Clinical Neurophysiology 165 (2024) 154–165

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Bilateral median nerve stimulation and High-Frequency Oscillations unveil interhemispheric inhibition of primary sensory cortex

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HIGHLIGHTS

- The interhemispheric connection between primary somatosensory areas can be probed by using bilateral median nerve stimulation.
- N20 potentials and the late component of the high-frequency oscillations vary significantly across interstimulus intervals.
- Findings suggest interhemispheric interaction between the primary somatosensory cortices, through corpus callosum.

ARTICLE INFO

Article history:
Accepted 19 June 2024
Available online

Keywords:
Interhemispheric interactions
Somatosensory evoked potentials
High-frequency oscillations
Bilateral median nerve stimulation
Primary somatosensory cortex

ABSTRACT

Objective: This study aimed at investigating the effect of median nerve stimulation on ipsilateral cortical potentials evoked by contralateral median nerve electrical stimulation.
Methods: We recorded somatosensory-evoked potentials (SEPs) from the left parietal cortex in 15 right-handed, healthy subjects. We administered bilateral median nerve stimulation, with the ipsilateral stimulation preceding the stimulation on the contralateral by intervals of 5, 10, 20, or 40 ms. We adjusted these intervals based on each individual's N20 latency. As a measure of S1 excitability, the amplitude of the N20 and the area of the High Frequency Oscillation (HFO) burst were analyzed for each condition.
Results: The results revealed significant inhibition of N20 amplitude by ipsilateral median nerve stimulation at interstimulus intervals (ISIs) between 5 and 40 ms. Late HFO burst was suppressed at short ISIs of 5 and 10 ms, pointing to a transcallosal inhibitory effect on S1 intracortical circuits.
Conclusions: Findings suggest interhemispheric interaction between the primary somatosensory areas, supporting the existence of transcallosal transfer of tactile information.
Significance: This study provides valuable insights into the interhemispheric connections between primary sensory areas and underscore the potential role of interhemispheric interactions in somatosensory processing.

1. Introduction

Interhemispheric inhibitory interactions between homologous motor cortices during bimanual movements occur, at least in part, through connections in the corpus callosum (Carson, 2005; Diedrichsen et al., 2003; Perez et al., 2014; Tazoe et al., 2013). One of the main functions of these interactions is the control of the mirror movements in the contralateral arm during unilateral movements (Beaulé et al., 2012; Mayston et al., 1999). A recent paired-pulse transcranial magnetic stimulation (TMS) study estimated a time course of interhemispheric facilitation between the two M1s at short interstimulus intervals (2–6 ms) and interhemispheric inhibition at longer intervals (8–15 ms) in healthy subjects (Ni et al., 2020). Maladaptive functioning of motor interhemispheric interactions has been described in several neurological diseases (Di Pino et al., 2014; Morone et al., 2022; Pilato et al., 2009).

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https://doi.org/10.1016/j.clinph.2024.06.011
1388-2457/

In comparison to the motor system, the existence of interhemispheric interactions between areas involved in other modalities, particularly the somatosensory system, remains poorly defined. Previous magnetoencephalographic studies have provided some evidence suggesting that the secondary somatosensory cortex (S2), which receives extensive interhemispheric projections from the contralateral body part, plays also a predominant role in the interhemispheric transfer of tactile information (Hoechstetter et al., 2001). Two functional magnetic resonance imaging (fMRI) studies on patients who underwent resection of the posterior half of the corpus callosum showed that the integrity of this structure is required to induce the fMRI ipsilateral activation of S2 and posterior parietal cortex following a unilateral tactile stimulation of the hand (Fabri et al., 2005, 1999). Furthermore, both the size of the intermediate callosal truncus and the residual callosal integrity seem to contribute to the ipsilateral S2 activation (Fabri et al., 2005; Stancak et al., 2002). The transcallosal conduction time between homologous S2 was estimated in previous studies and is supposed to range between 10 and 20 ms (Frot and Mauguière, 1991; Stancak et al., 2002).

Animal studies on macaque monkeys and rodents found neural responses in bilateral fields of the somatosensory area which is considered to be the homolog of the human primary somatosensory cortex (S1, Brodmann area 2). These responses were not found after lesioning the postcentral gyrus in the contralateral hemisphere, suggesting that the neurons in the bilateral receptive fields receive the sensory information from the contralateral brain through interhemispheric transfer (Iwamura et al., 2002, 2001, 1994; Pidoux and Verley, 1979).

In humans, postmortem anatomical analyses and in vivo MRI-diffusion tensor imaging have described connections between the S1 of the two sides through corpus callosum (Aboitiz, 1992; Fling et al., 2013). Furthermore, some fMRI studies revealed that not only the contralateral S1 but also the ipsilateral S1 is activated after the unilateral median nerve stimulation (Hlushchuk and Hari, 2006; Nihashi et al., 2005).

Therefore, an accumulating body of evidence suggests that normal interhemispheric transfer of tactile information might take place not only between the homologous S2s but also at an earlier sensory processing stage such as between S1 of both hemispheres (Clarey et al., 1991; Hlushchuk and Hari, 2006; Klingner et al., 2011; Meehan et al., 2011; Staines et al., 2002; Werhahn et al., 2002). In particular, a single TMS-fMRI study in 2006 showed that 10 Hz trains of TMS over the right parietal cortex increased the left S1 fMRI signal during the right radial nerve stimulation (possibly involving a thalamic circuitry), but decreased it in the absence of somatosensory input (possibly involving a transcallosal network) (Blankenburg et al., 2008). Furthermore, the primary involvement of S1 receives additional support from various studies on sensorimotor integration, including a recent investigation. This study emphasized that afferent inhibition can originate from direct thalamo-motor cortex pathways as well as from indirect pathways involving the mediation of the primary somatosensory area (Motolese et al., 2022).

Only a few neurophysiological studies investigated the interactions between contralateral and ipsilateral cortical activations using a paired median nerve somatosensory evoked potential (pSEP) protocol, in which a peripheral stimulation of the median nerve on one side (conditioning stimulus, CS) preceded the analogous stimulation of the contralateral median nerve (test stimulus, TS) at specific interstimulus intervals (ISIs). The rationale of these studies is that in the presence of a S1-S1 interaction, the SEP evoked by the TS is modified by the influence of the ipsilateral CS (Brodie et al., 2014; Ishii et al., 2021; Ragert et al., 2011).

Previous studies investigating interhemispheric inhibition in the somatosensory system have yielded conflicting findings (summarized in Table 1). While Ragert and colleagues (2011) (Ragert et al., 2011) and Brodie and coworkers (2014) (Brodie et al., 2014) observed significant inhibitory effects within specific time windows (particularly between 15 and 35 ms), Ishii et al. (2021) (Ishii et al., 2021) found no such effect despite examining the same time intervals as those of the aforementioned studies, along with numerous other intervals. The discrepancy in findings highlights the need for further research in this field.

Recently, the application of digital high-pass filtering to low-frequency SEP evoked by median nerve stimulation has enabled the isolation of a burst of low-amplitude, high-frequency (~600 Hz) oscillations (HFOs) that overlay N20 wave (Cruciani et al., 2022; Gobbelé et al., 1998). Furthermore, the HFOs burst is typically divided into an early component that is believed to reflect the action potentials of thalamo-cortical axons and a late component that arises from the activity of intracortical GABAergic interneurons situated within the somatosensory cortex (Ozaki and Hashimoto, 2011). Thus, HFOs have been used as a proxy to study the functionality of thalamo-cortical pathway in several central nervous system diseases (Capone et al., 2019; Insola et al., 2019; Restuccia et al., 2012).

Our investigation aims to evaluate and better characterize the interhemispheric connection between the two primary sensory areas, by studying the responses elicited by bilateral peripheral stimuli delivered locked on the latencies of each subject's N20 potential.

Table 1
Previous studies on pSEP paradigm: designs and findings. Abbreviations: SD, standard deviation; TS, test stimulus; ISI, interstimulus interval; lMNS, left median nerve stimulation; rMNS, right median nerve stimulation; 1w RM-ANOVA, one-way repetitive measure analysis of variance; N.A., not available.

Study	Population, mean age ± SD	TS side, epochs per condition	Conditions	Statistics (factors)	Results
Ragert et al. (2011)	*N* = 12 age 26.8 ± 2.9	Right, 150	lMNS rMNS ISIs (ms): 5, 10, 15, 20, 25, 30	1w RM-ANOVA (ISI) + post-hoc tests	Significant reduction of P14/N20 amplitude (p = 0.031), at 20 ms (p = 0.0038) and 25 ms (p = 0.0013). No significant ISI effect on other SEP components.
Brodie et al. (2014)	*N* = 10 age 28.3 ± 5.4	Left, 200	lMNS ISIs (ms): 0, 15, 20, 25, 30, 35	1w RM-ANOVA (ISI) + post-hoc tests	Significant ISI effect on P14/N20 (p = 0.003), at 25 ms (p = 0.037), 30 ms (p = 0.013) and 35 ms (p = 0.017). Significant ISI effect on N20/P25 (p = 0.004), at 15 ms (p < 0.001), 20 ms (p = 0.001), 25 ms (p = 0.001), 30 ms (p = 0.010) and 35 ms (p = 0.047).
Ishii et al. (2021)	*N* = 14 age 30.6 (N.A.)	Left, 500	lMNS rMNS ISIs (ms): 1, 2, 3, 5, 10, 20, 30, 40, 60, 100	1w RM-ANOVA (ISI)	No ISI significant effects on amplitudes of P14, P14/N20 and N20/P25.

2. Materials and methods

2.1. Ethical approval

The present study was conducted in accordance with the Declaration of Helsinki and the following amendments, and it was approved by the Ethics Committee of Campus Bio-Medico University (Approval ref.: 15/16 PAR ComEt CBM, 29/03/2016). All participants provided written informed consent.

2.2. Participants

Tests were performed on a total of 15 right-handed healthy subjects (mean age 29.8 ± 6.4 years). The handedness of the participants was tested by using the Edinburgh Handedness Inventory (Oldfield, 1971). The experiment was well tolerated, and no dropouts were reported.

2.3. Study design and neurophysiological assessment

SEPs after electrical stimulation of both median nerves were recorded in each subject.

We employed the pSEP setup outlined by Ragert and colleagues (2011). Following their methodology, we applied a conditioning stimulus (CS) targeting the left median nerve, and a test stimulus (TS) to the right median nerve. Conversely, studies by Brodie et al. (2014) and Ishii et al. (2021) employed the reverse configuration.

Standard bar electrodes with the cathode proximal were placed over the two median nerves, aligned with the wrist crease. Electrical pulses were triggered with a high-voltage stimulator (DS7A, Digitimer Ltd, UK).

A total of 1000 monophasic pulses of 200-μs duration were delivered at a frequency of 3.1 Hz for each condition. The electrical stimulus intensity was set at the lowest intensity capable of generating a slight thumb twitch. The cortical evoked responses were recorded through Ag/AgCl surface electrodes placed at CP3 (over the left S1, the active electrode), Fz (first reference electrode) and right ear (second reference electrode), according to the international 10–20 EEG system. We further recorded the right N20 from CP4 (active electrode), Fz (first reference electrode), and left ear (second reference electrode) to study the evoked potential of the opposite hemisphere. The use of non-cephalic ear references has been recognized for its efficacy in better discriminating the N20 from subcortical components. This is particularly important, as subcortical SEP components could potentially conceal the accurate identification of the N20 onset in a CP3/4-Fz derivation but are not shown in the CP3/4-ear montage (Desmedt and Cheron, 1982, 1981; Valeriani et al., 1998). Therefore, in our study, channels with ear references were employed as a visual control for a better identification of CP3/4-Fz potentials, whose parameters were measured. The skin-electrode impedance was kept below 5 k.

We first evaluated the peak latency of the N20 potential evoked on the contralateral hemisphere by single left and right median nerve stimulations (lMNS and rMNS, respectively); then we calculated the interval to apply between left CS and right TS in order to obtain the activation of right and left S1 at intervals of 5, 10, 20, and 40 ms. Therefore, we determined the peripheral ISI by subtracting from the target "cortical" interval the difference between left and right N20 latency. We referred to these peripheral ISIs as

Fig. 1. Determining corrected interstimulus intervals (cISIs) to address asymmetry in N20 latencies between the hemispheres. Three scenarios are presented. Abbreviations: cISI, corrected interstimulus interval; rMNS, right median nerve stimulation; lMNS, left median nerve stimulation; TS, test stimulus; CS, conditioning stimulus; S1, primary somatosensory cortex. **Scenario A.** When N20 latencies are comparable in both hemispheres, simultaneous rMNS and lMNS achieve concurrent activation of both S1 areas (cISI = 0 ms). Different cISIs can be obtained by matching the interval between stimuli to the desired interval between activations of the right and left S1 cortices (e.g., cISI = 5 ms for left S1 activation 5 ms after right S1 activation). **Scenario B.** When left N20 latency precedes the contralateral by *x* milliseconds, for the simultaneous activation of both primary somatosensory cortices (cISI = 0 ms), rMNS (TS) follows lMNS (CS) by *x* ms. For other conditions, x ms is consistently added to the desired delay (e.g., cISI = 5 ms + *x* for left S1 activation 5 ms after right S1 activation). **Scenario C.** When the stimulus arrival to the left S1 is delayed by *y* milliseconds compared to the contralateral side, rMNS (TS) precedes CS by y ms to achieve simultaneous S1 activation (cISI = 0 ms). Additionally, y ms is subtracted from the desired intervals for each block other than 0 ms (e.g., cISI = 5 ms - *y* for left S1 activation 5 ms after right S1 activation).

corrected ISIs (cISIs). For a clearer understanding of how the cISIs were determined, refer to Fig. 1.

In each subject, after the two separate blocks of lMNS and rMNS, we performed 5 additional blocks to test the different experimental conditions. Specifically, we delivered a control block with synchronous stimulation at cISI = 0 ms (i.e., the two median nerves evoking an N20 at exactly the same time), and 4 blocks at cISIs of 5, 10, 20 and 40 ms, respectively. Bilateral lMNS and rMNS at cISI of 0 ms was used as control condition (i.e., baseline) instead of single rMNS following Brodie et al. (Brodie et al., 2014), because it should not been influenced by selective attention (García-Larrea et al., 1991). The order of the 5 blocks (including the control condition, each of 1000 epochs) was randomized in each individual.

Participants were instructed to remain relaxed, close their eyes, and sit comfortably upright a chair with their arms resting in a supinated posture during stimulation.

2.4. Data analysis

For SEP evaluation, the sweeps within each specific condition were averaged, bandpass-filtered (0.5–2,000 Hz), and digitized at a sample rate of 5 kHz using a portable amplifier (BrainVision Recorder v1.10 and BrainAmp MR plus, Brain Products GmBH, Germany).

Furthermore, the peak-to-peak amplitudes of short-latency low-frequency N20 potential (measured as both the ascending P14/N20 and descending N20/P25 complexes, in μV) were recorded over CP3 and extracted manually for each subject and condition.

HFO data were processed offline through an in-house ad hoc MATLAB script (MathWorks, Inc., Massachusetts, USA, version: R2022b) script. In order to extract HFOs, we applied a digital 400–800 Hz bandpass Butterworth filter. Area and duration of the HFO's burst were calculated on the rectified signal from the point at which upward deflection exceeded 150% of the baseline signal to the point where amplitude returned below 150% of the baseline (Capone et al., 2019; Cruciani et al., 2024). For an in-depth elucidation of how the early and late components of HFOs are determined, please refer to Fig. 2. The N20 features and the HFO area and duration were then compared across conditions.

2.5. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR), when appropriate. Normality was assessed through the Shapiro-Wilk test.

SEP amplitudes were measured as the peak-to-peak amplitudes (in μV). Values deviating from the mean signal by >2SD were removed from the analysis (resulting into removal of 3.45% of the overall number of collected data). Following these preliminary analyses, we calculated baseline-corrected amplitudes for each participant by dividing the raw P14/N20 and N20/P25 amplitudes by the averaged amplitudes obtained during the cISI 0 ms block (i.e., the baseline condition).

Baseline-corrected amplitudes of N20 peak-to-peak measurements were entered in one-way repeated-measures analysis of variance (RM-ANOVA), with cISI (0, 10, 20, 40 ms) as within-subject factors. Greenhouse-Geisser sphericity corrections were applied when appropriate. Post-hoc Holm tests were performed to flag significant comparisons.

The same approach was used to analyze HFO areas (measured at CP3), expressed as total area under the curve (AUC, μV/ms) and subdivided into early and late components. We used the JASP software (JASP Team 2022, version 0.16.3) to perform the inferential statistics. A 2-tailed p value of <0.05 was considered significant for all tests.

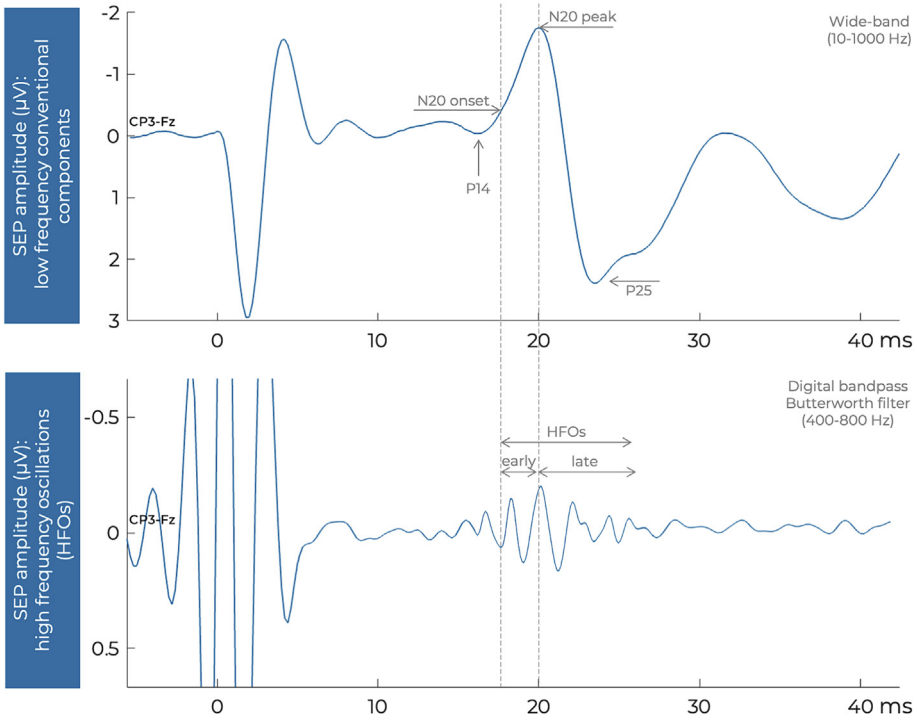


Fig. 2. Identification of high frequency oscillations and differentiation into early and late components. In the conventional visual analysis of somatosensory evoked potentials (SEPs), the initial step involves identifying the first and most consistent negative (upward) peak, typically occurring around 20 ms after the electrical stimulus of the contralateral upper limb (N20), that graphically represents the arrival of the somatosensory impulses at S1 (Nuwer, 1998). Afterwards, a bandpass 400–800 Hz filter is applied to decompose the N20 cortical response into a burst of high-frequency oscillations. Moreover, the N20 potential serves as a reference time-point for distinguish the early and late components of the HFO burst.

3. Results

Table 2 presents the average N20 latencies and raw results (peak-to-peak N20 amplitudes and HFO AUCs) acquired from two blocks of single left and right median nerve stimulation, as well as from the five experimental blocks of paired median nerve SEPs at different corrected interstimulus intervals.

Fig. 3 shows how a typical SEP (green boxes) and the corresponding HFO bursts (orange boxes) recorded from a representative individual change at different cISIs.

Two one-way RM-ANOVA revealed a significant cISI effect for both N20 measurements (P14/N20 $F = 6.306$, $p = 0.004$; N20/P25 $F = 9.735$, $p < 0.001$). Post-hoc Holm tests (Table 3 and Fig. 4) confirmed the significant difference of baseline-corrected P14/N20 amplitudes between cISI 0 ms and 5 ms ($t = 3.839$, $p = 0.003$), 0 ms and 10 ms ($t = 3.864$, $p = 0.003$), 5 ms and 20 ms ($t = -3.098$, $p = 0.023$), and 10 ms and 20 ms ($t = -3.123$, $p = 0.023$). With respect to the second N20 measurement (N20/P25), Holm tests revealed differences between 0 ms and 10–20-40 ms (0–10 ms $t = 5.180$, 0–20 ms $t = 4.852$, 0–40 ms $t = 4.740$, the three p-values < 0.001).

We conducted separate one-way RM-ANOVA for each component of HFO areas, demonstrating a significant effect of cISIs on the total HFO area ($F = 5.725$, $p = 0.003$) and on the area of the late HFO burst ($F = 4.038$, $p = 0.019$), but not on the area of the early HFO burst ($F = 1.760$, $p = 0.161$).

The Holm post-hoc tests for the total HFO area and its components are shown in Table 4 and Fig. 5. The significant differences are between cISI 0 ms and 5–10-20 ms for the total area (0–5 ms $t = 3.557$, $p = 0.018$; 0–10 ms $t = 3.332$, $p = 0.027$; 0–20 ms $t = 4.315$, $p = 0.003$) and between cISI 0 ms and 5–10 ms for the late component (0–5 ms $t = 3.238$, $p = 0.046$; 0–10 ms $t = 3.563$, $p = 0.026$).

4. Discussion

Our findings show that a conditioning stimulus (CS) delivered to the left median nerve preceding the right median nerve stimulation (test stimulus, TS) by 5–10 ms results in a reduction of the amplitudes in the earliest ascending segment of N20 potential recorded from the left somatosensory cortex. For longer interstimulus intervals (10–40 ms), the amplitude reduction affected the later part of N20 wave. Furthermore, we observed a reduction in the area of the late component of HFO bursts when the CS preceded the TS by 5–10 ms.

Ragert and coworkers first described the pSEP paradigm in 2011, showing that the N20 amplitude (measured as peak-to-peak P14/N20 amplitude), recorded over the left S1, decreased when a CS was applied to the left median nerve 20–25 ms before a right median nerve TS (Ragert et al., 2011).

Using a similar protocol, Brodie and colleagues in 2014 found that the N20 peak-to-peak amplitude (measured at P14/N20 and N20/P25) evoked by the TS to the left median nerve decreased when a prior CS to the right median nerve was applied at ISIs of 25, 30 and 35 ms (for the P14/N20 amplitude) and 15, 20, 25, 30 and 35 ms (for the N20/P25 measurement) (Brodie et al., 2014).

The authors of both studies concluded that their findings suggest interhemispheric inhibitory S1-S1 interactions through the corpus callosum within the critical time interval of 20–25 ms or 15–35 ms after median nerve stimulation. Additionally, Brodie

Table 2
Raw values of N20 latencies (in ms), amplitudes (in μV), and areas of HFO-bursts (in μV/ms). The low-frequency conventional N20 potential is measured as P14/N20 and N20/P25 peak-to-peak amplitudes. The HFO areas are measured as area under the curve (AUC). Abbreviations: cISI, corrected interstimulus interval; lMNS, single left median nerve stimulation; rMNS, single right median nerve stimulation; ampl., mean peak-to-peak amplitudes; tot-HFO area, total area of the high-frequency oscillation burst; e-HFO area, area of the early component of the high-frequency oscillations; l-HFO area, area of the late component of the high-frequency oscillations. Data are expressed as mean ± standard deviation or median and interquartile range according to the distribution.

			cISIs				
Condition:	lMNS	rMNS	0 ms	5 ms	10 ms	20 ms	40 ms
N20 latency (ms)	20.00 ± 1.07	20.19 ± 0.98	20.27 ± 0.93	25.23 ± 0.98	30.41 ± 1.12	41.00 ± 0.80	60.33 ± 0.91
P14/N20 ampl. (μV)	1.772 ± 1.042	2.218 ± 0.922	2.315 ± 1.202	1.705 ± 0.828	1.735 ± 0.766	2.430 ± 1.324	2.020 ± 0.952
N20/P25 ampl. (μV)	2.987 ± 1.969	3.370 ± 1.823	4.009 ± 1.981	3.469 ± 1.679	2.948 ± 1.395	2.873 ± 1.584	3.022 ± 0.952
Tot-HFO area (μV/ms)	N.A.	0.208 ± 0.237	0.243 ± 0.160	0.147 ± 0.102	0.159 ± 0.076	0.141 ± 0.110	0.195 ± 0.192
e-HFO area (μV/ms)	N.A.	0.078 ± 0.069	0.081 ± 0.089	0.045 ± 0.047	0.052 ± 0.103	0.030 ± 0.066	0.045 ± 0.075
l-HFO area (μV/ms)	N.A.	0.142 ± 0.098	0.158 ± 0.061	0.103 ± 0.045	0.094 ± 0.029	0.124 ± 0.145	0.143 ± 0.056

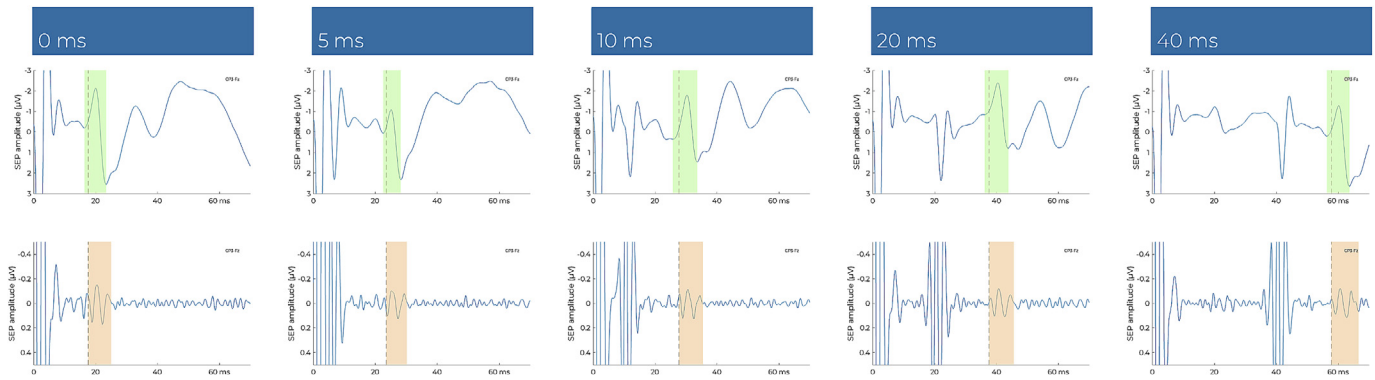


Fig. 3. SEP waveforms recorded at CP3 from a representative subject. The green boxes highlight the conventional N20 potential with its ascending (P14/N20) and discending (N20/P25) complexes, the orange boxes point out the corresponding high frequency oscillation bursts (HFOs), the dotted lines represent the onset latency of N20. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Post-hoc comparisons after one-way Repetitive Measure Analysis of Variance of baseline-corrected amplitudes of the short-latency SEP component at different corrected interstimulus intervals (cISIs). Abbreviations: P14/N20 ampl. baseline-corrected peak-to-peak P14/N20 amplitude; N20/P25 ampl., baseline-corrected peak-to-peak N20/P25 amplitude; SEP, somatosensory evoked potential.

		P14/N20 ampl. (*p*-value)	N20/P25 ampl. (*p*-value)
0 ms	5 ms	0.003**	0.103
0 ms	10 ms	0.003**	<.001**
0 ms	20 ms	0.925	<.001**
0 ms	40 ms	0.066	<.001**
5 ms	10 ms	0.980	0.068
5 ms	20 ms	0.023*	0.110
5 ms	40 ms	0.900	0.115
10 ms	20 ms	0.023*	1.000
10 ms	40 ms	0.900	1.000
20 ms	40 ms	0.318	1.000

* *p* value < 0.05.
** *p* value < 0.01.

and coworkers study revealed that the CS interfered with the N20/P25 complex but not the earlier P14/N20 at short ISIs (15–20 ms) implying the existence of a minimum time window required for the CS to influence distinct components of the SEP generated by the TS in the opposite hemisphere (Brodie et al., 2014).

However, both studies had some limitations, including small sample sizes (*e.g.*, 10 subjects in Brodie et al. study (Brodie et al., 2014)) and a limited number of epochs per condition (150 in Ragert et al. study and 200 in Brodie et al. study (Brodie et al., 2014; Ragert et al., 2011)). Additionally, the research conducted by Brodie et al. (Brodie et al., 2014) does not consider short interstimulus intervals (with the shortest ISI being 15 ms), lacking insight regarding faster-paced events. Furthermore, the two investigations differed in study design, delivering the CS on opposite hands.

The pSEP protocol was also employed in a work by Ishii et al. in 2021, utilizing a larger number of stimuli (500 epochs per condition) and a larger sample size (14 individuals). This study found no significant influence of right median nerve stimulation (CS) on SEPs elicited by left median nerve stimulation (TS) at any ISI (Ishii et al., 2021). However, the excessive number of conditions in Ishii and coworkers' study (1–2–3–5–10–20–30–40–60–100 m s, rMNS, and lMN) might account for the absence of significant results. Indeed, one should bear in mind that this elevated number of stimuli could have provoked the phenomenon of habituation, which refers to the progressive decrease in response after repeated stimulations (Callaway, 1973).

The discrepancies observed among the findings of the three studies concerning moderate-length ISIs (10–40 ms) motivated the current research's design. By employing an adequate sample size (15 subjects), an extensive number of epochs per block (1000), and the careful selection of relevant conditions (rMNS, lMSN, cISIs 0–5–10–20–40 ms), our study was, in fact, tailored to obtain highly reproducible information.

Moreover, the studies by Ragert and Ishii (Ishii et al., 2021; Ragert et al., 2011) observed that conditioning stimulation did not result in a reduction of SEP amplitude induced by contralateral median nerve stimulation (TS) at short ISIs (5 ms in Ragert et al. study, 1–2–3–5 ms in Ishii et al. study (Ishii et al., 2021; Ragert et al., 2011)). Because the response to the second stimulus delivered at a short ISI is directly influenced by the number of synapses between the stimulus location and the origin of the response in the brain, these findings suggested the absence of a direct mono/

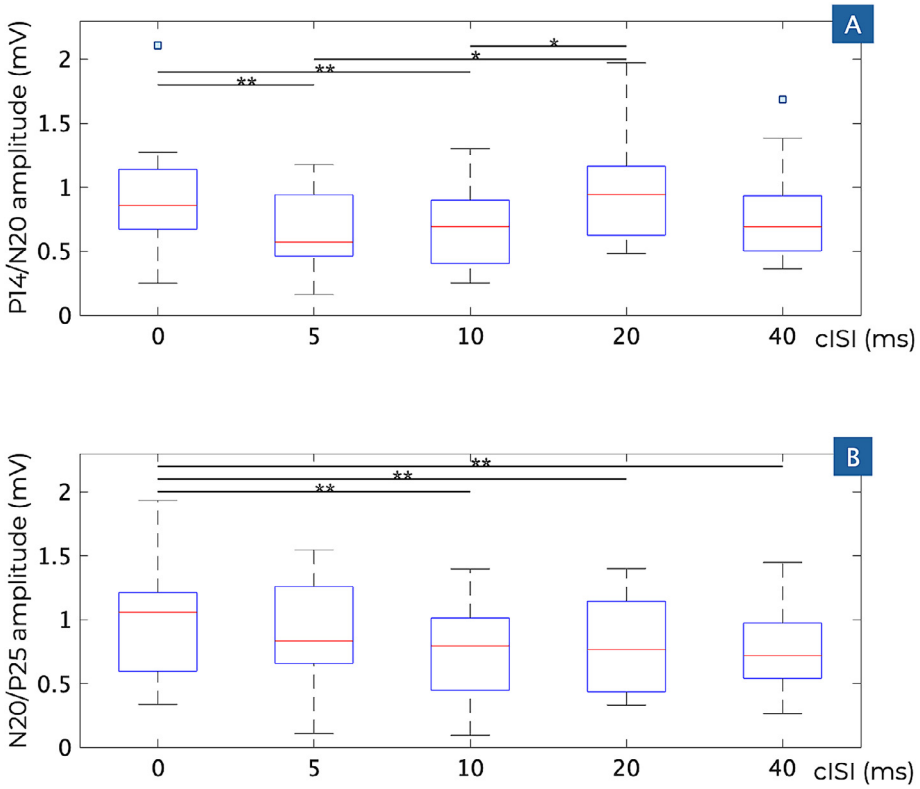


Fig. 4. Comparison of baseline-corrected N20 amplitudes, as P14/N20 (A) and N20/P25 (B), between corrected interstimulus intervals (cISIs). On the left: boxplots summarize the lower quartile, median, and upper quartile of distributions; whiskers extend up to 1.5 times the interquartile range; the significant results of 1w RM-ANOVA (one-way repetitive measure analysis of variance) at paired post-hoc comparisons are highlited (**p* < 0.05; ***p* < 0.01). On the right: raw baseline-corrected data are presented for each subject.

Table 4
Post-hoc comparisons after one-way Repetitive Measure Analysis of Variance of baseline-corrected values of the HFO area components at different corrected interstimulus intervals (cISIs). Abbreviations: tot-HFO area, baseline-corrected area of the total high-frequency oscillation burst; l-HFO area, baseline-corrected area of the late component of the high-frequency oscillations.

		Tot-HFO area (p-value)	l-HFO area (p-value)
0 ms	5 ms	0.018*	0.046*
0 ms	10 ms	0.027*	0.026*
0 ms	20 ms	0.003**	0.648
0 ms	40 ms	0.326	0.648
5 ms	10 ms	1.000	1.000
5 ms	20 ms	1.000	0.648
5 ms	40 ms	0.730	0.648
10 ms	20 ms	1.000	0.648
10 ms	40 ms	0.850	0.648
20 ms	40 ms	0.240	1.000

* p value < 0.05.
** p value < 0.01.

oligosynaptic neural connectivity between the left and right somatosensory pathways. (Hoshiyama and Kakigi, 2002).

Our data, however, show some different results from previous studies, revealing a significant decrease in the amplitude of the earliest cortical component of the SEP (P14/N20) at interstimulus intervals of 5 and 10 ms compared to simultaneous stimulation of both sides (cISI 0 ms) or other similar intervals (significant difference in P14/N20 amplitude between 5–10 ms and 20 ms). This evidence suggests the existence of a highly rapid and direct connection between the two sides of the central nervous system. On the other hand, our data on the N20 descending segment suggests slower and long-lasting inhibition, with significant findings at cISIs of 10, 20, and 40 ms, implying the involvement of more complex polysynaptic networks.

The discrepancies in results concerning short interstimulus intervals between the present study and previous ones may be due to differences in experimental methodologies and computational constraints related to the brief latencies involved. Moreover, given that intra-individual asymmetries in the conduction of sensory impulses are often within a few milliseconds, we hypothesize that the correction of interstimulus intervals performed in our study holds greater significance for brief intervals. Lastly, discrepancies with the results of Ishii and coworkers (Ishii et al., 2021) may arise due to potential differences in the roles played by the two hemispheres in modulating sensory perception of the contralateral S1. Ishii et al.'s study, in fact, investigated the influence of a conditioning stimulus delivered to the right median nerve on the homolateral sensory cortex, while the current study employs the opposite configuration.

Data on high-frequency oscillations (HFOs), revealing substantial engagement of the late component and non-significant alterations in the early component, provide evidence for the activation of complex intracortical connections from the early stages, with significant inhibition occurring at cISIs of 5–10 ms.

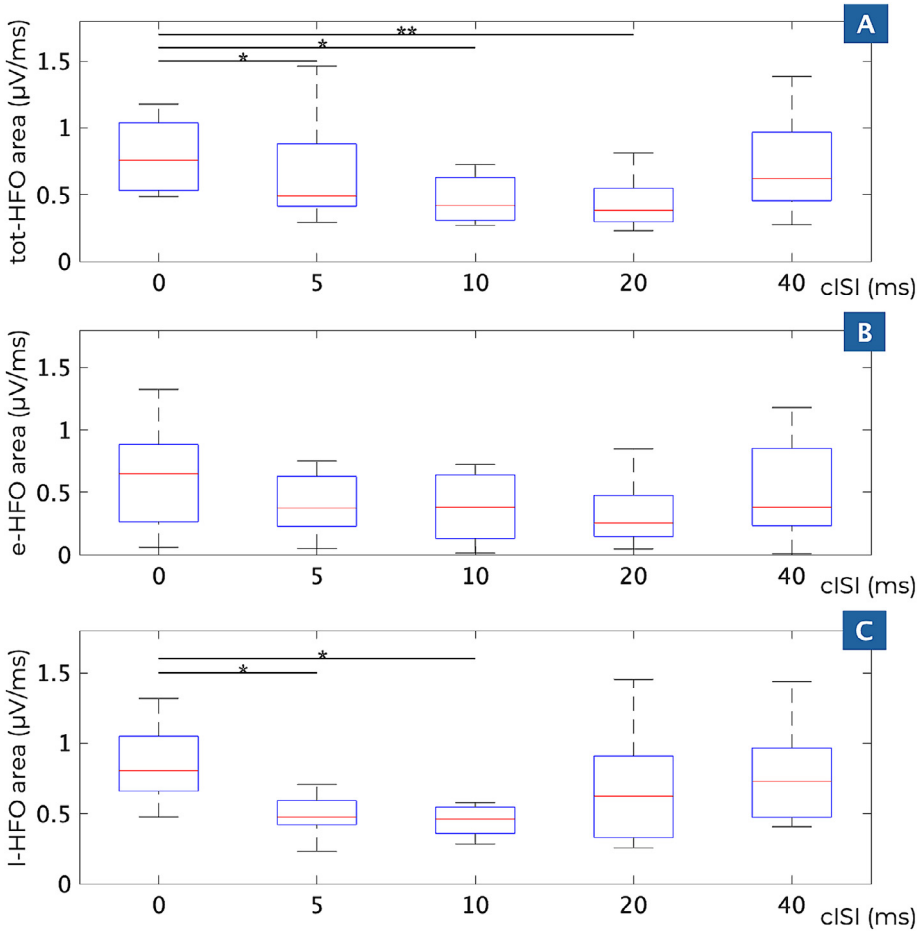
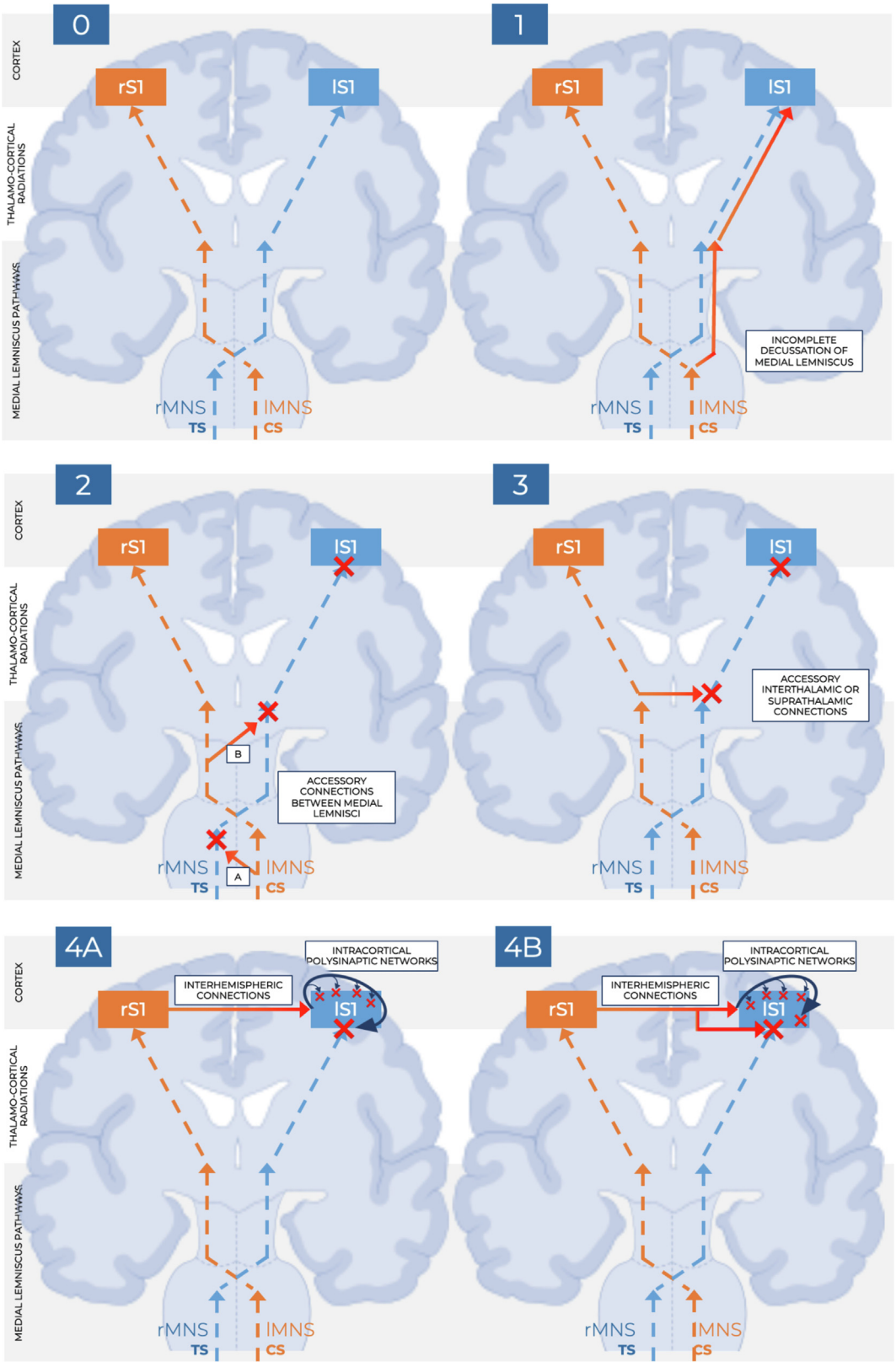


Fig. 5. Comparison of baseline-corrected data of the HFO (high frequency osciellation) total, early and late bursts between corrected interstimulus intervals (cISIs). On the left: boxplots summarize the lower quartile, median, and upper quartile of distributions; whiskers extend up to 1.5 times the interquartile range; the significant results of 1w RM-ANOVA (one-way repetitive measure analysis of variance) at paired post-hoc comparisons are highlited (*p < 0.05; **p < 0.01). On the right: raw baseline-corrected data are presented for each subject.


0
CORTEX
THALAMO-CORTICAL RADIATIONS
MEDIAL LEMNISCUS PATHWAYS
rS1
lS1
rMNS
TS
lMNS
CS
1
INCOMPLETE DECUSSATION OF MEDIAL LEMNISCUS
2
B
A
ACCESSORY CONNECTIONS BETWEEN MEDIAL LEMNISCI
3
ACCESSORY INTERTHALAMIC OR SUPRATHALAMIC CONNECTIONS
4A
INTERHEMISPHERIC CONNECTIONS
INTRACORTICAL POLYSINAPTIC NETWORKS
4B

While it is well established that early HFOs are generated from action potentials of thalamocortical axons upon their arrival at S1 (Curio, 2000; Gobbelé et al., 2004; Klostermann et al., 1999), more controversial is the role and implications of late HFOs (l-HFOs).

The l-HFOs burst emerges around the N20 peak and lasts until the second cortical response (i.e., the P30 SEP component) (Ozaki and Hashimoto, 2011). It is believed to originate postsynaptically in the cortex, as its occurrence is abolished after cortical injection of glutamatergic receptor antagonists (Ikeda et al., 2002). The debate centers around whether the late HFOs reflect excitatory activities, specifically from pyramidal cells (Jones and Barth, 2002), or if they are generated by inhibitory fast-spiking (FS) GABAergic interneurons (Hashimoto et al., 1996; Jones et al., 2000; Ozaki et al., 2001; Ozaki and Hashimoto, 2005).

In their 2011 review, Ozaki et al. discussed two potential circuits for the inhibitory hypothesis of l-HFO genesis: a feedforward inhibitory circuit and a feedback inhibitory circuit (Ozaki and Hashimoto, 2011). A dissociation or reciprocal relation between HFOs and N20 would suggest the activation of a feedforward inhibitory circuit (i.e., FS interneurons receiving thalamocortical projections and inhibiting pyramidal neurons), as demonstrated by several studies on SEPs or somatosensory evoked fields (Hashimoto et al., 1999, 1996; Mochizuki et al., 2003; Ogawa et al., 2004; Tanosaki et al., 2002). Conversely, parallel changes in HFOs and N20 would indicate the activation of a feedback inhibitory circuit by enhanced pyramidal cell activity.

Our findings, which show a decrease in the peak-to-peak amplitude of the N20 potential as well as a reduction in the area of the l-HFO, support the hypothesis of a feedback inhibitory circuit generating this burst.

From our present findings, four possible mechanisms have surfaced to elucidate the transfer of tactile information (Fig. 6).

1. **Incomplete decussation of the medial lemnisci.** A portion of the ascending fibers of the medial lemniscus pathway activated by the conditioning stimulus (CS) of the left median nerve does not decussate at the medulla oblongata but continues ipsilaterally, first activating the left thalamus and then the left primary sensory area (lS1). This should, in theory, result in a cortical SEP component preceding that derived from the test stimulus (TS) on the right median nerve by a total of milliseconds equal to the interstimulus interval used. However, such a potential was never recorded during our study, as evidenced by the N20 latencies at various interstimulus intervals, which were never earlier than expected. This hypothesis can therefore be ruled out based on our results.
2. **Connections between right and left dorsal column/medial lemniscus pathways.** The stimulation of the left median nerve (lMNS, CS) activates an accessory pathway at the spinal cord or brainstem level, extending to contralateral homologous structures. The signal, therefore, modulates the response of the left thalamus, when activated by the delayed stimulation of the right median nerve (rMNS, TS). The preserved integrity of the thalamus and its connections to the cortex may explain why the early phase of high-frequency oscillation is not significantly affected in our findings. To further investigate this hypothesis, it would be necessary to conduct studies simultaneously analyzing both cortical and subcortical components of the SEP.
3. **Bilateral subcortical connections either suprathalamic or interthalamic.** It is from the right thalamus (or its radiations to the cortex), activated by the conditioning stimulus (CS), that an accessory pathway extends to homologous contralateral structures, altering their function. The neurophysiological correlate should, therefore, manifest as an alteration in the early component of high-frequency oscillations (eHFO), which, in our study, did not undergo significant modifications. However, upon observing the raw values of eHFO, it is evident that the areas are reduced (though not significantly) at all interstimulus intervals when compared with stimuli administered simultaneously (cISI 0 ms). Hence, we cannot exclude the possibility that differences exist, and our study might not have been able to demonstrate them. A significant modulation of the eHFOs would also explain why comparisons of the total areas of HFOs (tot-HFO) at different interstimulus intervals may not perfectly mirror comparisons of the late component (l-HFO). For instance, tot-HFOs are significantly different at cISI 20 ms compared to cISI 0 ms, whereas l-HFOs remain unaffected.
4. **Interhemispheric interactions between left and right primary somatosensory cortices**
   A. The right S1 activated by the lMNS (CS) triggers inhibitory pathways that rapidly suppress the intracortical networks of the contralateral S1, resulting in a decreased area of late-component high-frequency oscillations HFOs. These inhibitory effects on intracortical networks yield two

Fig. 6. Proposed mechanisms for ipsilateral modulation of S1 responses. Our present findings reveal four potential mechanisms that elucidate the interaction between the right and left somatosensory systems. Abbreviations: cISI, corrected interstimulus interval; rMNS, right median nerve stimulation; lMNS, left median nerve stimulation; TS, test stimulus; CS, conditioning stimulus; lS1, left primary somatosensory cortex; rS1, right primary somatosensory cortex. **0: classical model of sensory impulse transmission via the medial lemniscus pathway.** Following a rMNS, the impulse travels along the peripheral branch of the pseudounipolar neuron (first-order neuron), passing through the dorsal root ganglion. It ascends through the central branch along the dorsal columns of the spinal cord. Upon entering the brainstem, the nerve fibers immediately synapse with the second-order neuron, whose axons decussate contralaterally and ascend to the ventral posterior nucleus of the left thalamus. Here, they synapse with the third-order neuron, whose thalamocortical projections terminate in the postcentral gyrus of the left parietal lobe within the lS1. The same process occurs contralaterally for a sensory stimulus applied to the left median nerve. **1: incomplete decussation of the medial lemnisci.** A portion of the ascending fibers of the medial lemniscus pathway activated by the lMNS- CS does not decussate at the medulla oblongata but continues ipsilaterally, first activating the left thalamus and then the lS1, altering the potentials evoked by rMNS – TS. **2: connections between right and left dorsal column/medial lemniscus pathways.** The lMNS - CS activates an accessory pathway at the spinal cord (A) or brainstem level (B), extending to contralateral homologous structures. The signal, therefore, modulate the left thalamus' response to the delayed rMNS - TS. **3: bilateral subcortical connections either suprathalamic or interthalamic.** It is from the right thalamus (or its radiations to the cortex), activated by the lMNS - CS, that an accessory pathway extends to homologous contralateral structures, altering their function. The neurophysiological correlate should, therefore, manifest as an alteration in the early component of high-frequency oscillations (eHFO) **4A: interhemispheric interactions between left and right primary somatosensory cortices.** The rS1, activated by the lMNS - CS, triggers inhibitory pathways that rapidly suppress the intracortical networks of the lS1. This leads to a decreased area of late-component high-frequency oscillations (l-HFOs). The inhibition of intracortical networks results in an immediate reduction of signals arriving at the lS1 (derived from the rMNS - TS), evident as a reduction in the amplitude of the N20 earliest part (P14/N20) observable at 5–10 ms. Additionally, there is a delayed activation of a polysynaptic circuit, causing the later and prolonged reduction of the later part of N20 (N20/P25) at 10–20–40 ms. **4B: interhemispheric interactions between left and right primary somatosensory cortices.** Sensitive impulses generated by the lMNS – CS activate the rS1. This activation initiates two inhibitory pathways. The first pathway acts directly, and rapidly reduces the left cortical response to sensory stimuli, leading to a reduction in the P14/N20 amplitude observed at 5–10 ms. The second pathway inhibits the polysynaptic intracortical network contralaterally, responsible for generating the l-HFOs. This inhibition causes a delayed and prolonged reduction in the N20/P20 observed at longer cISIs.

consequences: an immediate reduction of the signals arriving at left S1 (reflected by the reduction in the earliest part of N20 observable at 5–10 ms) and a delayed activation of a polysynaptic circuit, leading to the later and prolonged reduction of the later part of N20 (occurring at 10–20-40 ms).

B. The sensitive impulses produced by the lMNS (CS) activate the right primary somatosensory area, initiating two inhibitory pathways. The first pathway acts directly and rapidly reduces the left cortical response to sensory stimuli, leading to a reduction in the P14/N20 amplitude observed at 5–10 ms. The second pathway contralaterally inhibits the polysynaptic intracortical network responsible for generating the late burst of HFOs, causing the delayed and prolonged reduction in the later part of N20 shown at moderate-length ISIs.

Models 4A and 4B propose a connection between the two primary sensory areas that occurs within a few milliseconds (5–10 ms). Given the considerable anatomical distance between these cortices, the viability of these models depends on hypothesizing the presence of a complex, highly myelinated structure capable of rapidly transmitting stimuli from one hemisphere to another. Commisural structures, particularly the corpus callosum, fulfill this function precisely. Furthermore, this form of S1-S1 conduction occurs at a speed equivalent to that estimated in the literature for connections between the two motor cortices (Ni et al., 2020), indicating compatibility with a transcallosal direct pathway.

Models 1, 2, and 3, while capable of explaining certain findings from our study (i.e., the altered arrival of sensory information to S1 based on the conditioning stimulus), are nonetheless unable to account for the results concerning the late component of high-frequency oscillations, whose significant variations imply the modulation of polysynaptic intracortical pathways.

Moreover, there is supportive evidence for the transcallosal hypothesis, rendering it the most plausible and, consequently, the only one considered by Ragert and Brodie in their studies. Notably, postmortem anatomical findings (Aboitiz, 1992) and *in vivo* MRI evidence (Fling et al., 2013) identify transcallosal connections between the primary somatosensory cortices.

Even if our results do not provide definitive information regarding the specific site of the interhemispheric interaction, the mechanism described by the 4A model appears less likely to be valid due to its reliance on *ab initio* polysynaptic pathways, which are improbable candidates for explaining the rapid changes observed in N20 potential after 5 ms.

4.1. Strengths and limitations

Our investigation has some limitations that should be acknowledged. One limitation is the relatively small number of participants in our study (15 individuals). However, it is worth noting that our sample size is the largest among studies utilizing the pSEP protocol. Another limitation is our inability to analyze events occurring before 5 ms by examining shorter interstimulus intervals (ISIs), as explored by Ishii et and colleagues. This possibility was not initially considered in our experimental design due to the lack of prior research demonstrating any influence at short ISIs. Instead, our focus was on minimizing the number of conditions to mitigate the effects of the habituation phenomenon. This strategy allowed us to increase the number of epochs per condition, facilitating precise recording of high-frequency oscillation (HFO) bursts.

Another nuanced aspect of this study is that relying on scalp-recorded SEPs lacks the capability to discern the genesis of potentials within Brodmann areas 1, 2, 3a, or 3b. It could be interesting to revisit this protocol employing more refined techniques, such as magnetoencephalography or electrodes implanted in the cerebral cortex, to enhance precision in the localization of these specific areas.

While it is widely recognized that volume conduction and reference electrode usage can degrade the spatial resolution of scalp EEG recordings, a common assumption in traditional EEG recordings is that they possess a very high temporal resolution. Yet, there is compelling evidence regarding the impact of using bipolar derivations on temporal resolution (Burle et al., 2015; Nunez and Srinivasan, 2006). Nonetheless, using time-blocked evoked potentials and establishing time-blocked conditions (cISIs), we accurately measure impulse transmission time by comparing events across different conditions. This approach not only addresses interindividual variability but also considers intraindividual differences, enhancing the robustness of our findings.

A significant issue in previously published works on this topic was the establishment of appropriate ISIs. Setting a predetermined delay between conditioning and test stimuli can be problematic when assessing the timing of interaction between the S1 areas on both sides of the brain, as the two S1 areas do not consistently respond to the peripheral stimulus with the same latency. We overcame this potential bias by using the N20 latency to calculate *corrected ISIs* allowing to precisely determine the timing of cortico-cortical interactions. This aspect represents a notable strength of our study.

5. Conclusions

Our results showed significant differences in the peak-to-peak amplitudes of the short-latency SEP component (N20) across different cISIs suggesting that the interhemispheric connections between the primary somatosensory cortices are time-dependent, with different cISIs resulting in varying levels of interhemispheric modulation. These results support the existence of interhemispheric transfer of tactile information between the primary sensory areas, potentially involving a transcallosal network, underscoring the importance of considering the timing of stimuli in investigating interhemispheric connectivity.

Further research is warranted to explore the functional significance of these interhemispheric connections and their potential role in somatosensory processing and sensorimotor integration. Understanding the mechanisms underlying interhemispheric interactions in the somatosensory system can contribute to the development of therapeutic interventions for various neurological conditions affecting sensory processing.

Author contributions

Conception of the work, D.N., G.M., and V.dL.; design of the work, D.N., G.M., and F.P.; data acquisition, G.M., D.N., and A.T.; data analysis, D.N., A.C., and F.M.; data interpretation, D.N., F.P., F. R., S.L., and F.C.; drafting, D.N., G.M., and F.P.; critical revising, V. dL., S.L., F.R., A.T., A.C., and F.C.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, D.N. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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