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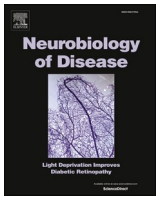

Differential induction of Parieto-motor plasticity in writer's cramp and cervical dystonia

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ABSTRACT

Objectives: To investigate the plastic effects of parieto-motor (PAR-MOT) cortico-cortical paired associative paired stimulation (cc-PAS) in patients with two forms of focal dystonia, writer's cramp and cervical dystonia, compared to healthy volunteers (HVs).
Methods: We used cc-PAS to induce associative plasticity using repeated time-locked paired transcranial magnetic stimulation (TMS) pulses over the parietal and motor cortices in 16 patients with writer's cramp (WC), 13 patients with cervical dystonia (CD), and 23 healthy volunteers. We measured parieto-motor corticocortical connectivity using posterior parietal cortex (PPC) to primary motor cortex (M1) facilitation and input-output curves (IOC) of the motor-evoked potential (MEP) before and after PAR-MOT cc-PAS. The PAR-MOT cc-PAS consisted of 100 pairs of TMS pulses every 5 s, with the conditioning pulse applied to the left angular gyrus in the intraparietal sulcus and the test pulse applied to the M1 hotspot of the first dorsal interosseous muscle.
Results: The cc-PAS increased the area under the IOC by increasing its maximum level in patients with WC but not in patients with CD or healthy volunteers. The cc-PAS had no significant effect on other IOC parameters. There were no significant differences in PPC to M1 facilitation changes after PAR-MOT cc-PAS among all groups.
Conclusions: This study suggests that PAR-MOT cc-PAS abnormally increases M1 excitability in patients with WC but not in those with CD. Additionally, this increased plastic response in patients with WC does not appear to be directly linked to PPC to M1 corticocortical connectivity.

1. Introduction

Focal dystonia, which includes focal hand dystonia and cervical dystonia (CD), is a neurological disorder thought to arise from abnormal connectivity between various brain regions responsible for precise movement control (Conte et al., 2019b; Jinnah et al., 2017; Schirinzi et al., 2018). Although the exact pathology of dystonia is unknown, numerous studies using transcranial magnetic stimulation (TMS) and neuroimaging techniques have provided insights into the pathophysiology of this disorder. The network hypothesis proposes that dystonia is a brain connectivity disorder that involves the basal ganglia, cerebellum, thalamus, primary sensorimotor areas, associative sensory cortex, premotor cortex, and supplementary motor cortex (Hallett et al., 2017; Jinnah et al., 2017). Disturbances in sensorimotor integration are

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a hallmark of dystonia, suggesting the presence of abnormal communication between the motor and sensory areas (Hallett, 2006; Lin and Hallett, 2009; Patel et al., 2014). Sensorimotor integration plays a critical role in the efficient execution of motor function, and deviations in this integration, resulting in compromised motor function, have been observed in patients with focal dystonia (Conte et al., 2019a; Patel et al., 2014). The posterior parietal cortex (PPC) is a crucial node for sensory and motor integration and participates in skilled motor actions (Koch et al., 2007; Koch et al., 2008; Vesia et al., 2013). Writer's cramp (WC), the most frequent form of focal hand dystonia, and CD are common forms of focal dystonia characterized by involuntary muscle contractions and abnormal postures that affect a specific body region (Albanese et al., 2013; Cohen and Hallett, 1988; Defazio et al., 2013). WC is considered a task-specific dystonia (TSD) associated with repetitive motor actions executed in the frame of functional alterations in fine motor skill circuits (Lin and Hallett, 2009; Shamim et al., 2011), whereas CD is not associated with any specific fine motor action. Consequently, there may be differences between the pathophysiology of TSD, such as WC, and non-task-specific dystonia (NTSD), such as CD. However, studies that directly compare these two conditions are scarce (Bianchi et al., 2019; Ramdhani et al., 2014; Tomić et al., 2021).

Corticocortical paired associative stimulation (cc-PAS) is a repetitive transcranial magnetic stimulation (TMS) method that induces long-term potentiation or depression-like plasticity. This technique can be used for assessing the pathophysiology of neurological disorders and fostering expectations for therapeutic purposes (Guidali et al., 2021; Koch, 2020; Koch et al., 2013). Dual-sites TMS paradigms can probe the corticocortical connections between two brain regions, for example, the posterior parietal cortex (PPC) and the ipsilateral motor cortex (M1). Conditioning TMS pulse of PPC increases the excitability of ipsilateral M1, suggesting the existence of facilitatory interaction between PPC and M1 mediated by specific interneurons.

This study aimed to determine whether the plastic effects of parieto-motor (PAR-MOT) cc-PAS differ between healthy volunteers (HVs) and patients with one of the two forms of focal dystonia (WC and CD) or between patients with WC and those with CD. The primary outcome was the change in M1 excitability in response to PAR-MOT cc-PAS in individuals with focal dystonia and HVs. We also investigated whether the PAR-MOT cc-PAS induced any changes in the discrete PPC to M1 interaction, as quantified using the dual-site TMS paradigm.

2. Materials and methods

2.1. Participants

This study included right-handed patients with confirmed WC (N = 16, WC group) and CD (N = 13, CD group), aged between 18 and 65 years. Patients with secondary forms of dystonia, including tardive dyskinesia and dystonic tremors (in which the tremor was the sole or principal abnormality), were excluded. All patients were examined at least 3 months after the last botulinum toxin injection. All participants were instructed to abstain from using any anticholinergics and benzodiazepines for at least five plasma half-lives of the respective drug prior to study participation. All participants were examined by board-certified neurologists who used the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for patients with CD and the Writer's Cramp Impairment Scale (WCIS) for those with WC. All WC patients were affected in their right hand. The direction of head and neck posture in CD patients is presented in Table 1.

The patients were recruited from the Movement Disorders Clinic of the National Institute of Health (NIH). HVs (N = 23) were recruited from a local community during the same period. The participants provided written informed consent for this study, which was approved by the National Institutes of Health Institutional Review Board and the NINDS Scientific Review Committee. All research was performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

Table 1
Demographic characteristics.

	HV (n = 23)	WC (n = 16)	CD (n = 13)
Age (years)	50.4 ± 10.7	52.4 ± 11.3	56.5 ± 5.1
WCIS score		23.1 ± 6.4	
Affected hand		Right 16, Left 0	
TWSTRS score			29.5 ± 16.1
Direction of Torticollis			Right 6, Left 7
Disease duration		19.1 ± 12.2	13.5 ± 9.7

WCIS, Writer's Cramp Impairment Scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; HV, healthy volunteers; WC, patients with writer's cramp; CD, patients with cervical dystonia.

2.2. Experimental setup

The experimental setup is shown in Fig. 1. Briefly, the input-output curve (IOC) and PPC to M1 connectivity were measured at the baseline, and the measurements were repeated at three different time points following the cc-PAS application.

2.3. Experimental protocol

2.3.1. Recording setup

Electromyographic (EMG) activity was recorded from the right first dorsal interosseous (FDI) muscle to capture the amplitude of motor-evoked potentials (MEPs) using disposable surface silver-silver chloride electrodes. The electromyography (EMG) signal was amplified using a conventional EMG machine with a bandpass filter of 10 and 2000 Hz. The signal was digitized at a frequency of 5 kHz and fed to a computer for offline analysis. Impedance was maintained below 10 kΩ.

The TMS test coil (a figure-of-eight-shaped coil with an external loop diameter of 60 mm, MagStim) was positioned over the left M1 on the motor hotspot of the right FDI (the site eliciting the maximum MEP amplitude for any given intensity) and connected to Bistim^{200}2 (MagStim). The coil orientation was kept tangential to the skull with the handle pointing backward and laterally at an angle of approximately 45° to produce a posteroanterior current perpendicular to the central sulcus. The precise position of each participant's FDI hotspot was empirically determined, stored, and monitored throughout the experimental sessions using a neuronavigation system and the study participant's own magnetic resonance imaging (MRI)-based three-dimensional

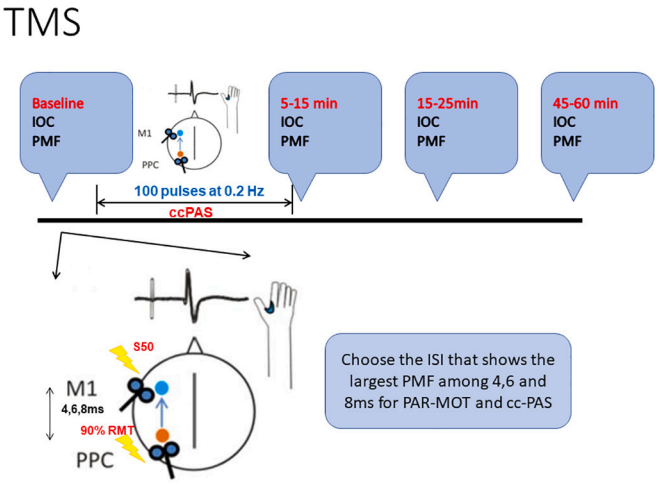

Fig. 1. The experimental protocol. The input-output curve (IOC) and parieto-motor facilitation (PMF) were measured at the baseline and the measurements were repeated at 5–15 min, 15–25 min and 45–60 min following the parieto-motor cortico-cortical paired associative stimulation (PAR-MOT cc-PAS). Interstimulus interval (ISI) for PAR-MOT cc-PAS was chosen the ISI that showed the largest parieto-motor facilitation among 4,6 and 8 ms.

reconstruction (BrainSight, Rogue Research.).

2.3.2. IOC

The IOC was obtained by delivering single TMS pulses at intensities ranging from 0 % to 100 % (increasing at 5 % intervals) of the stimulator output every ~10 s, in a random order. Three pulses with different intensities were delivered. The MEPs were recorded and their amplitudes were plotted against the corresponding stimulation intensities and fitted with a sigmoid curve using the Boltzmann function. The Boltzmann function is given by the equation: MEP amplitude = offset + MEP_{max}/ (1 + exp. ((S50 – X)/k)), where MEP_{max} is the MEP amplitude at the plateau, S50 is the stimulation intensity required to obtain a response of 50 % of the maximum, X is the stimulation intensity (independent variable), and k is Boltzmann's slope parameter, the inverse of which is directly proportional to the maximum steepness function at S50 (Devanne et al., 1997). The resting motor threshold (RMT) was defined as the x-intercept of the line drawn tangential to the midpoint of the curve. To compare the IOC between participants, the MEP amplitudes for stimulation intensities ranging from 80 % to 200 % of the RMT were calculated from the individual curve equations and normalized to the individual participant's MEPmax. The normalized IOCs were used for statistical analysis. The IOCs were obtained at the baseline and at 5–15 min (T1), 15–25 min (T2), and 45–60 min (T3) after cc-PAS (Fig. 2).

2.3.3. PPC to M1 connectivity

The test coil was positioned over the motor hotspot of the right FDI and test stimulation (TS) at S50 intensity was delivered. The conditioning stimulation (CS) was delivered to the angular gyrus in the PPC at 90 % of the RMT. The angular gyrus was visually identified on individual anatomical MRI between the intraparietal and parieto-occipital sulci (Seghier, 2013). The coil was positioned with the handle pointing posteriorly and slightly medial to the interhemispheric line by 15°. This spot was found, stored, and monitored with the same MRI-based neuronavigation system as for the M1 (BrainSight), accommodating the simultaneous tracking of the two TMS coils over the two targets. We determined the optimal interstimulus intervals (ISI) for each participant to induce consistent PPC to M1 facilitation. To this end, CS was applied with three different ISIs of 4, 6, and 8 ms before TS (Karabanov et al., 2013; Koch et al., 2007). Forty trials were recorded, consisting of 30 paired CS + TS trials (10 trials per ISI) and 10 TS-alone trials. These trials were performed randomly every 5 s with a 5 % random variation in time. Facilitation was calculated at the end of the block by determining the relative increase in the peak-to-peak MEP amplitudes in the CS + TS stimulations with respect to those in the TS stimulations. For each trial, the ISI that showed the largest facilitation for cc-PAS and the repeated measurements of PPC to M1 facilitation at T1, T2, and T3 after cc-PAS.

2.3.4. PAR-MOT cc-PAS

The cc-PAS intervention consisted of delivery of the same paired stimulation 100 times every 5 s (without variation in time), with the CS applied to the PPC spot (intensity, 90 % RMT) and the TS applied to the FDI hotspot (intensity, S50) using the ISI, which showed the largest PPC to M1 facilitation at the baseline.

2.4. Outcome measures

The primary outcome measure was normalized IOC. We calculated the area under the curve (AUC) between 80 and 200 % RMT, normalized MEP at 200 % RMT (MEP_{max}), and the slope of the normalized IOC at S50. Secondary outcome measures were the RMT, MEP size at S50, and PPC to M1 connectivity. For exploratory outcome measures, we conducted a correlation analysis between disease duration or severity and primary outcome measures.

2.5. Statistical analysis

A power analysis was conducted to determine the appropriate sample size required to detect a significant effect of cc-PAS on motor cortical excitability. Based on the results of 15 HVs in a previous study (Chao et al., 2015), we estimated that a minimum of 17 HVs, 17 patients with WC, and 17 patients with CD would require 80 % power to detect the difference of 0.4 mV in MEP size at a significance level of 0.05. To the best of our knowledge, no prior study has used IOC as an outcome measure in the power analysis. We were unable to reach the enrollment target within a reasonable amount of time.

For TMS outcome measures, natural logarithmic transformation was applied to all outcome variables to fulfill the assumptions for parametric statistics. For each outcome variable, a two-way repeated-measures analysis of variance was performed to evaluate the effect of Group, Time, and the interaction between Group and Time. A significant interaction effect indicates that the time effect depends on the group categorization. Group categorization with three levels (HV, CD, and WC groups) was a between-subjects factor, and Time was a within-subjects factor. The Time factor had four levels: baseline (T0), T1, T2, and T3. The Dunnett–Hsu method was used for post-hoc testing, with the baseline as the control for time and HVs as the control for the group variable. Back-transformed least-squares means and 95 % confidence intervals are reported. Pearson correlation analysis was used to examine the correlation between disease severity (assessed using WCIS and TWSTRS for patients with WC and CD, respectively), disease duration, and changes in the IOC measures from the baseline at each time point.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA), and $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Patient demographics

Sixteen patients with WC (mean age: 52.4 ± 11.2 years, 9 women),

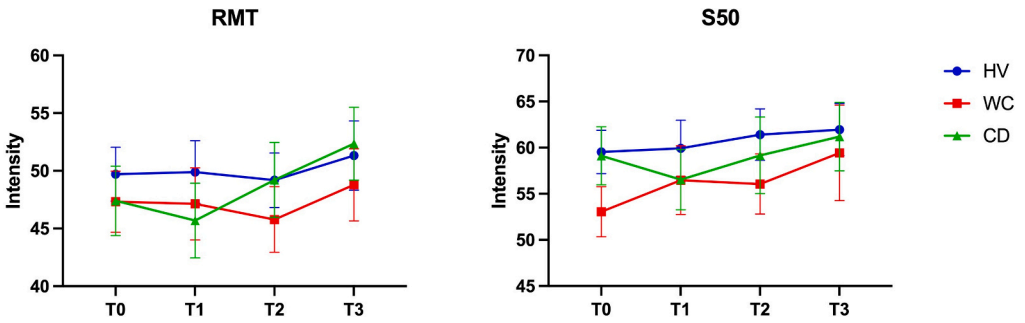

Fig. 2. The experimental protocol. The input-output curve (IOC) and parieto-motor facilitation (PMF) were measured at the baseline and the measurements were repeated at 5–15 min, 15–25 min and 45–60 min following the parieto-motor cortico-cortical paired associative stimulation (PAR-MOT cc-PAS). Interstimulus interval (ISI) for PAR-MOT cc-PAS was chosen the ISI that showed the largest parieto-motor facilitation among 4,6 and 8 ms.

and 13 patients with CD (mean age: 56.5 ± 5.1 years, 10 women) were enrolled, and all of them completed the study. Twenty-three age-matched HVs (mean age: 50.4 ± 10.7 years, 15 women) completed the study. No significant differences in age or disease duration were observed among the groups (Table 1).

3.2. Effect of cc-PAS on motor cortical excitability

There was no significant effect of Time (T0 − T3, $p = 0.55$), Group (HV, WC, and CD groups, $p = 0.37$), or Time–Group interaction ($p = 0.98$) on the RMT or S50. There were no significant changes in the RMT or S50 after cc-PAS in any of the groups (Fig. 2).

IOCs were obtained as a measure of motor cortical excitability (primary outcome measure). The application of cc-PAS shifted the IOC upward for the WC group but not for the CD or HV groups (Fig. 3). There was a significant effect of Group on the AUC ($F = 6.06$, $p = 0.007$) but no effect of Time ($F = 0.91$, $p = 0.44$) or Time–Group interaction ($F = 1.04$, $p = 0.41$). Tests of effect sizes showed group differences at T1, T2, and T3 ($p = 0.02$, $p = 0.006$, and $p = 0.006$, respectively) but not at the baseline ($p = 0.36$). *Post hoc* analysis showed that the AUC significantly differed between the WC and HV groups ($p = 0.006$) and between the WC and CD groups ($p = 0.02$) but not between the HV and CD groups ($p = 0.87$). A similar pattern was observed for the MEP_{max}. There was a significant effect of Group on the MEP_{max} ($F = 4.27$, $p = 0.03$) but no effect of Time ($F = 0.48$, $p = 0.70$) or Time–Group interaction ($F = 2.12$, $p = 0.06$). Tests of effect sizes indicated that the MEP_{max} differed between the groups at T1, T2, and T3 ($p = 0.03$, $p = 0.02$, and $p = 0.006$, respectively) but not at the baseline ($p = 0.95$). Testing of the effect sizes also showed that only the WC group demonstrated a significant effect of Time on the MEP_{max} ($F = 2.86$, $p = 0.05$). In contrast, there was no significant effect of Group ($F = 1.62$, $p = 0.22$), Time ($F = 1.05$, $p = 0.37$), or Time–Group interaction ($F = 0.89$, $p = 0.51$) on the IOC slope. Neither the absolute nor the relative changes in the IOC measures at T1, T2, and T3 were significantly correlated with disease duration or the WCIS or TWSTRS scores (exploratory outcome, Pearson correlation, data not presented graphically).

Changes in the MEP amplitudes at S50 in response to cc-PAS were compared among the HV, CD, and WC groups, with time (baseline, T1, T2, and T3) as a categorical variable (secondary outcome measure). There was no significant effect of Group ($F = 0.61$, $p = 0.55$), Time ($F = 2.33$, $p = 0.77$), or Time–Group interaction ($F = 1.15$, $p = 0.34$) on the changes in the MEP amplitudes.

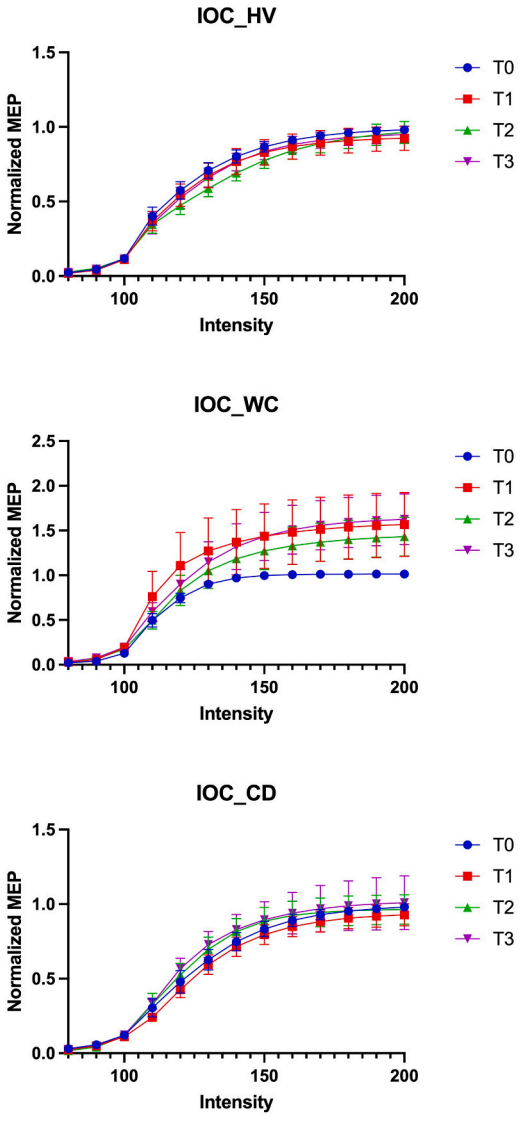

Fig. 3. The input-output curves before and after corticocortical paired-associative stimulation (cc-PAS) at different time points.
Normalized motor-evoked potentials are shown based on the increased stimulation intensities according to S50 at different time points after cc-PAS in the healthy volunteers (A), patients with writer's cramp (B), and patients with cervical dystonia (C). T0, T1, T2 and T3 represent the periods before cc-PAS and those 5–10 min, 15–25 min, and 45–60 min after cc-PAS, respectively. Asterisks indicate significant differences among groups.

3.3. Effect of cc-PAS on PPC to M1 connectivity

Time had a clear effect on PPC to M1 connectivity ($F = 16.4$, $p < 0.0001$). The degree of facilitation decreased after cc-PAS administration but did not turn inhibitory. There was no effect of Group ($F = 1.37$, $p = 0.27$) or Time–Group interaction ($F = 0.37$, $p = 0.89$) on PPC to M1 connectivity (Fig. 4).

4. Discussion

This study investigated the plastic responsiveness of PPC to M1 connectivity in patients with WC and CD compared to that in HVs. To this end, we used a corticocortical TMS technique with coils placed on the left angular gyrus and left M1. To determine whether the plastic effect developed at the corticocortical synapses or within the M1, we tested the effects of PAR-MOT cc-PAS on M1 excitability and the facilitatory effect of parietal stimulation on corticospinal excitability. This study has two main findings. First, PAT-MOR cc-PAS increased motor cortical excitability only in patients with WC but not in HVs or patients with CD. The plastic change induced by cc-PAS in patients with WC

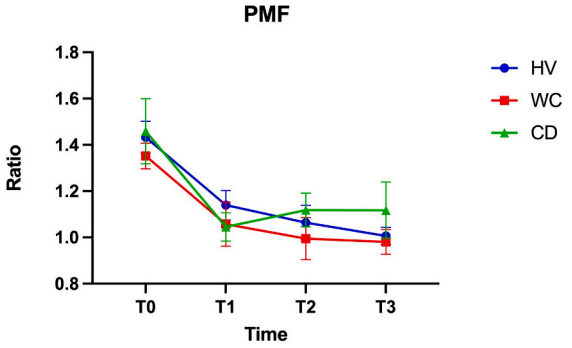

Fig. 4. Parieto-motor facilitation (PMF) expressed as ratio of conditioning motor evoked potential (MEP) and control MEP before and after corticocortical paired-associative stimulation at each time point in the healthy volunteers (circle), patients with writer's cramp (square), and patients with cervical dystonia (triangle).

became evident 5 min after cc-PAS and was still present at 60 min. Second, the PPC to M1 facilitatory connectivity reached similar levels in the HVs and patient groups, and cc-PAS had no significant effect on PPC to M1 facilitation across all groups. The cc-PAS attenuated the facilitatory effect of PPC to M1 in all groups to the same degree, without any differences between various time points.

Dual-site TMS paradigms have been developed to evaluate the physiological connections between various cortical areas (Koch, 2020). In the motor system, CS to the premotor cortex, supplementary motor area, and parietal cortex is known to modulate M1 excitability if applied before TS on the M1 with specific delays (Arai et al., 2012; Koch, 2020). The effect of the single-site paired-pulse TMS paradigm, in which CS facilitates or suppresses TS when applied on the M1 before TS within a certain interval, is well-known (Hallett, 2007). However, the exact mechanism of the dual-site TMS though which the CS affect the MEP size evoked by TS has not yet been clearly identified.

Previous studies have demonstrated that repeated application of cc-PAS can induce plastic changes in the cortex according to the stimulated site and the ISI between the CS and TS. In the motor system, the induction of long-term potentiation and depression in the response to cc-PAS can be probed by measuring changes in the MEP size of the M1. Chao et al. found that 100 repetitions of parieto-motor cc-PAS at a frequency of 0.2 Hz increased M1 excitability in HVs (Chao et al., 2015). Koch et al. also demonstrated Hebbian and anti-Hebbian spike-timing-dependent plasticity in the M1 after applying parieto-motor cc-PAS depending on the coil orientation in HVs (Koch et al., 2013). Contrary to previous studies, M1 excitability did not change in the HVs in our study. This discrepancy in findings can be explained by methodological differences. In this study, the PPC was stimulated using a neuro-navigation system to accurately target the angular gyrus, whereas in the study by Chao et al., the PPC was targeted using a 10–20 EEG system. Furthermore, we used individualized ISIs that produced the greatest facilitation of MEPs for cc-PAS instead of a fixed ISI used in previous studies(Chao et al., 2015; Koch et al., 2013). Our study assessed M1 excitability using the whole IOC, in contrast to previous studies that used an average of 10 MEPs generated by TS, producing 1 mV MEP at baseline. The choice of 1 mV as the baseline benchmark can be problematic in studies of excitability changes because its position in the IOC varies significantly from one individual to another. We did not observe any significant amplitude changes in the average of the 10 MEPs in any group in response to the cc-PAS, likely due to the use of the baseline S50 intensity for TS across all time points. Our study also used a distinctive methodology in terms of accurate PPC targeting using neuronavigation with individual brain MRI to confirm a functionally facilitatory PPC hotspot.

In our study, M1 excitability increased following PAR-MOT cc-PAS only in patients with WC. This finding suggests the presence of maladaptive plasticity in the M1 associated with sensorimotor connectivity in WC. Moreover, the increase in M1 excitability was not correlated with the severity of dystonia in patients with WC, suggesting that maladaptive plasticity may be related to specific circuit dysfunction in the parieto-motor network underlying the pathogenesis of WC rather than secondary changes due to clinical symptoms. In contrast, patients with CD did not demonstrate enhanced M1 plasticity. Our results support the hypothesis that the underlying pathophysiological mechanisms related to cortical plasticity differ between WC and CD. In previous studies, some common neurophysiological changes have been observed in WC and CD. Sensorimotor integration was impaired in the unaffected arm of patients with CD, and increased excitability in the M1 cortex, responsible for the unaffected hand in patients with CD, was observed (Edwards et al., 2006; Kimmich et al., 2014; Meunier and Hallett, 2005; Quartarone and Hallett, 2013; Quartarone et al., 2008). These findings suggest that physiological alterations in the brain may be endophenotypic traits of focal dystonia. However, application of repetitive TMS to the M1 hand region, which yielded clinical efficacy in patients with WC, did not result in clinical improvement in patients (Cho and Hallett, 2016; Shin and Hallett, 2020). Additionally, neuroimaging studies have shown that the pattern of structural changes differs between patients with TSD and those with NTSD (Bianchi et al., 2019; Fuertinger and Simonyan, 2018; Ramdhani et al., 2014; Tomić et al., 2021) The former group shows cortical thickening in areas related to sensorimotor processing, whereas the latter shows cortical thinning and decreased gray matter volumes in multiple regions involved in motor control and sensorimotor integration processes. These findings, in conjunction with the results of the present study, suggest that there may be a divergence in the pathophysiology of associative plasticity in CD and WC. Our hypothesis could have been more clearly proven if we had conducted PAR-MOT cc-PAS induced plasticity in the unaffected hemisphere (right hemisphere) in patients with WC. Therefore, we could not completely exclude the possibility that the difference in plasticity induced by PAR-MOT cc-PAS represents an epiphenomenon due to phenotypical differences between WC and CD.

Functional neuroimaging research has revealed widespread brain regions involved in the handwriting process, including the frontal, parietal, and temporal lobes, thalamus, putamen, and cerebellum (Gallea et al., 2016; Horovitz et al., 2013; Planton et al., 2013). Notably, the anterior portion of the left inferior parietal sulcus and posterior end of the superior frontal gyrus have been identified as central neural substrates underlying the handwriting process. A recent TMS study demonstrated enhanced functional connections between the anterior region of the intraparietal sulcus and the ipsilateral M1 during sensorimotor planning of grip, suggesting a close link of PPC to M1 connectivity with handwriting (Gallea et al., 2016; Horovitz et al., 2013; Vesia et al., 2013). Excessive repetition of a specific task in the presence of a deficit in homeostatic plasticity may result in aberrant plastic changes in the task-related brain areas. This may explain the task-specificity of maladaptive plasticity in certain cortical areas.

Chao et al. showed that PPC to M1 facilitation was attenuated with increasing M1 plasticity, and they proposed that the cc-PAS-induced M1 excitability increase may be the result of the modulation of inhibitory interactions between the parietal and motor cortices, with the attenuation of PPC to M1 facilitation being a consequence of increased M1 plasticity (Chao et al., 2015). Attenuation of PPC to M1 facilitation was also observed in our experiment, consistent with the results of Chao et al., although cc-PAS-induced M1 plasticity was not verified in HVs. Additionally, our study showed a similar degree of attenuation of PPC to M1 facilitation following PAR-MOT cc-PAS across all groups, whereas an increased M1 plasticity after PAR-MOT cc-PAS was observed only in the WC group. This suggests that the M1 response to the PAR-MOT cc-PAS may not be directly responsible for the modulation of facilitatory PPC to M1 connectivity. Aberrant plasticity in the M1 following PAR-MOT cc-PAS in patients with WC may be associated with polysynaptic connections in the PPC to M1 network, although a clear conclusion could not be drawn in the current study.

Our study has some limitations that should be considered when interpreting our results. First, we were unable to achieve the expected plasticity in the M1 from PAR-MOT cc-PAS in HVs. Although this could be due to the difference in the methodology used in our experiment from previous studies, it is also possible that the plasticity in M1 *per se* induced by PAR-MOT cc-PAS may be maladaptive, as it was only observed in patients with WC. Owing to the scarcity of previous studies and the use of different methodologies, this may be difficult to discern. Further studies may provide results to explain this discrepancy. Second, we were unable to reach the initially planned enrollment goal, and the number of participants was relatively small. In our experiment, we used the IOC as a parameter for assessing plasticity in M1 because it seems to be a more reliable and comprehensive method for evaluating M1 excitability than the average MEP at a single intensity (Kukke et al., 2014). We believe that the inability to achieve the initially planned number of participants does not impede the interpretation of the results. Third, the inherent variability of MEP related to multiple intrinsic and extrinsic factors might affect the data interpretation, particularly with a small numbers of subjects (Guidali et al., 2021; Minkova et al., 2019),

although this was partially mitigated by the use of IOC.

The current study showed that the pathophysiology of associative plasticity may differ between patients with CD and those with WC, with maladaptive plasticity being linked to deficient sensorimotor integration. This new insight into the divergent pathophysiological mechanisms of different focal dystonias could facilitate the development of targeted therapeutic interventions for each type of dystonia. Further research is needed to clarify the mechanisms underlying associative plasticity in focal dystonia and to develop more effective therapeutic interventions.

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CRediT authorship contribution statement

Hyun Joo Cho: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Hae-Won Shin:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Pattamon Panyakaew:** Writing – review & editing, Investigation. **Panagiotis Kassavetis:** Writing – review & editing, Investigation. **Traian Popa:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Tianxia Wu:** Writing – review & editing, Formal analysis. **Giorgio Leodori:** Writing – review & editing, Investigation. **Terance Camacho:** Writing – review & editing, Investigation. **Shivangi Singh:** Writing – review & editing, Investigation. **Sabine Meunier:** Writing – review & editing, Conceptualization. **Mark Hallett:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors report no conflicts of interest.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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