar fall-off at other intervals. In addition, the correlation between A-SAI and T-SAI values and non-significant rmANOVA analysis result indicate that A-SAI and T-SAI reflect a similar inhibitory mechanism for SAI. It is worth noting, however, that this close relationship between A-SAI and T-SAI may well be altered by pathology. The similar close relationship found in healthy subjects between A-SICI and T-SICI (Tankisi et al., 2021a) changes in some patients with motor neurone disease, when a switch from inhibition to facilitation in a subset of neurones affects T-SICI much more than A-SICI (Tankisi et al., 2021b).

Our second main finding was that within-subject variability is higher in T-SAI than in A-SAI-T (Fig. 4B), indicating that it would require more subjects to detect a change in SAI with threshold-tracking than with conventional amplitude measurements. This finding is consistent with the results of our previous study of SICI with these methods, which showed that within-subject variability was greater for T-SICI than A-SICI-T (Tankisi et al. 2021a). Our ICC results also show that A-SAI-T results order the subjects more reliably than the corresponding T-SAI ones.

The sex differences in Fig. 5 may appear to contradict a recent study finding that SAI was not different between males and females (Turco et al., 2021a), but reflect both a strength and limitation of this study. On the one hand, we unusually measured SAI at 12 different ISIs, to provide a clear indication of its time course, but on the other hand we did not measure the N20 latencies, so we could not make allowances for individual differences. Measurements of ISI relative to N20 latency might be expected to reduce the between-subject variability at short ISIs, but would be unlikely to affect within-subject variability.

In conclusion, the smaller within-subject variability of A-SAI-T suggests that the conventional method may be better at detecting changes in longitudinal and interventional studies, whereas comparable between-subject variability of the two SAI methods indicates a similar ability to detect an abnormal SAI in pathological conditions. Because the two methods may be affected differently by disease, however, studies in patient groups will be needed to determine their clinical diagnostic value.

Conflicts of interest

HB and JH receive from UCL shares of the royalties for sales of the Qtrac software used in this study. HB, HT, BC, and MK are shareholders of QTMS Science Ltd., which licences the QTMSG-13 recording protocols used. The remaining authors have no potential conflict of interest to declare, and there has been no significant financial support for this work that could have influenced its outcome.

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Figure Legends

Figure 1. Comparison between **A:** SAI as recorded as an amplitude change, and **B**: SAI measured by threshold-tracking. In both parts, average morning recordings in red, plotted against interval between conditioning electrical stimulus and test magnetic stimulus, are superimposed on afternoon recordings in blue. Dashed lines are means ± SD for the 31 healthy control subjects.

Figure 2. **A**: Relationship between A-SAI amplitudes and T-SAI threshold values for the 12 different ISIs recorded. For each ISI, the 62 data points are represented by an ellipse, one standard error from the mean A-SAI and T-SAI values. B: The same data replotted with a logarithmic *x*-axis. Straight line is best fitting line through the *x*=100, *y*=100 point of zero inhibition to the 310 points for ISIs 18-22 ms when inhibition is most pronounced.

Figure 3. Comparative distributions of 62 A-SAI and T-SAI values for the ISI of 20ms, at which peak inhibition occurred. **A**: A-SAI points plotted on linear amplitude scale, with horizontal lines indicating mean and 95% confidence limits on the assumption of normality, which is contradicted by lower limit at an impossible negative value. **B**: Same data plotted on logarithmic amplitude scale, with horizontal lines indicating geometric mean and geometric 95% confidence limits. **C**: T-SAI and transformed A-SAI-T points plotted on linear threshold scale, with horizontal lines indicating mean and mean ± SD.

Figure 4. Variability of A-SAI-T and T-SAI compared. **A**: Mean ± SD T-SAI values (black) and A-SAI-T values (grey) as a function of ISI. **B:** Between-subject (filled circles) and within-subject (open circles) SDs of A-SAI-T (grey) and T-SAI (black) values as functions of ISI.

Figure 5. Sex differences in A-SAI and T-SAI. **A**: Geometric A-SAI means of 18 male (filled circles) compared with those of 13 female subjects (open circles). **B**: Arithmetic T-SAI means plotted similarly. Asterisks indicate sex differences that are significant by Mann-Whitney U test (* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$).

Figure 1

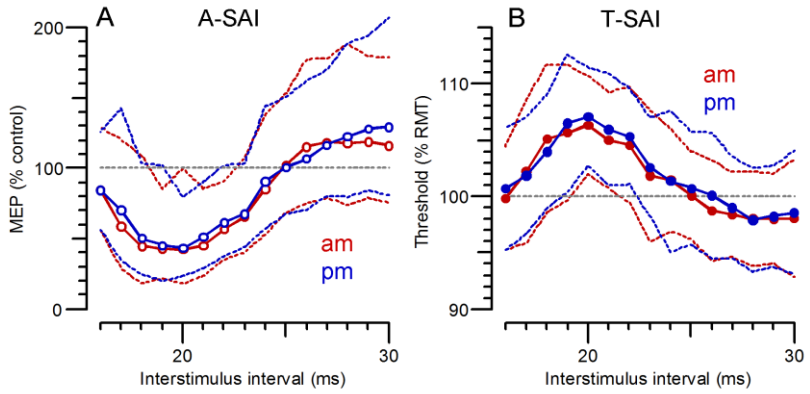
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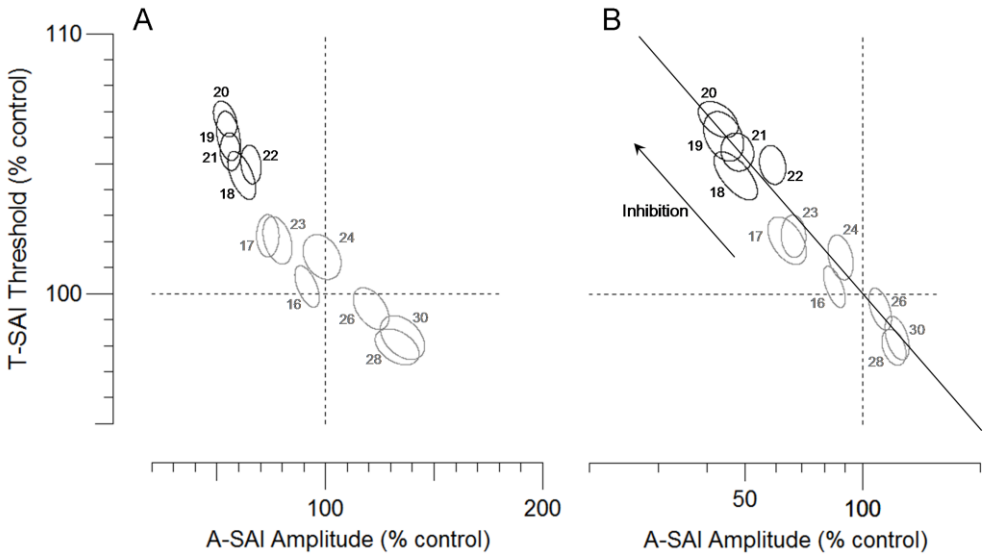
Figure 2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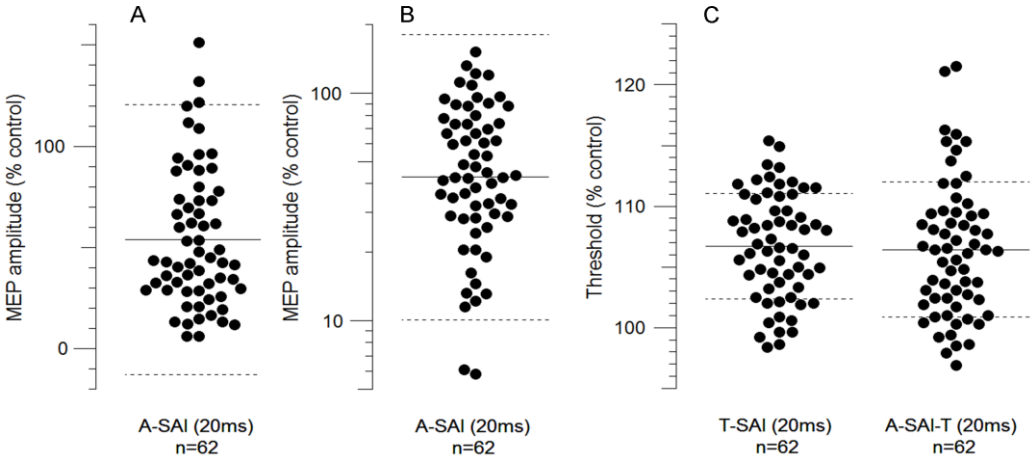
365 Figure 3



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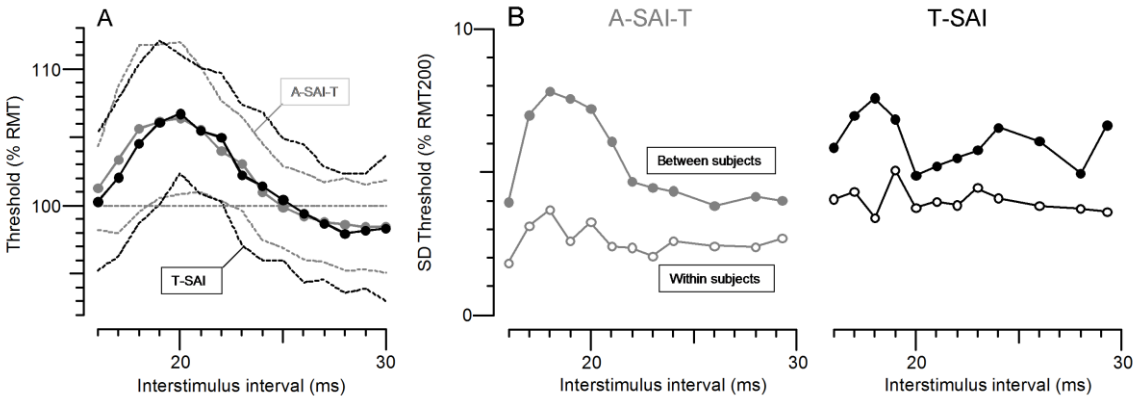

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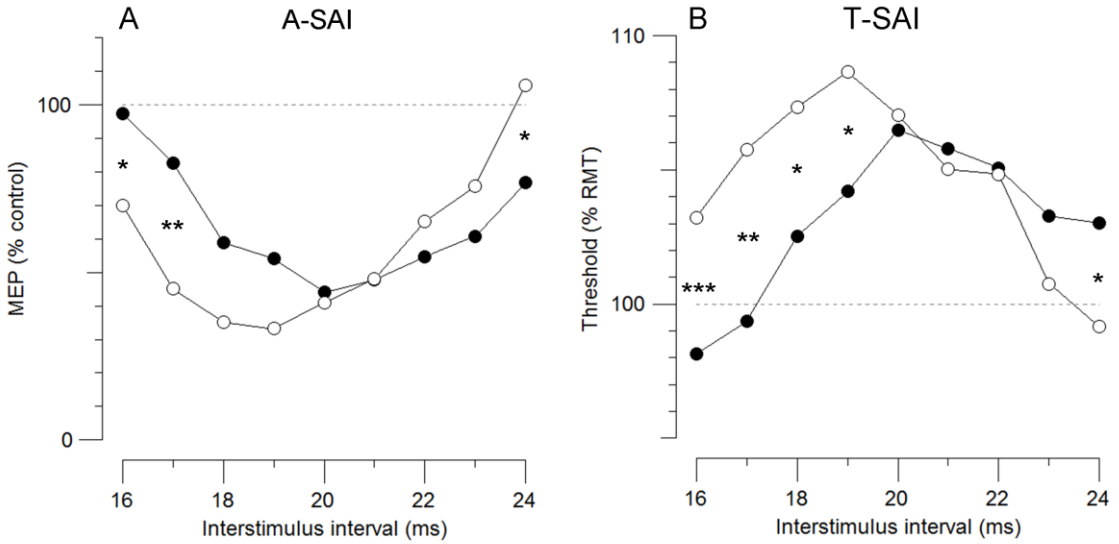

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