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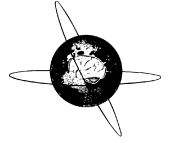
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Altered excitation-inhibition balance in the primary sensorimotor cortex to proprioceptive hand stimulation in cerebral palsy



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HIGHLIGHTS

- Strong beta suppression in diplegic cerebral palsy (CP) can reflect hyperexcitation/activation of the primary sensorimotor (SM1) cortex contralateral to the stimulation.
- Weak beta rebound in the ipsilateral SM1 cortex may indicate broadly impaired control of cortical inhibition in diplegic CP.
- Strong ipsilateral rebound in controls may reflect the importance of interhemispheric inhibitory regulation in fine-motor actions.

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ABSTRACT

Objective: Our objective was to clarify the primary sensorimotor (SM1) cortex excitatory and inhibitory alterations in hemiplegic (HP) and diplegic (DP) cerebral palsy (CP) by quantifying SM1 cortex beta power suppression and rebound with magnetoencephalography (MEG).

Methods: MEG was recorded from 16 HP and 12 DP adolescents, and their 32 healthy controls during proprioceptive stimulation of the index fingers evoked by a movement actuator. The related beta power changes were computed with Temporal Spectral Evolution (TSE). Peak strengths of beta suppression and rebound were determined from representative channels over the SM1 cortex.

Results: Beta suppression was stronger contralateral to the stimulus and rebound was weaker ipsilateral to the stimulation in DP compared to controls. Beta modulation strengths did not differ significantly between HP and the control group.

Conclusions: The emphasized beta suppression in DP suggests less efficient proprioceptive processing in the SM1 contralateral to the stimulation. Their weak rebound further indicates reduced intra- and/or interhemispheric cortical inhibition, which is a potential neuronal mechanism for their bilateral motor impairments.

Significance: The excitation-inhibition balance of the SM1 cortex related to proprioception is impaired in diplegic CP. Therefore, the cortical and behavioral proprioceptive deficits should be better diagnosed and considered to better target individualized effective rehabilitation in CP.

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Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; SM1, primary sensorimotor; HP, hemiplegic; DP, diplegic; TD, typically developed; MACS, Manual Ability Classification System; TFR, Time-frequency representation; TSE, Temporal spectral evolution.

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1. Introduction

The location and extent of the brain lesion vary widely among patients with cerebral palsy (CP) explaining the consequent wide spectrum of their symptoms. The etiologies of brain injuries are diverse in CP and can occur at different developmental stages from the prenatal to the postnatal period (Bax et al., 2005). A common distinct symptom of CP is the motor impairments manifested by difficulties in performing and coordinating movements as well as

maintaining body posture and balance. These motor impairments may partly be due to deficient somatosensory perception and central processing in CP (Kriger, 2006; Robert et al., 2013; Wingert et al., 2008).

The most common CP category is spastic, with typical symptoms such as muscle stiffness, exaggerated movements, and limited mobility. CP can also be classified according to the degree of the motor impairments using, e.g., Gross Motor Function Classification System (GMFCS; Palisano et al., 2008). Furthermore, the topographical classification of the impairments is widely used. Hemiplegia indicates unilateral involvement of the arm and/or leg, whereas in diplegia both sides are involved with emphasis on the lower extremities. (Kriger, 2006; Rosenbaum et al., 2007).

Varying tactile and proprioceptive somatosensory impairments have been identified in CP (Brun et al., 2021; Clayton et al., 2003; Goble et al., 2009; Poitras et al., 2021; Wingert et al., 2009), which have been suggested to derive from impaired thalamocortical somatosensory connections (Hoon Jr et al., 2009; Papadelis et al., 2014). These suggestions are supported by findings from several functional neuroimaging studies in which the function of the primary sensorimotor (SM1) cortex is altered in CP (Brun et al., 2021). For example, individuals with CP show a more bilateral representation of the SM1 responses and weaker activation to somatosensory stimulation than their healthy peers (Kurz and Wilson, 2011; Nevalainen et al., 2014, 2012; Piitulainen et al., 2020; Trevarrow et al., 2021). In addition, oscillatory activity to somatosensory stimulation of the hand or the movement of the hand is altered especially in beta and gamma frequencies in CP (Guo et al., 2012; Hoffman et al., 2019; Kurz et al., 2015; Pihko et al., 2014). However, the sample size in the previous studies has been relatively small, and thus the different types of CP have not been systematically compared before. Indeed, the CP population is a very heterogeneous group varying in etiology, consequent neurophysiological abnormalities, and behavioral deficits.

Modulation of beta rhythm power has been proposed to reflect excitation and inhibition of the SM1 cortex (Cassim et al., 2001; Cheyne, 2013; Engel and Fries, 2010; Neuper et al., 2006; Takemi et al., 2013). Cortical excitation-inhibition balance can be assessed through a degree of modulation of the beta power to various afferent somatosensory stimuli (i.e., tactile-, and proprioceptive stimulus) or voluntary movement (Houdayer et al., 2006; Illman et al., 2020; Pfurtscheller and Lopes da Silva, 1999). Beta power is typically suppressed shortly after the onset of stimulation or even seconds before voluntary movement, relating to preparation and initiation of movement (Alegre et al., 2003; Kaiser et al., 2001; Szurhaj et al., 2003). This reduction of the rhythm power is called beta suppression (or event-related desynchronization, ERD), and it is thought to represent the activation or excitation of the SM1 cortex (Cheyne, 2013). The beta suppression is followed by a longer-lasting increase of the beta power called beta rebound (or event-related synchronization, ERS), which is suggested to reflect the inhibition of the SM1 cortex (Cassim et al., 2001; Gaetz et al., 2011; Salmelin et al., 1995). Therefore, these power modulations provide a neurophysiological biomarker for detecting abnormal SM1 cortex function. For example, beta modulation has been suggested as a good biomarker for predicting recovery from stroke (Laaksonen et al., 2012; Parkkonen et al., 2018; Tang et al., 2020). Previous studies have shown that the beta rebound is diminished in both hemiplegic and diplegic CP (Hoffman et al., 2019; Pihko et al., 2014). However, it is not known whether beta modulation is altered in the proprioceptive domain, which is a crucial afference for motor control of the brain. Here we use a novel proprioceptive stimulation of the hand to explore the related SM1 cortex functions in CP and its hemi- and diplegic subtypes. The quantification of the sensorimotor cortex excitation-inhibition balance using beta mod-

ulation to proprioceptive stimulation is a potential biomarker to assess the brain basis of motor dysfunctions in CP.

We examined beta power modulations to proprioceptive stimulation in children and adolescents with CP and their typically developed (TD) peers using proprioceptive stimulators to evoke the passive flexion–extension movement of the index finger in MEG. Our primary objective was to examine and compare the strengths of beta suppression and rebound as an indicator of excitation-inhibition balance in the SM1 cortex in hemiplegic (HP) CP, diplegic (DP) CP, and TD adolescents in the proprioceptive domain. Proprioception is the most crucial somatosensory domain to support smooth motor performance and thus a potential factor explaining some of the CP-related motor impairments. However, the excitation-inhibition balance in CP has not been examined before in the proprioceptive domain. Therefore, the gained new knowledge is essential for the future use of beta modulation as a biomarker to better target and follow individualized rehabilitation and treatment in children with CP.

2. Methods

2.1. Participants

All the children and adolescents who participated in the study were between 10 and 18 years old.

CP participants. In total 28 children and adolescents (mean $13.2 \pm$ SD 2.3 years) with a confirmed diagnosis of spastic cerebral palsy (CP) participated in the study. 16 of them were diagnosed with hemiplegic HP (females 11, age: mean $13.3 \pm$ SD 2.4 years) and 12 with diplegic DP (females 6, age: mean $13.2 \pm$ SD 2.2 years) CP. Participants with CP had no diagnosed cognitive or co-operative deficiencies.

Control participants. 32 healthy typically developed (TD) adolescents participated in the study (females 19, age: mean $14.0 \pm$ SD 2.4 years). The age of TD participants did not differ significantly from the age of CP participants ($P = 0.41$).

Handedness. The Edinburgh Handedness Inventory (Oldfield, 1971) test scores were used to define the hand dominance of the TD and CP participants, however, with HP the dominant hand was the less-affected side. Five of the 17 hemiplegics (mean score: -30.5 ; range: -90 – 100) and nine of the 12 diplegic participants (mean score: 33.9 ; range: -100 – 100) were right-handed dominant. The majority of TD participants were right-handed (30 out of 32, mean score: 71.1 ; range: -85 – 100). The results of the TD and CP participants' dominant hand were compared with each other, as well as the results of the non-dominant hand, respectively. For the hemiplegia participants, the less-affected side was defined as the dominant side.

The study was conducted with the standards of the Declaration of Helsinki, and the protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa. All the volunteered participants and their guardians signed the written consent form prior to the study.

2.2. Sensorimotor performance in CP and TD

All the participants with CP had mild symptoms and their gross motor function was classified at level 1–2 in the GMFCS (Palisano et al., 2008), indicating the ability to walk independently but limited to the minimal ability to execute gross motor skills such as running and jumping. Their manual ability classification system (MACS) was at levels 1–3, demonstrating that they were able to cope independently with most hand functions in daily activities.

Table 1 provides more detailed demographic and lesion information for the CP participants.

The sensorimotor skills of CP and TD participants' both hands were tested with a Box and Block (Mathiowetz et al., 1985a) and Nine-Hole Peg (Mathiowetz et al., 1985b) tests. The Box and block test quantifies gross-motor dexterity, while the Nine-Hole Peg focuses on testing fine motor dexterity. The test results of the dominant and non-dominant hand were correlated with the corresponding hand's beta suppression and rebound strengths. The sensorimotor skills tests were missing in three DP, two HP, and six TD participants, so they were excluded from the correlation tests.

2.3. Experimental design

Proprioceptive stimulation (i.e. brief passive movements) of the right and left index fingers was performed with a custom-made pneumatic-movement actuator (Piitulainen et al., 2015). The participant's hands were placed comfortably on the support surface of the movement actuator and the index fingers were taped to the artificial muscles (Fig. 1A). In addition, the fingertips were gently wrapped with surgical tape to minimize possible tactile sensations caused by the movement. The timing of the movement in relation to the trigger pulse onset was detected at a 1 kHz sampling rate with 3-axis accelerometers (ADXL335 iMEMS Accelerometer, Analog Devices Inc., Norwood, MA, USA) mounted on the fingers. In a random sub-group of our participants, the

3D-accelerometer signals in the x-, y-, and z directions were averaged in relation to the proprioceptive stimulus triggers ensuring that no vibration or tactile sensation was conducted simultaneously to the opposite hand during the stimulation. The participant used earplugs during the experiment, and in addition, white noise was played to mask any possible sounds from the stimulus equipment. During the experiment, the participants were asked to fix their eyes on a slow landscape video, and a visual barrier was placed to avoid visual contamination caused by the movement actuators.

Left- and right-hand index fingers and both ankles were stimulated randomly with separate movement actuators with an inter-stimulus interval (ISI) of 4 s with a jitter of 250 ms. The beta modulations to ankle stimulation were clearly weaker compared to hand stimulation in several participants and thus were not feasible to analyze further, and therefore, would have diminished our sample size dramatically. Thus, only the results of hand stimulation are reported here.

Finger stimulation started with a flexion (mechanical delay of the pneumatic system 55 ms, duration ~ 400 ms) followed by the extension (mechanical delay of the pneumatic system 35 ms, duration ~ 500 ms). Fig. 1 illustrates the timing and duration of the finger movement in relation to the stimulus trigger pulse detected with an accelerometer and laser beam. The movement range of artificial muscle measured by laser beam was ~ 9.5 mm with the applied air pressure of 5 bar. In total, 60–65 flexion–extension stimuli were evoked for each participant.

Table 1
Background information of the adolescent with CP.

Type of CP	Gender	Age	GA	Timing of injury	GMFCS	MACS	Dominant hand	Lesion type	Weak beta value	
									Supp	Rebound
DP01	Female	11	38 + 1	2	2	2	R	2	-	-
DP02	Female	11	34 + 4	1	1	1	R	2	-	N1 + 2i, D2i
DP03	Male	11	40 + 2	1	1	1	R	2	-	-
DP04	Male	14	33 + 1	2	2	3	L	2	-	-
DP05	Male	14	37 + 3	2	1	1	R	2	-	-
DP06	Male	12	28 + 4	2	1	1	L	2	-	N1c
DP07	Male	11	28 + 5	2	2	1	L	2	-	-
DP08	Female	16	40	-	1	1	R	3	-	D + N1c, N1 + 2i
DP09	Female	11	-	-	2	1	R	2	-	-
DP10	Male	17	-	-	2	-	L	4	-	N2i
DP11	Female	15	-	-	2	-	R	4	-	-
DP12	Male	15	-	-	2	-	R	3	-	D + N1c
HP01	Female	17	36 + 1	2	1	1	L	1	-	N2c
HP02	Female	13	42 + 2	2	1	3	L	1	-	-
HP03	Male	11	37	1	1	2	L	2	D1 + 2i	-
HP04	Male	12	34 + 5	2	1	2	L	1	D1i	-
HP05	Male	13	-	-	1	2	L	1	-	-
HP06	Female	14	33 + 2	2	1	1	L	2	-	-
HP07	Female	13	39 + 4	1	1	-	R	2	-	-
HP08	Male	15	30 + 4	2	1	2	L	2	-	D1c
HP09	Female	17	-	1	1	1	R	1	-	-
HP10	Female	18	-	-	1	-	L	5	-	-
HP11	Male	14	24 + 5	2	1	1	R	2	N1 + 2c, D + N1 + 2i	-
HP12	Female	12	42	1	1	2	L	2	-	-
HP13	Female	11	40 + 1	1	1	2	R	1	-	D1i, D2i
HP14	Female	10	42	1	1	2	L	1	-	D + N1c
HP15	Female	11	40 + 2	1	1	1	R	2	-	-
HP16	Female	14	40 + 2	1	1	1	L	5	-	-

Type of CP: DP = Diplegic, HP = Hemiplegic.

GA = Gestational age (week + day).

Timing of injury: 1 = prenatal, 2 = perinatal, 3 = postnatal.

GMFCS = Gross Motor Function Classification System: 1 = mild, ..., 5 = severe.

MACS = Manual Ability Classification System: 1 = mild, ..., 5 = severe.

R = right, L = left.

Lesion type: 1 = grey matter (infraction), 2 = white matter, 3 = normal, 4 = miscellaneous, 5 = maldevelopment.

Weak beta value: 1 = flexion, 2 = extension, c = contra, i = ipsi, D = dominant hand, N = Non-dominant hand.

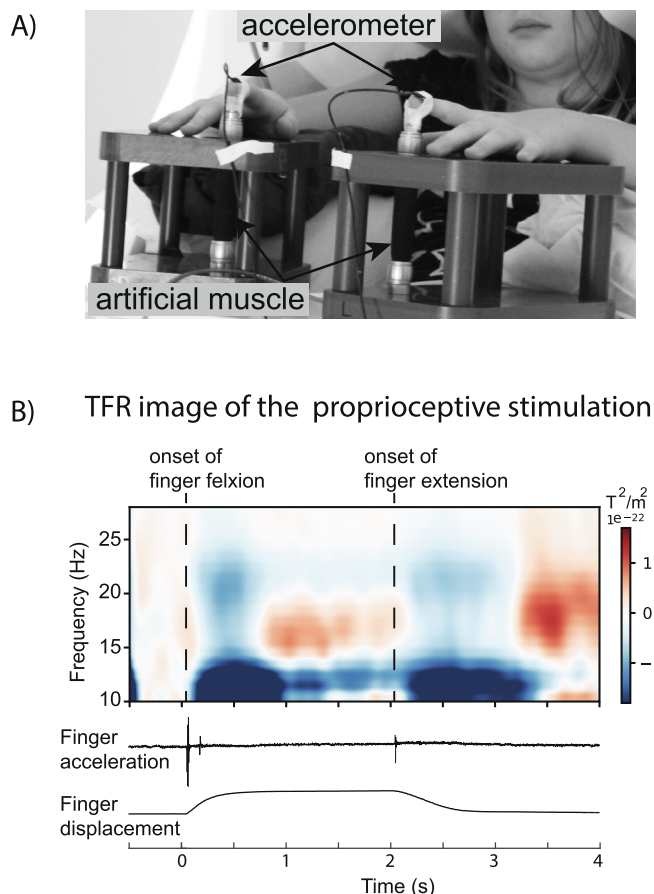


Fig. 1. (A) Experimental design for proprioceptive stimulation of the index finger. The fingers are attached to the artificial muscles of the movement actuators and accelerometers were taped on the nail of the index fingers. (B) Time-frequency representation (TFR) image of the contralateral response to the dominant hand proprioceptive finger stimulation averaged over all typically developed (TD) participants. Dashed lines illustrate the onset of the movements. The signals below the TFR image show finger acceleration and displacement.

2.4. Data acquisition

The MEG measurements were conducted in a magnetically shielded room (MSR; Imedco AG, Hägendorf, Switzerland). MEG data were collected with a 306-channel (204 planar gradiometers, 102 magnetometers) whole-scalp MEG system (Elekta Neuromag, Elekta Oy, Helsinki, Finland) at the MEG Core, Aalto Neuroimaging, Aalto University. Prior to the MEG acquisition, three head position indicator coils to the forehead and one behind each ear to define the participant's head position with respect to the MEG sensors. Location of the five head position indicator coils, three anatomical landmarks (left and right preauricular points and nasion), and ca. 100 additional points from the scalp and nose were determined with a 3-D digitizer (Fastrak 3SF002, Polhemus Navigator Sciences, Colchester, VT, USA). Continuous head position recording was used to track the head position throughout the MEG recording. During the MEG recording, the participants were sitting comfortably in the MEG chair, head in a helmet-shaped MEG sensor array.

The MEG sampling rate was 1000 Hz and a band-pass filter of 0.1–330 Hz was used prior to sampling.

2.5. Data processing and analysis

Preprocessing. Maxfilter software (v2.2; Elekta Oy, Helsinki, Finland) was utilized for preprocessing the MEG raw data. The

signal-space separation method with temporal extension (tSSS) and head movement compensation were exploited (Taulu and Simola, n.d.).

Data analysis. MNE python (ver.0.17) was applied for the raw data analysis. Interfering evoked responses generated by the finger movements were subtracted from the raw data, and eye movement artifacts were removed (signals from the magnetometer and two gradiometers) using a principal component analysis (PCA) prior to frequency analyses (Uusitalo and Ilmoniemi, n.d.).

Beta rhythm frequency band. Time-frequency representations (TFRs) were computed for the right and left finger movements with the Morlet wavelet transformation at frequencies of 5–35 Hz, and with a time window of –500 to 4000 ms with respect to the stimulus trigger onset (Tallon-Baudry et al., n.d.). The spectral and temporal resolution of the TFRs was balanced by scaling the number of cycles to $f/2$. TFRs were used for the visual inspection to determine the lower and higher frequencies of the beta suppression and rebound individually for each participant.

Beta rhythm modulation. Temporal spectral evolutions (TSEs) were computed for the proprioceptive stimulation of both fingers with a time window of –500 to 4000 ms with respect to trigger onset. The raw data was first bandpass filtered with individually selected frequency band (between 13–26 Hz) and bandwidth (10 to 12 Hz) determined from the TFRs. After bandpass filtering, a Hilbert transform was applied to obtain the envelope signal, and then the data was averaged with respect to trigger onset.

Amplitudes of the beta suppression and rebound for the left and right finger extension and flexion were determined individually from the TSE curves. The individual peak amplitudes were determined from the time interval of 200–800 seconds for the suppression and 1000–1800 seconds for the rebound in relation to the onset of the finger flexion and extension movements respectively. The channel showing peak suppression amplitude and the channel showing peak rebound amplitude among the channels over the left and right SM1 cortex respectively were manually defined. The peak channel for suppression and rebound were determined separately as these responses may have a slightly different cortical origin (Jurkiewicz et al., 2006; Salmelin and Hari, 1994). These selected channels were then used to compute the final beta modulation, its latency, and the beta power baseline. In some individuals, the suppression and rebound were more pronounced in different channels, in which case the definition was performed from two different channels in one hemisphere. For the final analysis, the amplitudes of the beta suppression and rebound were converted into relative percentage strengths with respect to the pre-stimulus baseline (–200–0 ms) for better comparability.

2.6. Statistical analysis

Shapiro–Wilk test (IBM SPSS Statistics 27) was utilized to test the normal distribution of the latencies and relative values of beta rhythm suppression and rebound. Since the data proved to be non-normally distributed, nonparametric tests were applied for further analyses. Three-way ANOVA with aligned rank transform (type III Wald F test with Kenward-Roger df) with R statistical software (version 4.2.1) (R Development Core Team. R Core Team, 2020) was used to test the interaction of suppression and rebound strengths between hemisphere, movement direction (flexion/extension) and stimulated hand in TD controls. Hereafter, Wilcoxon signed-rank test was used to analyze significant differences within the groups, presented with Bonferroni corrections. Kruskal-Wallis (Kruskal and Wallis, 1952) H test (one-way analysis of variance, ANOVA) was used to analyze whether the independent samples of the groups originate from the same data distribution. If the test showed significant differences between the groups, Conover's (Conover, 1999) post hoc test with FDR-correction

(Benjamini and Hochberg, 1995) of multiple comparisons was exploited for more detailed testing of pairwise differences. Correlations between the strength of beta modulation and hand motor function were tested with Spearman's correlation coefficient. A P -value < 0.05 was considered statistically significant.

3. Results

Beta power modulations for the proprioceptive stimulation of the index finger flexion and extension were well detectable in the majority of TD and CP participants. In some TD and CP participants, the beta modulations were weak at or below the noise level (see Table 1), without consistent pattern within the different beta modulations examined (ipsilateral and/or contralateral and suppression and/or rebound). These participants were included in the analysis but had zero values in the respective beta power modulations. Fig. 1B illustrates group averaged TRF of dominant hand proprioceptive stimulation of the controls. Both the finger flexion and extension movements produced clear beta suppression and rebound in the contra- and ipsilateral hemispheres in relation to the stimulated hand at the group level.

Beta power at baseline. The beta rhythm power at the baseline periods of the suppression and rebound for the dominant and non-dominant hand before the onset of the finger stimulation did not show significant differences between TD (mean for suppression and rebound baseline across the hemispheres \pm SD; 25.5 ± 8), HP (26.1 ± 5), and DP groups (23.6 ± 6), $P = 0.12$ – 0.55 .

Subjects' head position in the device coordinates. Subjects' head coordinates were extracted from tSSS filtering output. There were no significant differences in head positions between TD, HP, and DP groups in the x, y, and Z directions ($P = 0.07$ – 1). The head coordinates (mean \pm SD) in the x-direction were 0.0 ± 3 mm for TD, 0.5 ± 5 mm for HP, 3.2 ± 5 mm for DP; in the y-direction -1.8 ± 7 mm for TD, -3.4 ± 5 mm for HP, 0.9 ± 8 mm for DP; and in the z-direction 47.6 ± 7 mm for TD, 44.7 ± 8 mm for HP and 49.3 ± 7 mm.

Sensorimotor performance and correlation to the beta modulation. All the CP participants had mildly impaired motor function according to MACS and GMFCS. Individuals with DP appeared to have slightly lower motor function based on GMFCS (mean 1.6 vs. 1.0) than HP participants, while MACS were more similar between the groups (1.3 vs. 1.6). The MACS and GMFCS values of the CP participants are shown individually in Table 1.

Hand motor skills appeared to be weaker in the DP and HP groups compared to the TD group. The Box and Block test showed that gross-motor skills were significantly higher for the non-dominant hand in TDs than in HPs (mean \pm SD; 70 ± 8 vs. 39 ± 15 , $P < 0.01$), whereas TD vs. DP was below significance (50 ± 17 , $P = 0.09$). Similar differences were not seen for the dominant hand in either CP group compared to TD (72 ± 7 vs. HP 67 ± 12 , $P = 1$, and DP 57 ± 11 , $P = 0.09$). The Nine-Hole Peg test demonstrated that fine-motor skills were significantly weaker for the non-dominant hand in HP compared to TD (59 ± 32 vs. 19 ± 2 , $P = 0.01$), but not between DP and TD (32 ± 17 vs. 19 ± 2 , $P = 0.09$). No significant differences between TD and CP were also found for the dominant hand (TD 17 ± 2 vs. HP 19 ± 3 , $P = 0.17$; DP 25 ± 16 , $P = 0.17$). We did not find any correlations between the hand motor skill tests and the strength of beta suppression and rebound in HP, DP, or TD.

3.1. Beta modulations to proprioceptive stimulation in TD

Fig. 2 illustrates grand averaged beta power modulation to the proprioceptive stimulation for both hands in TD participants. A three-way ANOVA test for the suppression strength showed signif-

icant main effects for the variables of hemisphere (contra/ipsi, $P < 0.001$) and movement direction (flexion/extension, $P < 0.01$), but not for stimulated hand or the mixed effects. Correspondingly to the strength of the rebound, significant main effects emerged for the variables of hemisphere (contra/ipsi, $P < 0.01$), movement direction (flexion/extension, $P < 0.01$), as well as the interactions between hemisphere and movement direction ($P < 0.001$), and hemisphere and stimulated hand ($P = 0.05$). No interactions between hemisphere, movement direction, and hand were observed in suppression or rebound strengths. Paired tests showed some differences between flexion and extension stimuli and between contra- and ipsilateral hemispheres. However, no significant differences were observed in the beta power modulation between the dominant and non-dominant hands, except for a stronger rebound contralateral to the non-dominant hand finger extensions (34 ± 3.8 % vs. 24 ± 2.5 %, $P = 0.05$).

Finger flexion vs. extension. Ipsilateral beta power suppression was significantly stronger for finger flexion than extension in the dominant (-21 ± 1.6 % vs. -17 ± 1.4 %, $P < 0.05$) and non-dominant (-24 ± 1.9 % vs. -16 ± 1.4 %, $P = 0.06$) hand. However, no significant differences were seen in the contralateral suppressions.

Contralateral beta power rebound was significantly stronger for the finger extension than flexion both in the dominant (24 ± 2.5 % vs. 15 ± 2.4 %, $P < 0.01$) and non-dominant (34 ± 3.8 % vs. 18 ± 2.4 %, $P < 0.001$) hand stimulation. On the contrary, the ipsilateral rebounds were stronger for the finger flexion than extension in the dominant (22 ± 2.9 % vs. 16 ± 1.6 %, $P < 0.01$), but no significant differences were seen in the non-dominant hand.

Contra- vs. ipsilateral responses. Contralateral beta power suppression was stronger for the finger extension both in the dominant (-24 ± 1.5 % vs. -17 ± 1.4 %, $P < 0.01$) and non-dominant (-19 ± 1.9 % vs. -16 ± 1.4 %, $P < 0.001$) hand, and for the finger flexion in the non-dominant hand (-26 ± 1.8 % vs. -24 ± 1.9 %, $P < 0.01$). Contralateral beta power rebound was stronger for the finger extension (dominant hand 24 ± 2.5 % vs. 16 ± 1.6 %, $P < 0.01$; and non-dominant 34 ± 3.8 % vs. 20 ± 2.1 %, $P < 0.001$), while it was weaker for the dominant hand finger flexion (15 ± 2.4 % vs. 22 ± 2.9 %, $P < 0.01$). However, a non-significant difference was seen in the non-dominant hand finger flexion.

Latency for the peak beta suppression and rebound. The latency of the peak suppression was observed around 500 ms after the onset of the movement and for the rebound around 1300 ms, respectively. Table 2 shows the peak modulation latencies. Non-significant differences were seen between the dominant and non-dominant hand stimulation ($P = 0.14$ – 1). However, suppression after dominant hand finger flexion peaked significantly later in the ipsilateral than in the contralateral hemisphere ($P < 0.05$). In addition, the contralateral rebound peaked later for the dominant hand extension than flexion ($P < 0.01$).

3.2. Differences in beta modulation strengths between TD and CP

Fig. 3A illustrates the grand averaged beta power modulation curves for the proprioceptive stimulation separately for all three participant groups (TD, DP, and HP). Beta modulation responses are presented to the dominant and non-dominant hand stimulation in both the contra and ipsilateral hemispheres. Fig. 3B shows the relative peak strengths of beta suppression and rebound determined from the beta modulation curves.

3.2.1. DP versus TD

Suppression. Relative suppression strengths appeared to be stronger in DP compared to TD. However, the statistical significance was exceeded only in the contralateral hemisphere for the

Beta rhythm modulation in TD participants (N = 32)

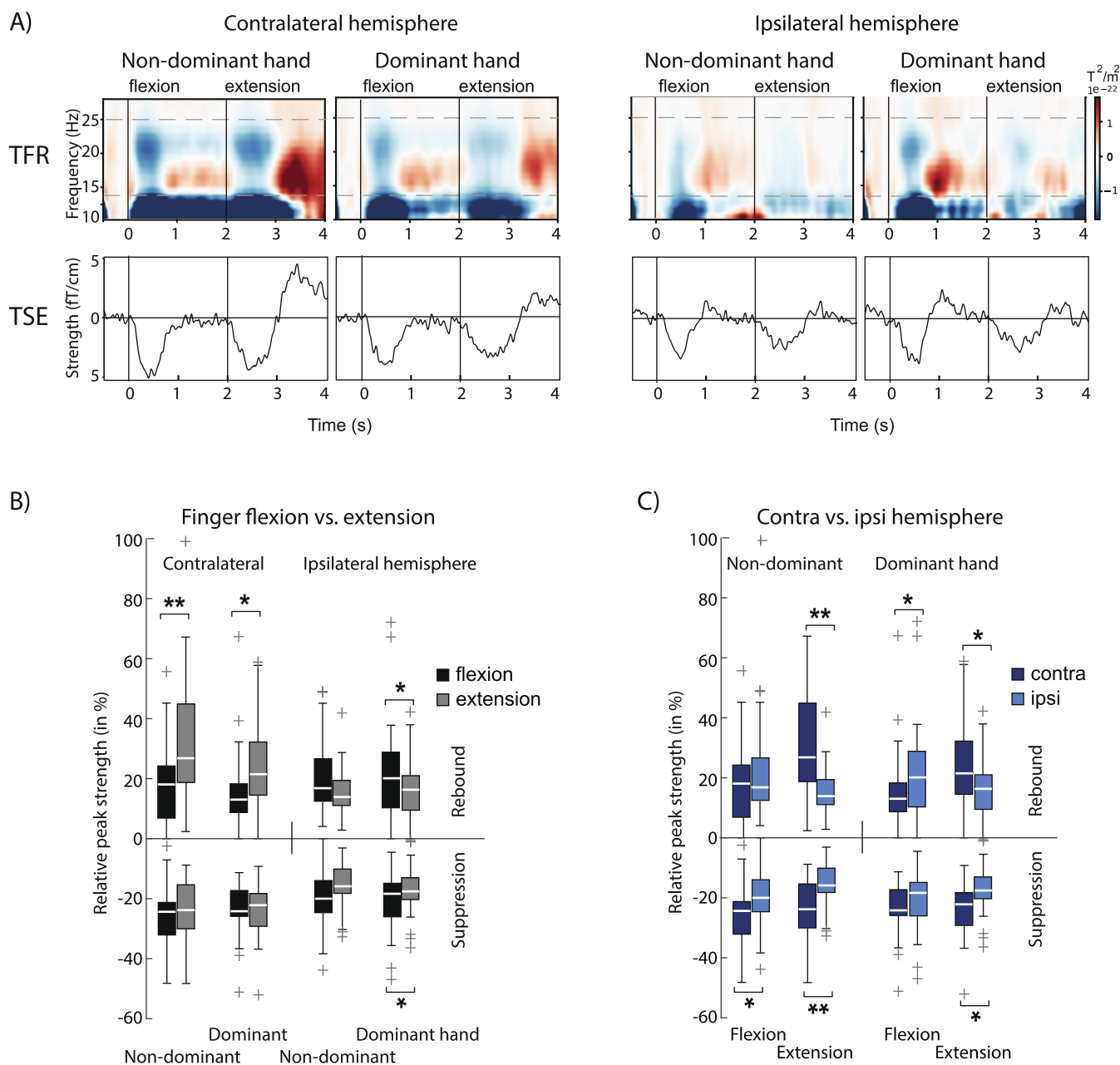


Fig. 2. Modulation of the beta power to the proprioceptive stimulation of index finger in both flexion and extension directions in typically developed (TD) adolescents. (A) Grand averaged time–frequency representation (TFR) images and temporal spectral evolution (TSE) curves for contra- and ipsilateral hemispheres in response to stimulation of the dominant and non-dominant hand. The grey dotted lines in the TFR image show the common beta band frequency. Boxplots show relative strengths of the suppression and rebound. (B) presents a comparison of finger flexion and extension, and (C) a comparison of contra- and ipsilateral responses. The asterisks in the images indicate significant differences. In the boxplots, the boxes include 50 % of the data points and the white lines inside the boxes indicate median values. The whiskers illustrate the range of data, and the crosses outside the whiskers indicate data outliers. Statistical significances are denoted as * $P < 0.05$ and ** $P < 0.001$.

dominant hand finger flexion showing stronger suppression in DP than in TD participants ($-30 \pm 1.9\%$ vs. $-24 \pm 1.5\%$, $P < 0.05$).

Rebound. The ipsilateral rebound was weaker for the non-dominant hand finger flexion in DP ($12 \pm 3.3\%$) than in TD ($20 \pm 2.1\%$, $P < 0.05$), and respectively for the dominant hand finger flexion ($9 \pm 1.8\%$ vs. $22 \pm 2.9\%$, $P < 0.01$). Differences between contralateral rebound strengths for the dominant and non-dominant hand finger flexion and extension were non-significant between DP

and TD ($P = 0.06 - 0.47$). All values of the relative strengths are presented in Table 2.

3.2.2. DP versus HP

Beta power suppression strengths between DP and HP were non-significant. Ipsilateral rebounds for the finger flexion were weaker in DP than HP participants (non-dominant $12 \pm 3.3\%$ vs. $25 \pm 3.7\%$, $P < 0.01$, and dominant $20 \pm 2.8\%$, $P < 0.01$ hand). In

Table 2
Relative strengths and latencies (mean \pm SEM) of the beta suppression and rebound.

	Suppression							
	Contralateral response				Ipsilateral response			
	Non-dominant		Dominant		Non-dominant		Dominant hand	
	flexion	extension	flexion	extension	flexion	extension	flexion	extension
TD (N = 32)								
Strength, %	-26 \pm 1.8	-19 \pm 1.9	*-24 \pm 1.5	-24 \pm 1.5	-24 \pm 1.9	-16 \pm 1.4	-21 \pm 1.6	-17 \pm 1.4
Latency, ms	429 \pm 30	498 \pm 31	*442 \pm 34	527 \pm 30	477 \pm 25	552 \pm 25	*545 \pm 39	649 \pm 35
DP (N = 12)								
Strength, %	-27 \pm 2.4	-26 \pm 2.7	*-30 \pm 1.9	-27 \pm 3.0	-23 \pm 2.9	-21 \pm 3.1	-22 \pm 2.8	-20 \pm 2.6
Latency, ms	460 \pm 63	461 \pm 53	489 \pm 49	515 \pm 51	537 \pm 38	566 \pm 68	425 \pm 36	578 \pm 63
HP (N = 16)								
Strength, %	-22 \pm 2.4	-21 \pm 2.8	-24 \pm 1.9	-24 \pm 1.8	-16 \pm 1.7	-14 \pm 1.4	-16 \pm 2.7	-17 \pm 3.0
Latency, ms	448 \pm 42	532 \pm 69	455 \pm 48	521 \pm 54	466 \pm 58	484 \pm 56	398 \pm 40	514 \pm 56
	Rebound							
	Contralateral response				Ipsilateral response			
	Non-dominant		Dominant		Non-dominant		Dominant hand	
	flexion	extension	flexion	extension	flexion	extension	flexion	extension
TD (N = 32)								
Strength, %	18 \pm 2.4	34 \pm 3.8	15 \pm 2.4	24 \pm 2.5	*20 \pm 2.1	16 \pm 1.5	*22 \pm 2.9	16 \pm 1.6
Latency, ms	1281 \pm 76	1468 \pm 52	*1204 \pm 70	*1514 \pm 38	1227 \pm 62	1353 \pm 61	1281 \pm 64	1415 \pm 59
DP (N = 12)								
Strength, %	10 \pm 2.8	22 \pm 3.8	12 \pm 3.9	20 \pm 3.9	*12 \pm 3.3	12 \pm 2.8	*9 \pm 1.8	*10 \pm 1.6
Latency, ms	1300 \pm 102	1352 \pm 114	*1611 \pm 66	1495 \pm 108	1338 \pm 78	1290 \pm 88	1242 \pm 98	1369 \pm 104
HP (N = 16)								
Strength, %	19 \pm 2.6	25 \pm 4.7	19 \pm 3.3	36 \pm 7.1	*25 \pm 3.7	18 \pm 2.7	*20 \pm 2.8	*19 \pm 2.4
Latency, ms	1107 \pm 91	1325 \pm 81	*1142 \pm 64	1465 \pm 55	1170 \pm 76	1344 \pm 86	*1017 \pm 74	1271 \pm 94

TD, typically developed; DP, diplegic; HP, hemiplegic.

*P < 0.05.

addition, ipsilateral rebound for finger extension was weaker in the dominant hand in DP than in HP (10 \pm 1.6 % vs. 19 \pm 2.4 %, P < 0.05).

3.2.3. HP versus TD

Contralateral and ipsilateral beta modulation strengths for the finger flexion or extension did not show significant differences between the HP and TD. More accurate beta modulation strengths are shown in Table 2.

3.3. Differences in beta modulation latencies between TD and CP

Rebound latency in the contralateral hemisphere to the dominant hand finger flexion was delayed when comparing DP to TD (P < 0.01) and HP (P < 0.01), and in the ipsilateral hemisphere when comparing the TD and HP (P < 0.05) participants. Differences in suppression latencies between the TD, HP, and DP participants were non-significant (P = 0.09–0.85). Latencies are presented in Table 2.

4. Discussion

Our unique proprioceptive-stimulation design revealed new insights into the regulation of excitation and inhibition balance in SM1 cortices contra- and ipsilateral to the stimulated hand in typically developed controls and adolescents with CP. Firstly, our results indicated that the cortical inhibition (i.e., the beta rebound) related to the processing of the evoked proprioceptive afference in the SM1 cortex was weaker particularly in the ipsilateral hemisphere in diplegic CP when compared to hemiplegic CP or typically developed peers. This result suggests predominant impairment of the cortical inhibition in diplegic CP, which may be due to deficient intra- and/or interhemispheric inhibitory regulation. Secondly, stronger contralateral beta suppression was observed in DP, indicating increased cortical excitation and activation possibly due to

a lack of inhibition. A secondary finding among the typically developed controls was that there were significant differences in the beta suppression and rebound between the direction of proprioceptive finger stimulation (finger flexion vs. extension) and between hemispheres (contralateral vs. ipsilateral). These findings in the controls may reflect the importance of interhemispheric inhibition needed in fine motor control of the hands.

4.1. Altered excitation-inhibition balance of the SM1 cortex in CP

To the best of our knowledge, current results of beta modulation changes are the first ones to indicate differences between HP and DP in their SM1 cortex excitation and inhibition during cortical processing of somatosensory afference. Beta modulation to the proprioceptive stimulation was significantly altered in diplegia, while only minor alterations were observed in hemiplegia. In the contralateral SM1 cortex, the beta suppression was stronger in DP, whereas respective beta rebounds were at a similar level. In the ipsilateral SM1 cortex, the beta rebound was significantly weaker, suggesting that the ipsilateral hemisphere plays a particularly important role in proprioception-mediated cortical inhibitory regulation. Our observations presumably indicate a widespread disruption of the excitation and inhibition of the SM1 cortices in the group of DP.

Pihko et al. (2014) demonstrated that the contralateral SM1 cortex beta power suppression and rebound to median nerve stimulation were weaker in the lesioned, but not in the structurally intact hemisphere in hemiplegic CP children, which also appears to be the case in the current study. In individuals with diplegic CP, a goal-directed isometric task of the knee joint has been shown to produce stronger beta suppression both during the planning and execution of the movement (Kurz et al., 2017), whereas a button-pressing task showed weaker beta rebound when compared to healthy controls (Hoffman et al., 2019). Furthermore, a more

Beta power modulation in CP and TD adolescents

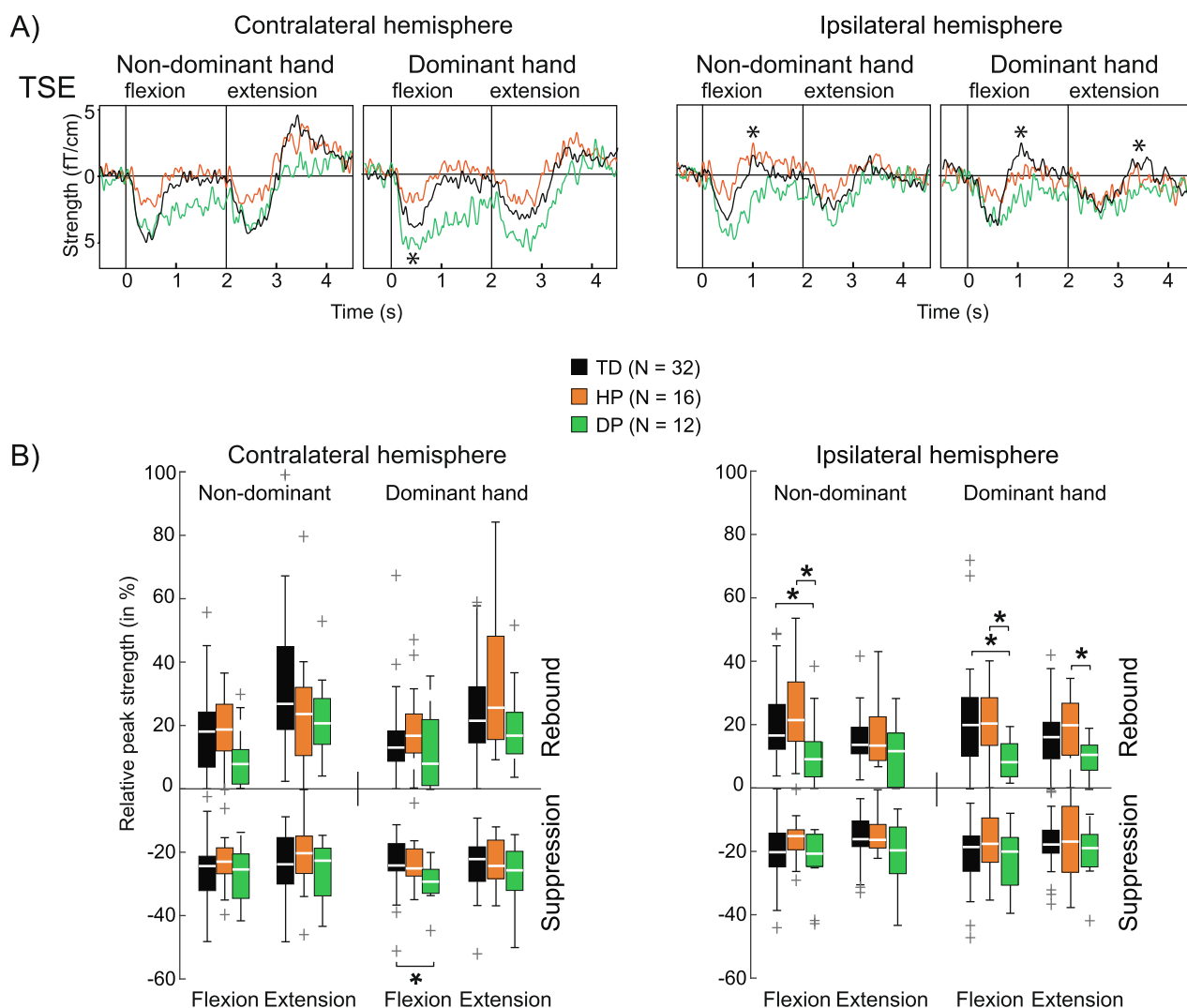


Fig. 3. Strength of the beta suppression and rebound for the proprioceptive finger stimulation in cerebral palsy (CP) and typically developed (TD) adolescents. (A) Grand averaged temporal spectral evolution (TSE) curves illustrate the strength and timing of the beta power modulation in relation to the onset of the finger flexion and extension in TD, diplegic CP (DP), and hemiplegic CP (HP) participants. The asterisks show the location of the significant differences between the groups. (B) Boxplots of relative strengths of the suppression and rebound separately in TD, HP, and DP participants. The asterisks indicate significant differences ($* P < 0.05$) in strengths between the groups.

complex volitional dual cognitive-motor finger task has been shown to reduce both beta suppression and rebound in diplegic and hemiplegic CP (Trevarrow et al., 2022). However, in the aforementioned studies, the sample sizes have been limited, experimental setups variable, and clinical conditions heterogeneous, it is hard to draw precise conclusions about the alterations of the SM1 cortical excitation and inhibition in CP.

4.1.1. Stronger beta suppression in diplegia suggests hyperexcitation of the SM1 cortex?

Beta suppression is suggested to be a result of activation and excitation of the SM1 cortex due to peripheral somatosensory afference via the thalamocortical pathway, thus reflecting the SM1 cortex activation/excitation (Hall et al., 2011; Neuper et al., 2006). Abnormally strong beta suppression has previously been observed with the voluntary movement of the knee joints in diplegic and hemiplegic CP (Kurz et al., 2017, 2014). We observed strong contralateral beta suppression to passive finger movements in

individuals with diplegic CP. These results are supported by a recent fMRI study (partly from the same children with CP than in the present study), which showed stronger contralateral SM1 cortex activation to the proprioceptive finger stimuli in CP when compared to TD (Nurmi et al., 2021). The exceptionally strong contralateral cortical excitation in the current study may reflect difficulties in perceiving, performing, and maintaining well-balanced hand movements (Brun et al., 2021). However, weak beta suppression has also been associated with slow reaction time and worse motor performance of the hand (Hoffman et al., 2019; Trevarrow et al., 2022). Diminished proprioceptive afference or its impaired cortical processing may hinder the brain's capacities to acquire an accurate estimate of the internal state of the locomotor system through proprioception, e.g., the position and movement of limbs and joints within the body. Moreover, the stronger suppression may reflect the activation of more extensive networks of the brain, and thus a more non-specific and less efficient function of the SM1 cortex.

4.1.2. Weaker beta rebound in diplegia suggests impaired inhibition of the SM1 cortex?

Abnormal ipsilateral SM1 cortex beta rebound has not been detected earlier in CP when using MEG or EEG. However, the current study was the first one in the proprioceptive domain. The weaker beta rebound of the ipsilateral SM1 cortex in DP may indicate inadequate intra- and/or interhemispheric inhibition of the ipsilateral SM1 cortex (Cassim et al., 2001; Houdayer et al., 2006; Neuper et al., 2006). Premature infants' brain is known to be particularly sensitive to white matter damage, which is largely the result of impaired oligodendrocyte maturation and consequent deficient myelination of white matter axons (Back, 2017). Moreover, perinatal brain injury has been shown to lead to the loss of GABAergic inhibitory interneurons in the grey matter as well as in white matter pathways (Robinson et al., 2006; Stolp et al., 2019).

Interhemispheric pathways have been shown to play an essential role in inhibitory sensorimotor control (Takeuchi, Oouchida, and Izumi, 2012) and may thus explain the disturbance in the cortical excitatory-inhibition balance observed bilaterally in our DP group. Afferent and efferent sensorimotor pathways in CP have been shown to have a loss of integrity and a deficit in inhibitory control of the spinal cord motoneurons has been shown to correlate with the severity of motor impairments in diplegic adults (Condliffe et al., 2016; Scheck et al., 2012). However, in a recent study, it was demonstrated that only weaker beta suppression was associated with greater loss of spinal cord total and white matter cross-sectional areas in a diplegic CP population (Trevarrow et al., 2022). Therefore, the impaired inhibitory regulation of the SM1 cortex in CP likely results from widespread neurodevelopmental structural and functional deficits throughout the sensorimotor system, causing heterogeneous sensorimotor impairments depending on the damaged structure(s), the extent of the damage and the related neurodevelopmental consequences.

4.1.3. Possible mechanisms of different excitation and inhibition impairments between DP and HP

Differences in cortical excitation and inhibition between DP and HP arise from the different timing of their initial brain injury. In DP, brain injury occurs often in the early third trimester and typically affects periventricular structures, causing white matter damage accompanied by widespread developmental disruptions in the grey matter growth (Back, 2017; Reddihough and Collins, 2003). In HP, brain insults commonly occur at the end of the third trimester due to middle cerebral artery injuries, leading often lesions located unilaterally in grey matter (Jaspers et al., 2016; Krägeloh-Mann, 2004; Krägeloh-Mann and Horber, 2007). The underlying structural changes are not restricted to visible lesions but affect many other structures of the central nervous system. Pathways contributing to the sensorimotor network, such as the corticospinal, thalamocortical, and callosal tracts, are shown to be widely affected both in hemiplegic and diplegic CP (for a review see Scheck et al., 2012) and seem to contribute to the sensorimotor performance (for a review see Mailleux et al. 2020). Furthermore, the cortical organization can be altered which can be seen i.e., in the finger somatotopy of the primary somatosensory cortex in diplegic and hemiplegic CP (Papadelis et al., 2014). Despite the wide evidence of altered brain structure in CP, there is little research on the differences between hemiplegic and diplegic patients. A recent study using the same dataset as here demonstrated that the cross-sectional area of the corpus callosum was more significantly reduced in hemiplegic CP whereas diplegic patients seemed to have more extensive microstructural damage along the callosal sensorimotor pathway (Jaatela et al., 2023). In addition, an enlarged proportion of uncrossed ipsilateral efferent corticospinal projections from the undamaged hemisphere to the brain stem and spinal cord has been observed especially in HP depending on

the timing and size of the brain injury (Jaspers et al., 2016; Thickbroom et al., 2001; Thomas et al., 2005). The additional connections have been suggested to be a compensatory mechanism for retaining control of the affected hand. These varying impairments in the sensorimotor function and pathways may cause different degrees of somatosensory, proprioceptive, and motor abnormalities. We suggest that the sensorimotor neuronal networks are more extensively affected in DP compared to HP, which is evidenced in functional level as weaker ipsilateral inhibition and stronger contralateral excitation of the SM1 cortex in DP. Different etiology between the diplegic and hemiplegic CP groups (Fehlings et al., 2021) is therefore likely to explain some of the differences observed in beta modulation in the present study.

4.2. Modulation of the SM1 cortex beta power in healthy controls

The results of healthy controls showed an interaction in rebound strengths between hemisphere and movement direction, and hemisphere and hand, while no interactions were found for suppression strengths. Closer inspection showed that finger flexion and extension induced a different degree of beta suppression and rebound both in the contra- and ipsilateral hemispheres in our sample of healthy adolescents. Thus, movement-direction-specific differences in cortical proprioceptive processing can be detected using proprioceptive stimulation in MEG.

4.2.1. Finger extension elicited strong contralateral beta rebound in healthy individuals

The extension of the index finger (i.e., the stretch of finger flexor muscles) generated stronger contralateral beta rebounds compared to finger flexion (i.e., the stretch of the finger extensors), whereas no similar differences were observed for beta suppression. Beta suppression is generally known to be more stable than rebound to different stimuli as well as changes in stimulus properties, such as speed, length, and range of movement (Cassim et al., 2000; Fry et al., 2016; Gerloff and Andres, 2002; Houdayer et al., 2006; Zhang et al., 2020). As the antagonist's muscles, the finger flexors and extensors are functionally overlapping but have largely specific roles, which likely explains why the proprioceptive afference arising primarily from the muscle spindles (i.e., muscle afferents) are processed differently in the cortex. In our design, the finger flexors were in a more pre-stretched initial position compared to the extensors. This position likely enhanced the mechanical conduction of the extension-movement evoked stretch of the flexor muscles and its muscle spindles, by limiting the tendon slack. This may have produced a stronger or temporally synchronous volley of proprioceptive afference to the cortex. However, it is known that muscle spindles are extremely sensitive detecting even a few μm movements (as low as 5 μm during vibration) of their parent muscle (Brown et al., 1998), thus the spindles were very likely efficiently activated also in extensor muscles during the finger flexion, but probably in a less synchronous manner.

4.2.2. Dominant hand finger flexion elicited strong ipsilateral beta suppression and rebound in healthy individuals

A unilateral somatosensory afference arising from the right or left hand is known to modulate the SM1 cortex beta rhythm in both hemispheres. The somatosensory signal from the contralateral to the ipsilateral hemisphere is mediated via interhemispheric callosal connections. These transcallosal pathways are thought to play a significant role in interhemispheric inhibition (Carson, 2005; Swayne et al., 2006; Takeuchi et al., 2012). Furthermore, it has been proposed that ipsilateral brain activation during unilateral active hand tasks is regulated by inhibitory neural mechanisms, which it suggested to be particularly relevant in motor control, such as coordination and fine-tuning of skilled hand

movements (Bueteftisch et al., 2014; Reid and Serrien, 2014; Tinazzi and Zanette, 1998). In addition, intrahemispheric GABAergic interneurons have been shown to have a significant role in the inhibitory regulation of the SM1 cortex. MEG studies have demonstrated that GABAergic drugs affect especially the strength of SM1 beta rebound (Hall et al., 2011; Muthukumaraswamy et al., 2013), and GABA concentrations measured by magnetic resonance spectroscopy correlate with beta rebound strength (Gaetz et al., 2011), which indicates that beta rebound reflects an inhibitory SM1 cortex function. The beta rebound typically appears to be stronger in the contralateral hemisphere with somatosensory stimulation or movement of the hand, whereas beta suppression is equally strong in both hemispheres (Fry et al., 2016; Salenius et al., 1997; Salmelin and Hari, 1994). However, we detected inter-hemispheric differences in the rebound strengths between finger flexion and extension in healthy individuals. A strong ipsilateral rebound for finger flexion may reflect the importance of inter-hemispheric inhibitory regulation at the beginning of the movement. As this was more pronounced in the dominant hand, it may indicate an emphasis on the inhibitory neural mechanism on the fine motor skills of the dominant hand. Our study was not designed to examine the effect of the proprioceptive stimulation features on beta modulation, but indeed the evoked movement appears to provide well controlled and naturalistic design to study these effects on the excitatory-inhibitory balance in the SM1 cortices.

5. Perspectives and limitations

A wide range of rehabilitation approaches have been used to improve the motor function of CP patients, but only a few of them have shown to be sufficiently effective (Novak et al., 2013). In addition to new more effective rehabilitation approaches, novel tools are needed to evaluate the effectiveness of therapies and rehabilitation methods in a reproducible way both at behavioral and cortical levels. Readily measurable cortical beta rhythm modulation to somatosensory stimulation has shown to be a feasible measure of the SM1 cortex function (Laaksonen et al., 2012; Parkkonen et al., 2018; Tang et al., 2020). Therefore, it is suggested as a neurophysiological biomarker for detecting rehabilitation-related changes in the SM1 cortex excitation and inhibition in CP in proprioceptive and other somatosensory domains. However, it is good to note that cortical lesions can alter the shape of the cerebral cortex which may affect the detectability of the cortical oscillations when using MEG. MEG signal strength is sensitive to the orientation and depth of the cortical source (Hämäläinen et al., 1993; Hillebrand and Barnes, 2002), but this effect should be random in group patients with cortical lesions. Nevertheless, MEG is an excellent method for detecting cortical activity, especially in hand regions of the SM1 cortex. Therefore, beta modulation provides a feasible approach to monitoring the effects of rehabilitation on the SM1 cortex function.

In this study, the individually determined frequency band for peak beta modulations was used, because the frequency band could have been specific in children compared to the frequency band typical for adults. However, the beta modulation peaked at a similar 13–25 Hz band in children as previously shown for adults (Illman et al., 2020), and therefore the fixed 13–25 Hz band is feasible in further studies examining beta modulation in children.

Beta modulation can be induced with various sensory stimuli and motor tasks. Mechanical tactile and proprioceptive stimuli have been shown to generate similar and highly reproducible beta rhythm modulations, which is an essential feature for the usability of biomarkers, especially in follow-up studies (Illman et al., 2022). The novel proprioceptive stimulation in the current study offers a new approach for detecting SM1 cortex beta power modulations

that can be used to quantify interhemispheric excitation-inhibition balance in the proprioceptive domain. The effect of kinematic features of the proprioceptive stimulation itself could be further investigated, whether, e.g., certain movement velocity or range would optimize the strength of the induced responses in MEG. However, a recent study from healthy adults indicated that beta modulation is not highly sensitive to the kinematic features of the proprioceptive stimuli, such as speed or the range of the evoked finger movement (Nurmi et al., 2023). Finally, our findings from the index finger cannot be readily transferred to other joints and limbs, as beta modulation may be muscle, muscle group, and joint specific.

6. Conclusion

Our results provided new insights into the neural excitation and inhibition balance between the SM1 cortices both in adolescents with CP and their typically developed peers. Our novel proprioceptive stimulation induced a peculiarly strong inhibition in the hemisphere ipsilateral to finger-flexion stimuli in healthy adolescents. This inhibition was found to be significantly reduced in adolescents with diplegic CP, and their contralateral hemisphere exhibited emphasized excitation, whereas no similar alterations were observed in adolescents with hemiplegic CP. These disturbances in cortical excitation-inhibition balance in diplegic CP are suggested to arise from extensively altered sensorimotor networks and impaired integration between the related interhemispheric SM1 cortices resulting in multifaceted sensorimotor impairments. Since these disturbances are lifelong, appropriate timing and effectiveness of rehabilitation methods play an important role in improving the quality of life in children with CP. Therefore, comprehensive cortical and behavioral measures are needed to evaluate the effectiveness of rehabilitation in both hemiplegic and diplegic CP. In this evaluation, the SM1 cortex beta rhythm modulation can be proposed as a possible biomarker to detect changes in cortical excitation and inhibition.

CRedit Author Statement

All the authors contributed to the Conceptualization, and Writing – review & editing of the manuscript. M.I. was responsible for Investigation, Analysis, Methodology, Validation, Visualization, Writing – the original draft and review & editing of the manuscript. H.P. was also responsible for Investigation, Funding acquisition and Supervision, and J.J. T.N. and J.V. contributed to the Investigation and J.J. and J.V. to the Formal analysis.

Conflict of Interest

None of the authors have potential conflicts of interest to be disclosed.

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